STUDIES ON THE SYNTHESIS OF NEW AMINONUCLEOSIDES: REACTIONS OF SULPHONYLATED PYRIMIDINE NUCLEOSIDES WITH AMINES

Thesis
submitted to the
UNIVERSITY OF POONA
for the degree of
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

by
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February - 1996

to my mother

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Studies On The Synthesis Of New Aminonucleosides: Reactions Of Sulphonylated Pyrimidine Nucleosides With Amines"** submitted by **Mr. K. SAKTHIVEL** was carried out by him under my supervision at National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledgeed in the thesis.

Date: Feb. 19, 1996

National Chemical Laboratory,
Pune-411008.

(**Dr. T. Pathak**)
Research Guide

DECLARATION

I hereby declare that the thesis entitled **"Studies On The Synthesis Of New Aminonucleosides: Reactions Of Sulphonylated Pyrimidine Nucleosides With Amines"** submitted for Ph.D. degree to the University of Poona has not been submitted by me for a degree to any other University.

Date: 19.2.96.

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Acknowledgment

I take this opportunity to express my deep sense of gratitude to my research guide, Dr. T. Pathak for not only giving guidance but also for inspiration. His never diminishing encouragement in the progress of my work is gratefully acknowledged.

I would like to thank Dr. K. N. Ganesh and Dr. S. Rajappa for their constant encouragement. I am also grateful to Dr. M. S. Shashidar and Dr. A. A. Natu for their cooperation in the laboratory.

I extend my thanks to Dr. Eric De Clercq (Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium) and Prof. B. Oberg (Medivir, Sweden) for antiviral screening of few compounds. I am also thankful to Dr. C. G. Suresh (Division of Biochemical Sciences, National Chemical Laboratory, Pune) for X-ray analysis of some of the compounds.

Help from spectroscopic, Microanalytical and Library group is gratefully acknowledged. Special thanks are due to Dr. R. Krishna Kumar and Mr. A. G. Samuel for doing special NMR experiments. I extend my thanks to Dr. G. J. Langley (The University, Southampton, UK) for providing me high resolution mass data of some compounds.

Special thanks are due to my colleagues, Sanjeeb, Rajeev, Tanya, Praveen, Bindhu, Dr. Barawkar, Jadav, Gopal, Anand, Vipul, Ramesh, Pallan, Gangamani, Monisha and Dr. Sanjayan for maintaining cheerful atmosphere in and around NCL. Thanks are due to Mr. R. B. Makhar, for his help in day to day laboratory maintenance.

Many thanks are due to my friends, Dr. Jayaraman, Dr. Kumaran, Srirajan, R. G. Ravi, Karthikeyan, Anbu, Dr. Mani, Balamurugan, Prakash, Ramani, Venkatraman, Balaji, Ramalingam, Sourav, Sanjay, Rasidul, Patkar, Prasad, Pavan and others for their cheerful company.

Thanks are due to my family members, especially Mr and Mrs. A. Thayumanavan who have provided me constant enthusiasm through out the study. I would like to extend my thanks to T. Rajeswari and T. Saravanan for their cheerful company at home.

Finally I am grateful to the CSIR for the financial assistance and to the Director, NCL, Pune, for permitting me to submit this work in the form of thesis.

(K.SAKTHIVEL)

CONTENTS

Abbreviations

Ac	:	Acetyl
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
Ad	:	Adenine
Bn	:	Benzyl
Boc	:	*t*-Butyloxycarbonyl
Bz	:	Benzoyl
DAST	:	Diethylaminosulphur trifluoride
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	:	Dicyclohexylcarbodiimide
DEAD	:	Diethyl azodicarboxalate
DMF	:	N,N-Dimethyformamide
DMSO	:	Dimethylsulphoxide
DMTr	:	4,4'-Dimethoxytriphenylmethyl
Et	:	Ethyl
EtOAc	:	Ethylacetate
Me	:	Methyl
Ms	:	Methanesulphonyl
MMTr	:	4-Monomethoxytriphenylmethyl
M.P.	:	Melting point
Nu^-	:	Nucleophile
NaOBz	:	Sodiumbenzoate
Piv	:	Trimethyacetyl
PPh_3	:	Triphenylphosphine
Py	:	Pyridine
T	:	Thymine
TBDMS	:	*t*-Butyldimethylsilyl
TBAF	:	*t*-Butylammoniumfluoride
Tf	:	Trifluromethane sulphonyl
Tr	:	Triphenylmethyl
Ts	:	4-Toluenesulphonyl
TMS	:	Trimethylsilyl
U	:	Uracil

Synopsis of the Thesis

STUDIES ON THE SYNTHESIS OF NEW AMINONUCLEOSIDES: REACTIONS OF SULPHONYLATED PYRIMIDINE NUCLEOSIDES WITH AMINES

CHAPTER-I

Synthetic approaches towards sugar modified aminonucleosides and their biological properties - A Review.

Nucleoside analogues in general display a wide range of biological activities. In the past, a variety of aminonucleosides were synthesised to study their biological properties. Since the discovery of anti-HIV (Human Immunodeficiency Virus) activity of 3'-deoxy-3'-azidothymidine (AZT), various modifications have been made at the 2'- and/or 3'-sites of nucleosides. It was reported that 3'-amino-3'-deoxythymidine was formed from 3'-deoxy-3'-azidothymidine (AZT) in some cells as a reduced product. In another report, 3'-amino-3'-deoxy- thymidine was synthesised and studied against HIV. It was observed that 3'- amino-3'-deoxythymidine itself inhibited HIV weakly with high toxicity, whereas 5'-triphosphate of 3'-amino-3'-deoxy-thymidine showed a strong inhibition against HIV-1. As AZT was shown to be more lipophilic than 3'-aminothymidine, several modification have been made at 3'-sites using lipophilic group containing amino modifications to enhance the lipophilic parameter. In a recent report, several 2'-deoxy-2'-alkylamino- and 3'-deoxy-3'-alkylamino- derivatives have been synthesised and studied against HIV. Moreover, 3'-amino-3'-deoxythymidine was shown to be active against p815 mouse leukemia cells. Various 5'-deoxy-5'-amino-substituted nucleosides were also synthesised and found to be active against Herpes Simplex Virus (HSV). Some aminonucleosides are important building units for various naturally occurring antibiotics such as, nikkomycins (neopolyoxins). Recently, in the rapidly developing area of anti-sense technology, several research groups have replaced the phosphate backbones of oligonucleotides by amino, amido, sulphamido, urea etc. linkages where the nitrogen atoms are part of the carbohydrate moieties of the nucleoside units; some of these "oligonucleosides" were more resistant towards nucleases and have shown comparable or higher melting temperatures (T_m) than the corresponding phosphate linked oligomers. In the light of the above discussion, it becomes apparent that it would be useful to develop strategies for the synthesis of new aminonucleosides as, a full evaluation of the biological activities of this type of compounds will be possible only when they are easily accessible. In this chapter, various synthetic approaches towards aminonucleosides and their biological properties will be discussed as an introduction to the present thesis work.

CHAPTER-II

Reactions of 3',5'-di-O-mesylthymidine with secondary amines.

The main aim of this work is to synthesis 3',5'-dideoxy-3',5'-dihetero- substituted-thymidine derivatives. We have shown that 3',5'-di-O-mesylthymidine **1** (DMST) on reaction with secondary amines undergoes "one-pot-two-steps" transformation to produce a new class of 2,3'-O-anhydro- 5'-deoxy-5'-alkylaminothymidines (**Scheme-1**). DMST **1** was reacted with morpholine, piperidine, thiomorpholine, pyrrolidine, N-methylpiperazine, N-acetylpiperazine, ethyl*iso*nipecotate and diethylamine to produce compounds **2a-2h** respectively. It was concluded from further studies that the course of reactions between DMST **1** and secondary amines was controlled by the nucleophilicities of the amines and not by their basicities.

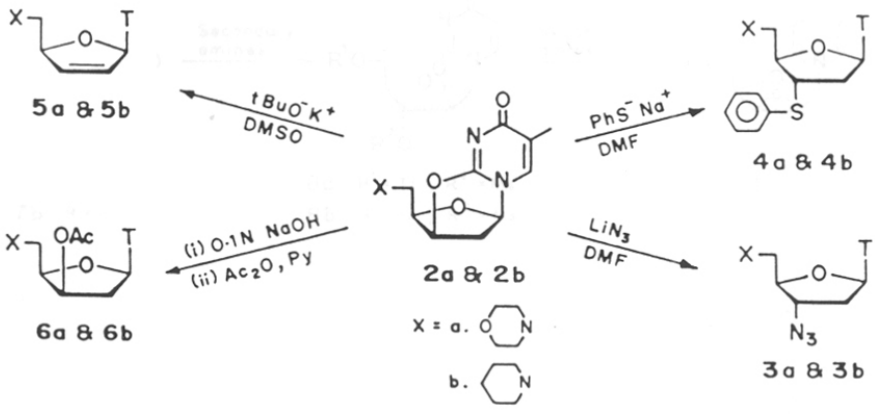
Scheme-1

1 **2a-2h**

X = a. ; b. ; c. ; d. ; e. ; f. ; g. ; h.

In order to synthesis 3',5'-dideoxy-3'-substituted-5'-alkylaminothymidines, compound **2a** and **2b** on reaction with lithium azide, sodium thiophenolate, potassium-*tert*-butoxide and 0.1N aqueous sodium hydroxide solution followed by acetylation produced compounds **3a-6a** and **3b-6b** respectively (**Scheme-2**).

Scheme-2



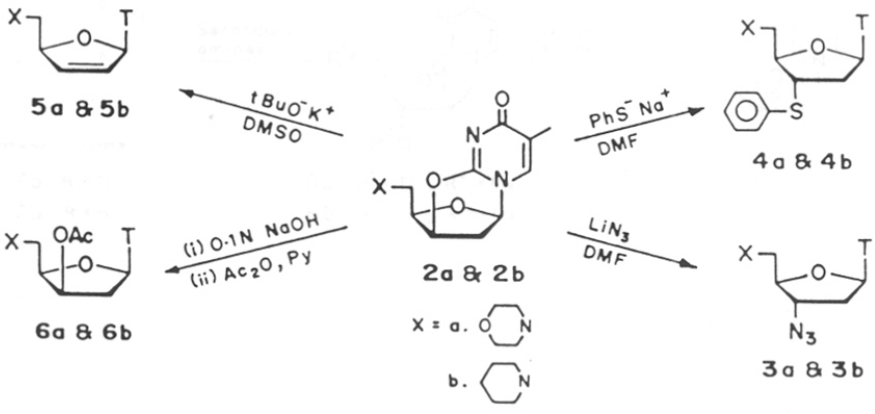
CHAPTER-III

Reactions of 2',3'-di-O-mesyl-5'-O-trityluridine with secondary amines.

To broaden the scope of the reactions of DMST **1** with secondary amines, we decided to react mesylated uridine with secondary amines. As a result of this study, we observed that 2',3'-di-O-mesyl-5'-O-trityluridine **7a** on reaction with secondary amines, such as, piperidine, pyrrolidine, ethyl*iso*nipecotate and N-methylpiperazine produced isocytidine derivatives, 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*-furanosyl)-2-dialkylamino-4-pyrimidones **9a-9d**, *via*, the formation of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityl- uridine **8a** (**Scheme-3**). Extensive cleavage occurred when compound **7a** was treated with diethylamine, N-acetylpiperazine and N-methylethanolamine. As attempted detritylation of compounds **9a-9d** produced inseparable mixtures, we chose to study the reactions of secondary amines with 2,2'-O-anhydro-3'-O-mesyl-uridine **8b**. Thus compound **8b** on reaction with piperidine, pyrrolidine, ethyl*iso*nipecotate and N-methylpiperazine produced compounds **10a-10d** respectively.

It was reported earlier that 2,2'-O-anhydrouridine **11** on reaction with primary amines produced C-2 amino substituted *ara*-uridine **12** but remained unaffected by secondary amines due to "steric hindrance" (**Scheme-4**). It was concluded from the present study that the presence of an electron withdrawing group and leaving group adjacent to the C-2' position of 2,2'-O-anhydrouridine enhanced the electrophilicity of C-2 carbon, thereby nullifying the steric effect.

Scheme-2



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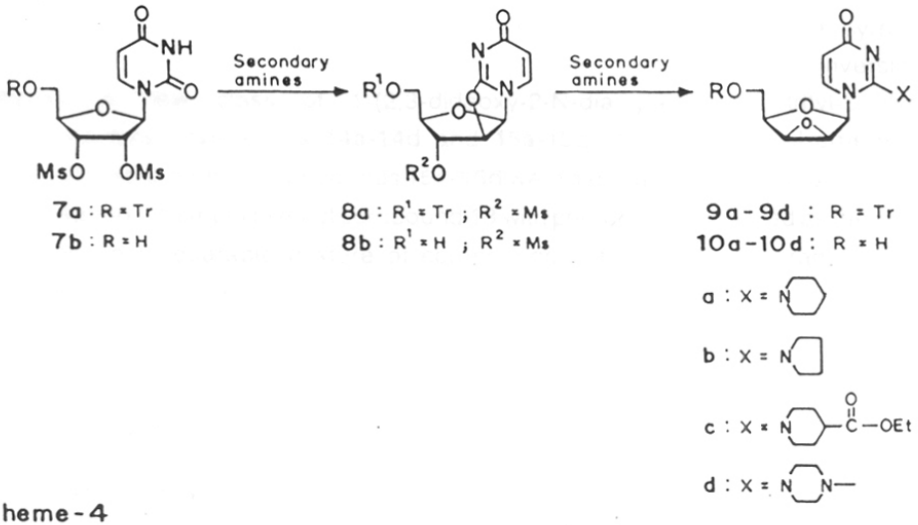
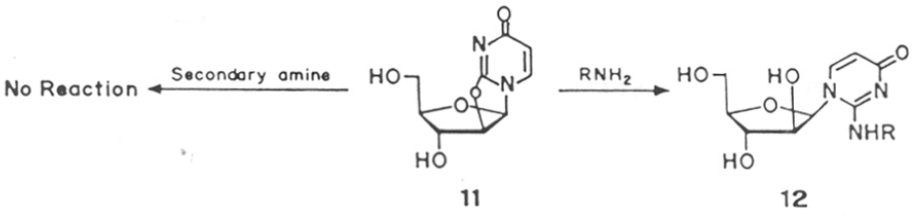
Scheme-3



Scheme-4



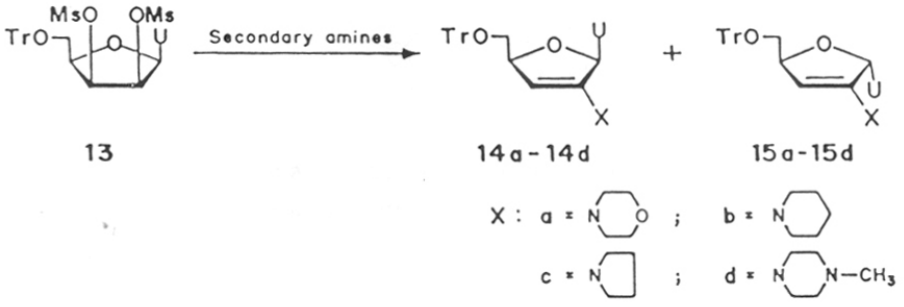
CHAPTER-IV

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*lyxo*-uridine with amines.

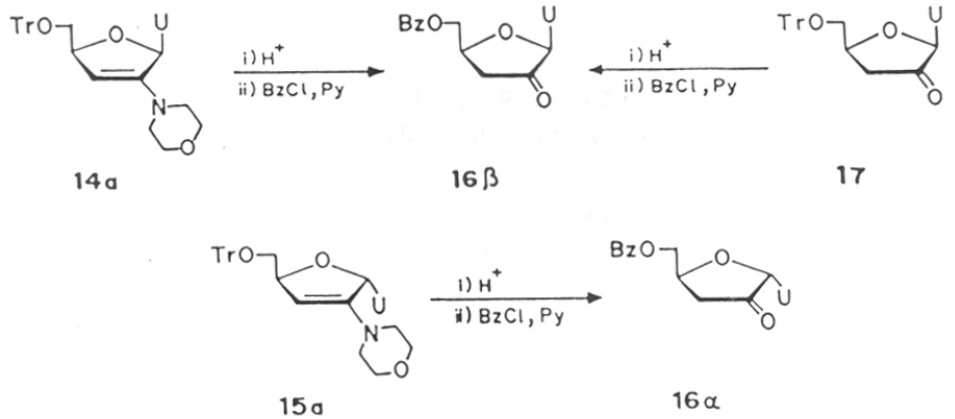
It was evident from the results described in the previous chapter that 2',3'-di-O-mesyl-5'-O- trityluridine **7a** was not particularly useful for the functionalisation of the sugar moiety as the first step, especially in the presence of basic reagents like amines, was always 2,2'-O-anhydro- ring formation. We, therefore, reasoned that a study on the reactions between amines and 1-(2,3-di-O-mesyl-5-O-trityl-β-D-*lyxo*-furanosyl)-uracil **13** would give new insight into the area of the functionalisation of the nucleosides, as unlike in the case of the *ribo*-uridine derivative, compound **13** would not undergo any intramolecular cyclisation.

In this chapter, we will be reporting that 1-(2,3-di-O-mesyl-5-O-trityl-β-D-*lyxo*-furanosyl)-uracil **13** on reaction with morpholine, piperidine, pyrrolidine and N-methylpiperazine undergoes a novel "one-pot-multi-steps" conversion to generate a new class of 1-(2,3-dideoxy-2-N-dialkylamino-5-O-trityl-D-*glycero*-pent-2-eno-furanosyl)-uracils **14a-14d** and **15a-15d** respectively (**Scheme-5**). The pure α-anomers, namely, compounds **15a-15d** were separated from the mixture through crystallisation. Attempts to react compound **13** with primary amines failed as the reaction produced an inseparable mixture of compounds indicating the degradation of the starting material.

Scheme-5



Scheme-6



The identity of the β-isomer present in the mother liquor was established through the hydrolysed product of the representative example **14a**. The enamine **14a** was hydrolysed using acid (THF-water 5:1, conc.HCl, 3 eqv; reflux, 12h). The detritylated ketone was converted to its benzoyl derivative **16**β. The hydrolysed product obtained from the mother liquor was similar (mixed NMR) to the authentic compound **16**β obtained

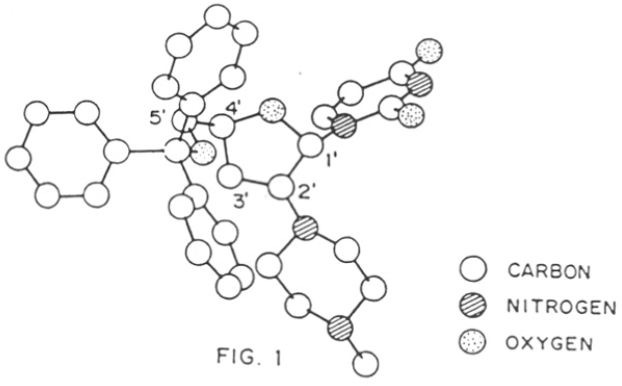


FIG. 1

from known **17**. The α-enamine **15a** was also hydrolysed under acidic conditions and rebenzoylated to generate 5'-O-benzoyl-3'-deoxy-2'-keto-α-uridine **16**α in anomericaly pure form (**Scheme-6**).

The crystallised enamine was established to be the α-anomer with the help of X-ray crystal structure analysis (**FIG.1**) of the representative example **15d**.

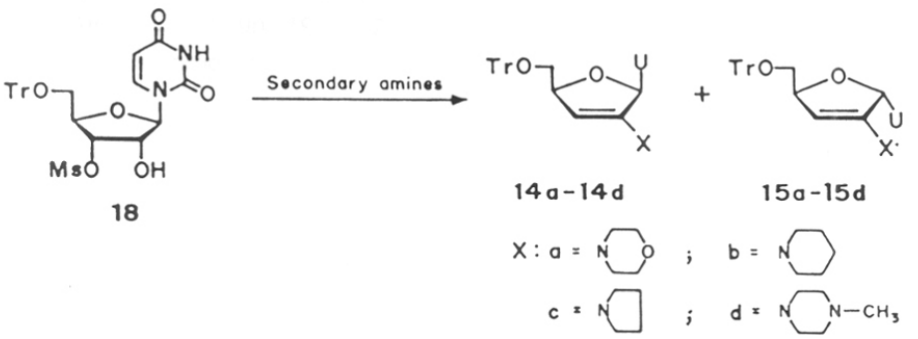
CHAPTER-V

Reactions of 5'-O-trityl-3'-O-mesyl-uridine, 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine and 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine with amines.

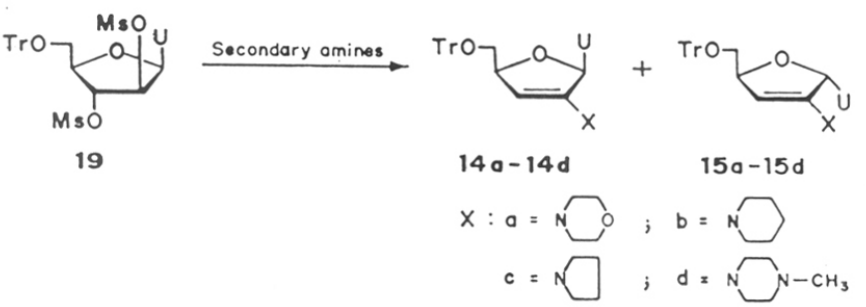
In chapters III and IV, we described that the presence or absence of intramolecular cyclisation reactions played crucial role in determinig the nature of the products. We envisaged, therefore, that suitably functionalised pyrimidine nucleosides with no leaving group at C-2' position could also be made to form enaminonucleosides. Since it was also reported earlier that the 2,3'-O-anhydro- ring formation was less facile than 2,2'-O-anhydro- ring formation and required very harsh reaction conditions, we decided

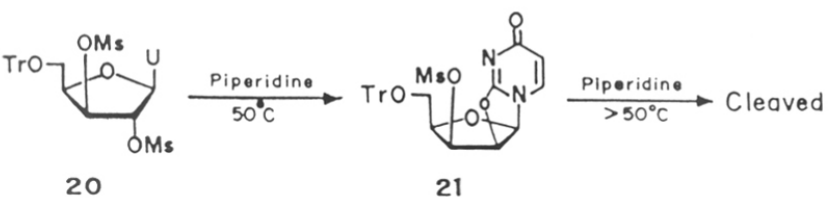
to use a *ribo*-uridine derivative as the starting material for enamine synthesis. Thus, 5'-O-trityl-3'-O-mesyluridine **18** on treatment with secondary amines, morpholine, piperidine, pyrrolidine and N-methylpiperazine produced the anomeric mixture of compounds **14a-14d** and **15a-15d** respectively (**Scheme-7**).

Scheme-7



Scheme-8





To conclude the studies on the reactions of sulphonylated pyrimidine nucleosides with amines, we also studied the reactions of 2',3'-di-O-mesyl- 5'-O-trityl-*ara*-uridine **19** and 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine **20** with amines. 2',3'-Di-O-mesyl-5'-O-trityl-*ara*-uridine **19** was treated with secondary amines, morpholine, piperidine, pyrrolidine and N-methylpiperazine to produce the anomeric mixture of compounds **14a-14d** and **15a-15d** respectively. 2',3'-Di-O-mesyl-5'-O-trityl-*xylo*-uridine **20** on treatment with piperidine at 50°C produced 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityl-*lyxo*-uridine **21** which eventually got cleaved at high temperature (**Scheme-8**). Compound **19** and **20** on treatment with primary amines produced mixture of unidentified products.

List of Publications

This thesis is based on the following original publications. Some related unpublished results are also included in this thesis.

Chapter-II Reactions of Dimesylthymidine With Secondary Amines: Easy access to 3',5'-Dideoxy-3'-Substituted-5'-Alkylaminothymidines- New Classes of Potential Antiviral Aminonucleosides.
K. Sakthivel, R. Krishna Kumar, T. Pathak; *Tetrahedron*, **1993**, 49, 4365-4372.

Chapter-III One-step Synthesis of C-2 Dialkylamino-substituted 2',3'-O- Anhydro-*lyxo*- Uridines: First Report on the Opening of 2,2'-O-Anhydro -bridge of 2,2'-O-Anhydrouridine by Secondary Amines.
K. Sakthivel, S. Bera, T. Pathak; *Tetrahedron*, **1993**, 49, 10387-10392.

Chapter-IV Reactions of 2',3'-Di-O-mesyl-*lyxo*-Uridine with Secondary Amines: First report on the One-Pot Conversion of Mesylated Nucleosides to Enamino nucleosides And the Crystal Structure of α-Enamine.
K. Sakthivel, C.G. Suresh, T. Pathak; *Tetrahedron*, **1994**, 50, 13251-13260.

5'-O-Benzoyl-2'-keto-3'-deoxy-α-uridine:Synthesis, Crystal Structure and its use to Estabilish the Anomerisation of 2'-Ketouridines under Basic Conditions.
K. Sakthivel, C.G. Suresh, T. Pathak; *Tetrahedron*, **1996**, 52, 1767-1772.

5'-O-Benzoyl-2'-keto-3'-deoxy-α-uridine, $C_{16}H_{14}N_2O_6$.
C.G. Suresh, **K. Sakthivel**, T. Pathak; *Acta.cryst.C;* **1996**, *accepted for publication.*

Chapter-V One-pot Deoxygenative Conversion Of A Ribonucleoside to Enamino nucleosides involving 1,2-Hydride Shift Rearrangement.
K. Sakthivel, T. Pathak; *Tetrahedron*, **1996**, *accepted for publication.*

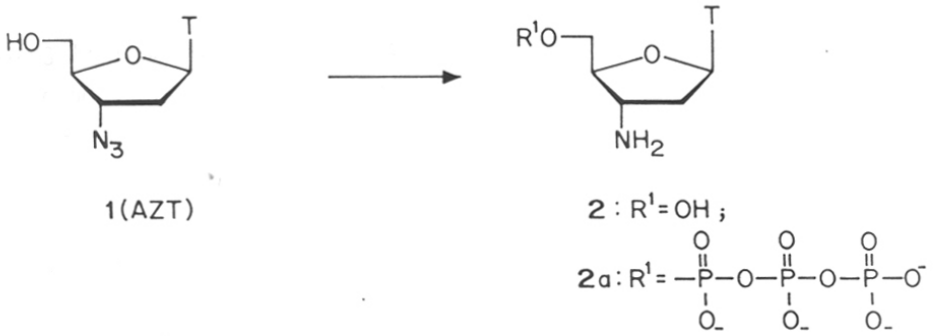
CHAPTER-I

Synthetic Approaches Towards Sugar Modified Aminonucleosides and their Biological Properties - A Review

1.1. Introduction

Nucleoside analogues in general, display a wide range of biological activities[1-2]. In the past, a variety of amino- nucleosides were synthesised to study their biological properties[3]. Since the discovery of the anti-HIV (Human Immunodeficiency Virus) activity of 3'-deoxy-3'-azido thymidine[4] **1** (AZT), various modifications have been made at 2' and /or 3'-sites of nucleosides[5]. It was reported that 3'-amino-3'-deoxythymidine **2** was formed from 3'-deoxy-3'-azidothymidine (AZT) in some cells as the reduced product[6]. In another report, 3'- amino-3'-deoxythymidine **2** was synthesised and studied against HIV. It was observed that 3'-amino-3'-deoxythymidine **2** itself inhibited HIV weakly with high toxicity, whereas the 5'-triphosphate derivative **2a** showed strong inhibition[7] against HIV-1 (**Scheme-1.1**); the

Scheme - 1·1



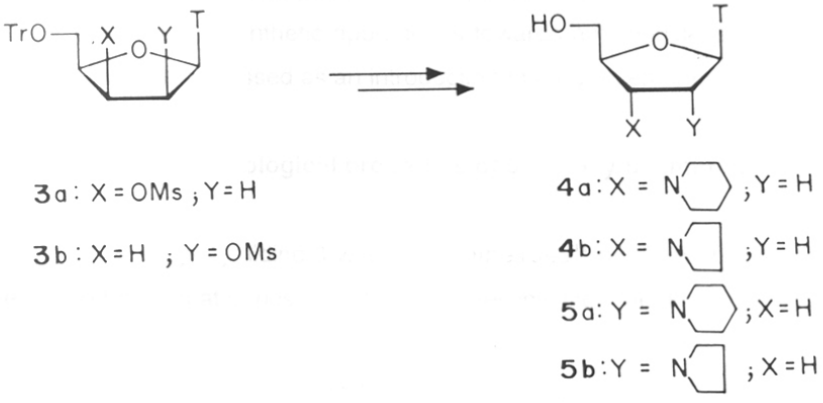
1(AZT)

2 : R^1 = OH ;

2a : R^1 = $-P(O^-)(=O)-O-P(O^-)(=O)-O-P(O^-)(=O)-O^-$

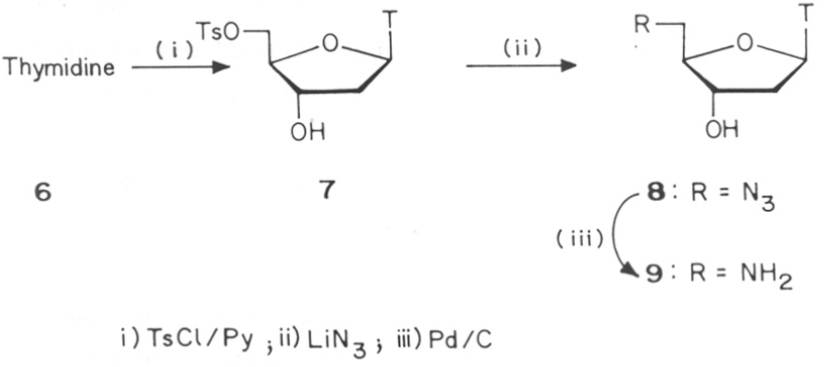
inactivity of compound **2** was attributed to its high polar nature. To enhance the lipophilic parameter, several modifications have been made at 3'-sites using lipophilic group containing amino- functionalities[8]. In addition, several 3'-deoxy-3'-alkylamino- **4a-b** and 2'-deoxy-2'-alkylamino- derivatives **5a-b** have been synthesised[9] from compounds **3a** and **3b** (**Scheme-1.2**) and studied against HIV. 3'-Amino-3'-deoxythymidine **2** was also active against p^{815} mouse leukemia cells. Various 5'-deoxy-5'-amino substituted nucleosides **9**, **11** and **12** were also synthesised[10,11] and found to be active against Herps Simplex Virus (HSV). Various 5' , 3' and 2' amino, alkylamino, and dialkylamino derivatives of sugar modified nucleosides showed interesting biological properties. In recent years, various nitrogen

Scheme-1·2



containing dephospho-backbone modified di-nucleotides were synthesised for developing oligonucleotides with anti-sense properties. Some naturally occurring nucleoside antibiotics containing aminosugar moieties have also been reported.

Scheme-1·3



In the light of above discussion, it becomes apparent that it would be useful to develop strategies for the synthesis of new aminonucleosides as, a full evaluation of the biological activities of this type of compounds will be possible only when they are easily available. In this chapter, various synthetic approaches towards aminonucleosides and their biological properties will be discussed as an introduction to the present thesis work.

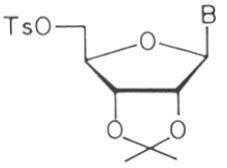
1.2. Synthesis and biological properties of 5'- deoxy-5'-aminonucleosides

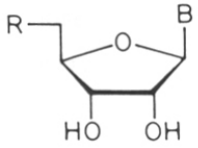
5'-Amino-5'-deoxy-thymidine **9** was first synthesised[12] by Horwitz *et.al.* The introduction of the amino function at 5'-position of nucleosides involved the direct displacement reaction of 5'-O-tosylthymidine **7** with azide followed by reduction (**Scheme-1.3**). It was also reported that 5'-aminothymidine **9** showed good anti-viral activity against the replication of Herps Simplex Virus both *in vivo & in vitro*[11]. In another report, 5'-aminothymidine was shown to be a good competitive inhibitor of phosphorylation of thymidine kinase[13] and a modest inhibitor of thymidilate kinase[14,15]. In 1968, Hampton and coworkers synthesised[16] 5'-amino-5'-deoxyinosine **11a** by using direct displacement reaction of 5'-tosyl-2',3'-isopropylidineinosine **10a** with azide followed by reduction (**Scheme-1.4**). It was also reported that 5'-amino-5'-deoxyinosine **11a** inhibited multiplication of L5178Y mouse lymphoma cells by 50% after 48 hours at 1mM concentration[16]. It was also reported[17,18] that 5'-O-tosyl-5'-deoxynucleosides **10b** and **7** (purines[17] and pyrimidines[18]) on reaction with various primary and secondary amines produced 5'-deoxy-5'-aminonucleosides **11b-c** (**Scheme-1.4**) and **12a-d** (**Scheme-1.5**) respectively. Some of these 5'-aminonucleosides showed inhibition against thymidilate kinase.

5'-Deoxy-5-N-(1,2,3)-triazolylthymidine derivatives **13a-d** have been synthesised[19] from 5'-azidothymidine **8**. Compound **8** on treatment with dimethyl acetylenedicarboxlate afforded the cyclised 5'- N-(1,2,3)triazolylthymidine **13a**, which on further treatment with amines produced corresponding diamido triazolyl derivatives **13b-d** (**Scheme-1.6**). None of these compounds showed any significant antiviral activity.

Baker and coworkers reported[20] the synthesis of 5'-C-tetrazole derivatives of thymidine from methyl ester of uronic acid **14a-d.** Compounds **14a-d** were converted to the corresponding amide derivatives using amines; the amides on further reaction with $POCl_3$ produced

Scheme - 1·4





10 a , b

a: B = Hypoxanthine

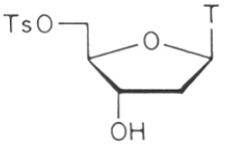
b: B = Adenine

11a: R=NH_2 ; B = Hypoxanthine

11b: R=NH_2 ; B = Adenine

11c: R =  ; B = Adenine

Scheme - 1·5



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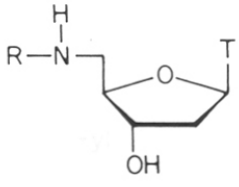
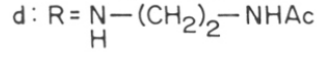


12 a - d

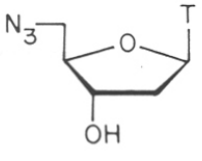
a: R = CH_2CH_3

b: R = $CH_2(CH_2)_2CH_3$

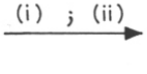
c: R = $CH_2(CH_2)_4CH_3$

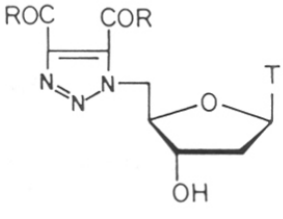
d: R = 

Scheme - 1·6



8





13 a-d

(i) $CH_3O_2CC \equiv CCO_2CH_3$

(ii) RNH_2

a: R = OMe

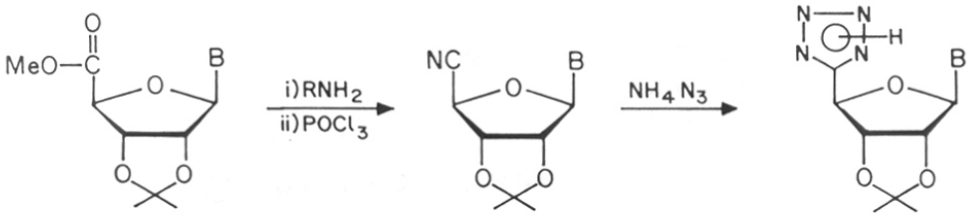
b: R = NH_2

c: R = $NH(CH_2)_3CH_3$

d: R = $NHCH_2Ph$

5'-deoxy-5'-cyanothymidine **15a-d**. Compound **15** on treatment with azides produced 5'-deoxy-5'-C-tetrazolylthymidines **16a-d** (**Scheme-1.7**). All these compounds were tested against various bacterial and viral strains. No significant *in vitro or in vivo* activity was observed.

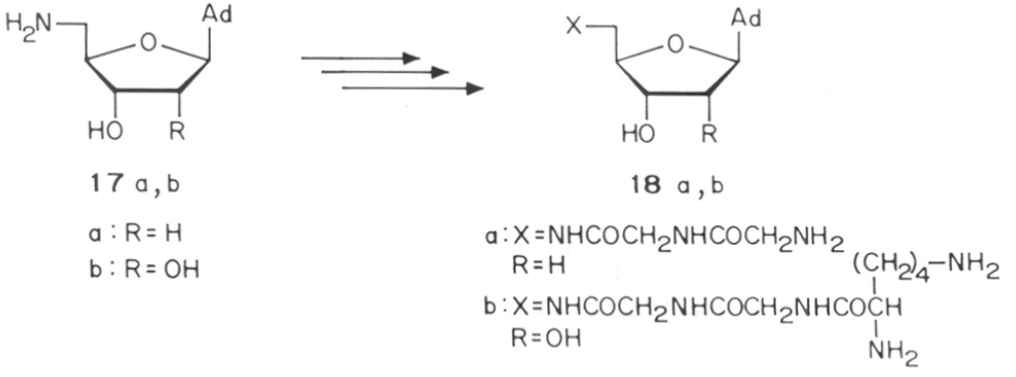
Scheme-1·7



14 a-d 15 a-d 16 a-d

a : B = Uracil-1-yl
b : B = 5-Fluro-Uracil-1-yl
c : B = 6-Azauracil-1-yl
d : B = Adenine-9-yl

Scheme-1·8

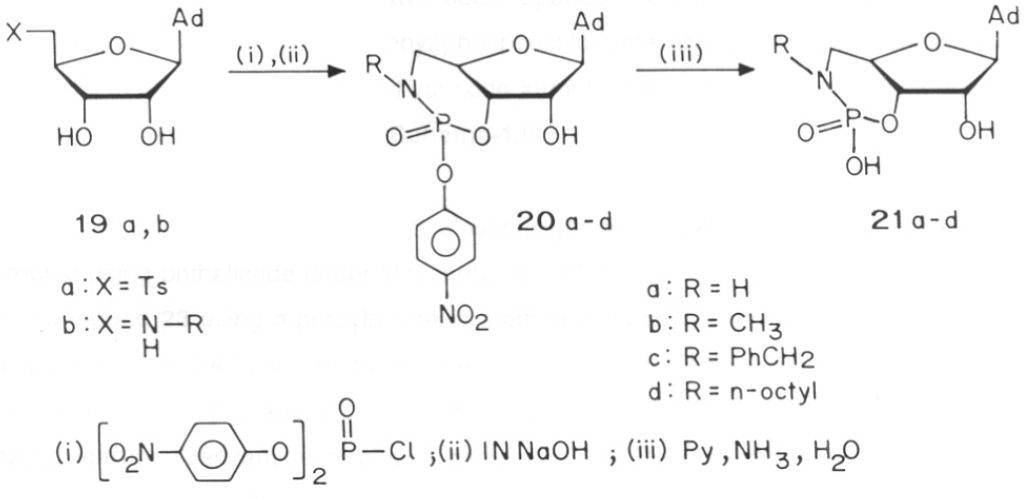


17 a, b 18 a, b

a : R = H
b : R = OH

In 1970, M. J. Robins and coworkers reported[21] the synthesis of 5'-aminoacylpeptide derivatives of guanosine, adenosine and deoxyadenosine **18a-b** from 5'-deoxy-5'-aminonucleosides **17a-b** (**Scheme-1.8**). Synthesis of 5'-amido analogues of

Scheme-1·9



19 a, b

a : X = Ts

b : X = N—R (H)

20 a-d

a : R = H

b : R = CH_3

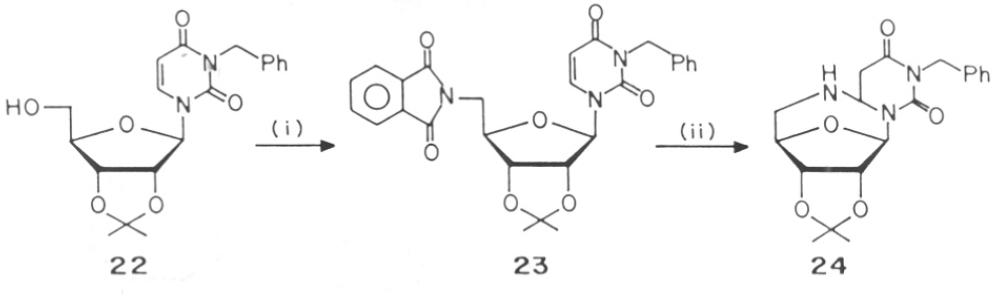
c : R = $PhCH_2$

d : R = n-octyl

21 a-d

(i) $\left[O_2N-\text{C}_6\text{H}_4-O\right]_2 P(O)-Cl$; (ii) IN NaOH ; (iii) Py, NH_3, H_2O

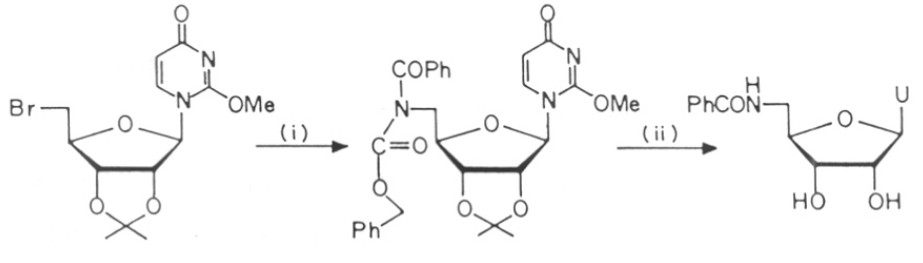
Scheme-1·10



22 23 24

(i) pthalimide, DEAD, PPh_3

(ii) $nBuNH_2$



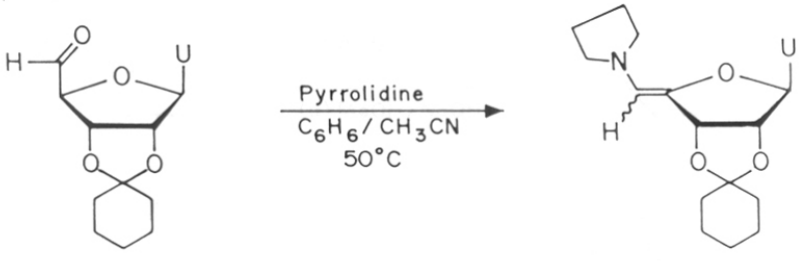
25 26 27

(i) $Ph-C(=O)-\bar{N}-C(=O)-OCH_2Ph$ (ii) a) Pd/C , b) $AcOH \cdot H_2O$

3',5'-cyclic monophosphate **21a-d** have been reported[22]. Compounds **19a** and **19b** were phosphorylated using di- (*p*-nitrophenyl)phosphochloridate and the resulting compounds **20a-d** were treated with 1N sodium hydroxide in methanol to give 5'-amido analogues of 3',5'-cyclic-monophosphates **21a-d** (**Scheme-1.9**).

Synthesis of 5'-aminouridine from 2',3'-isopropylidine-3N-benzyluridine **22** has been attempted using phthalimide under Mitsunobu conditions[23]. The removal of phthaloyl group from compound **23** using n-propylamine in methanol led to the formation of 5',6-epimino-derivative of uridine **24**. However, the synthesis of 5'-O-benzoylaminouridine **27** was reported using a modified procedure[23]. Compound **25** on treatment with sodium salt of benzyloxycarbonylbenzamide produced compound **26**. Compound **26** was converted to 5'-benzoylaminouridine **27** by catalytic reduction followed by acid treatment (**Scheme-1.10**). It has been reported[24] that 2',3'-O-cyclohexylidine-5'-aldehydouridine **28** on reaction with pyrrolidine produced 1-(5-deoxy-5'-pyrrolidino- 2,3-O-cyclohexylidine-β-D-*erthyro*-pent-4-enofuranosyl)uracil **29** (**Scheme-1.11**).

Scheme - 1.11

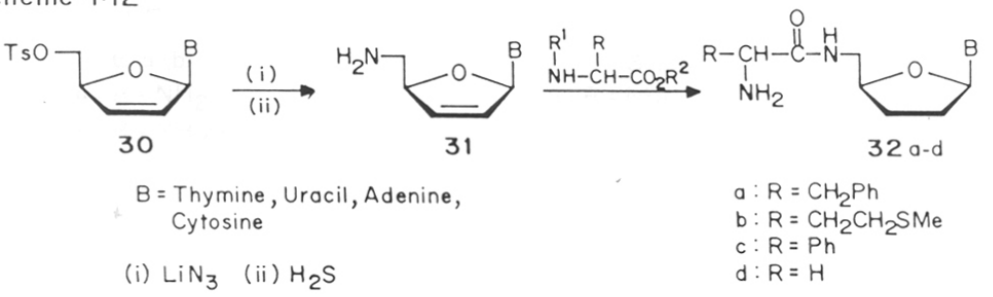


28 29

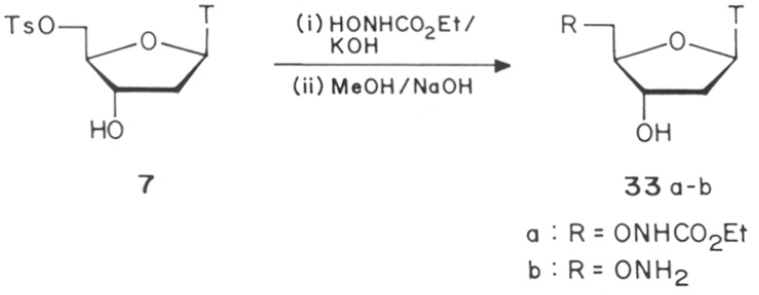
1-(5-Amino-2,3,5-trideoxy-β-D-glycero-pent-furanosyl)- nucleosides **31** and their 5'-aminoacylated derivatives **32a-d** were prepared[25,26] from compound **30** and examined for antitumor activity against sarcoma 180 (solid tumor). None of these compounds exhibited significant antitumor activity (**Scheme-1.12**).

5'-O-Amino-thymidine **33a-b** was synthesised and reported as potential thymidine kinase inhibitor[27]. 5'-O-Tosylthymidine **7** was treated with the ethyl ester of potassium hydroxycarbamate and the resulting urethane derivative **33a** was hydrolysed to give **33b** in 13% overall yield (**Scheme-1.13**).

Scheme-1·12

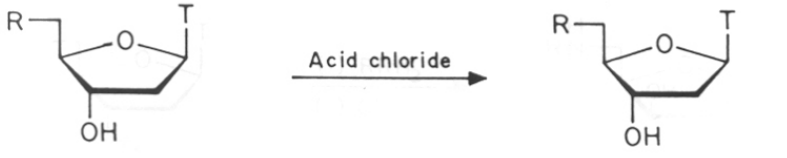


Scheme-1·13



Synthesis of various 5'-amido-5'-deoxythymidines **34a-f** was reported[28]. 5'-amino- and 5'-methylamino-5'-deoxythymidines **6a-b** on treatment with various acid chlorides produced compounds **34a-f** (**Scheme-1.14**). Among them, 5'-bromo- and 5'-iodo- acetamidothymidine **34a-b** showed good antiviral activity against P^{388} leukemia in mice. Analogues of various S-adenosyl methionine with modifications at the 5'-position **36** were prepared[29] as potential inhibitors of S-adenosyl methionine decarboxylase from compound **35** (**Scheme-1.15**).

Scheme-1·14



6 a-b

a : R = NH_2

b : R = $NHCH_3$

34 a - f

a : R = $NHCOCH_2Br$

b : R = $NHCOCH_2I$

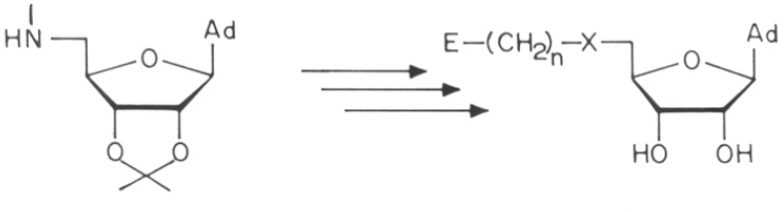
c : R = $NHCOCH_2Cl$

d : R = $NHCOCH(CH_3)Br$

e : R = $N(CH_3)COCH_2Br$

f : R = NCH_3COCH_2Cl

Scheme-1·15



35

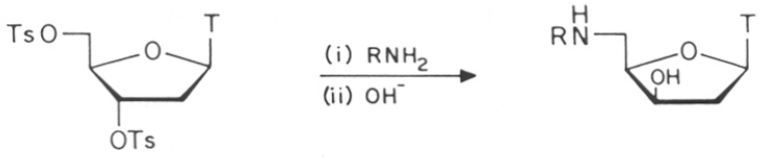
36

X = NCH_3, NH

E = $NH-C(=O)NHNH_2$, $NH-C(=S)-NHNH_2$, $NH-C(=NH)-NH_2$

n = 2

Scheme-1·16



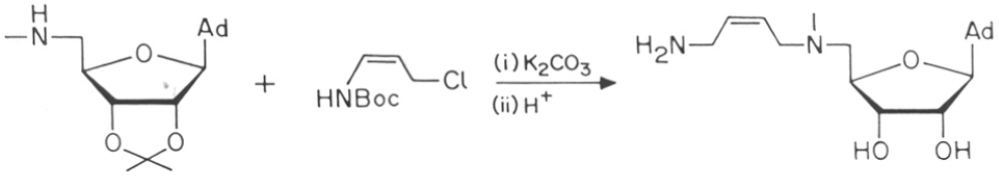
37

38 a-b

a : R = CH_3

b : R = H

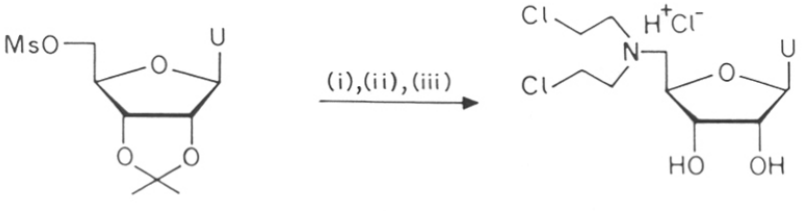
Scheme-1·17



35

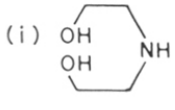
39

Scheme-1·18



40

41

(i) 

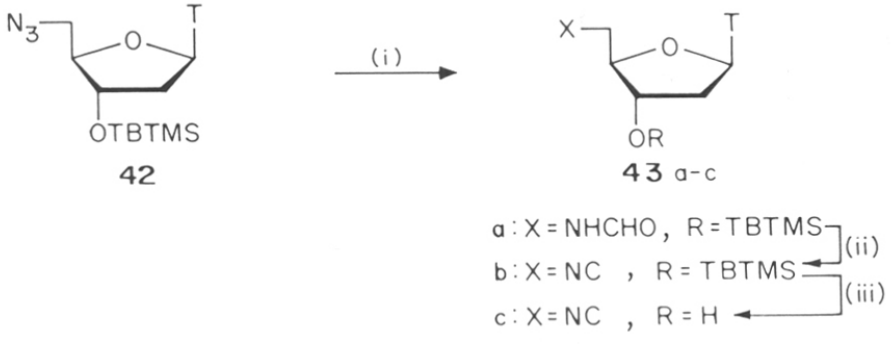
(ii) $SOCl_2$ (iii) HCl aq.

A novel conversion of 3',5'-O-di-tosylthymidine **37** to 5'-aminothymidine analogues with inversion of the 3'-hydroxyl group **38a** and **38b** was reported[30] (**Scheme-1.16**). A potent inhibitor of S-adenosyl-L-methionine decarboxylase 5'-{[(Z)-4-amino-2-butenyl]methylamino}- 5'-deoxyadenosine **39** was synthesised[31] from 5'-deoxy-5'-methylaminoadenosine **35** (**Scheme-1.17**).

5'-[Bis(2-chloroethyl)amino] -5'-deoxyuridine **41**, a uridine mustard, was synthesised for its antitumor activity[32]. Compound **40** was treated with diethanolamine to get 5'-N-substituted uridine derivative. The subsequent reaction with thionyl chloride followed by acid treatment produced 5'-[bis(2-chloroethyl)amino] -5'-deoxyuridine **41** (**Scheme-1.18**).

5'-Isocyanothymidine **43b** and its 3'-azido derivative **45** were prepared[33] and studied against HIV. 3'-Protected-5'-azidothymidine **42** on treatment with triphenylphosphine/acetic anhydride/acetic formicanhydride produced 5'-N- formamide derivative **43a** which was dehydrated to 5'-isocyano derivative **43b** using tosyl chloride in pyridine (**Scheme-1.19**). 3'-Azido-5'-isocyanothymidine **45** was prepared as reported in the scheme (**Scheme-1.20**). Neither of these derivatives showed any significant anti-HIV activity.

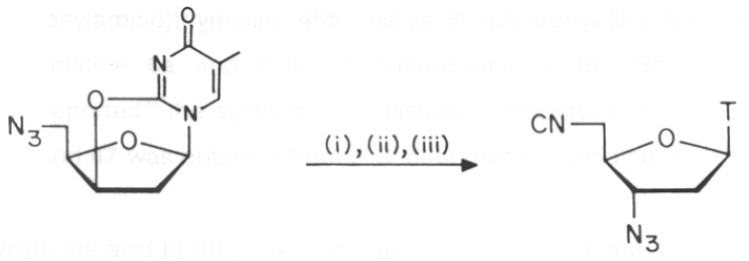
Scheme - 1·19



42 43 a-c

(i) PPh_3/HCO_2COCH_3 (ii) TsCl / Py (iii) TBAF

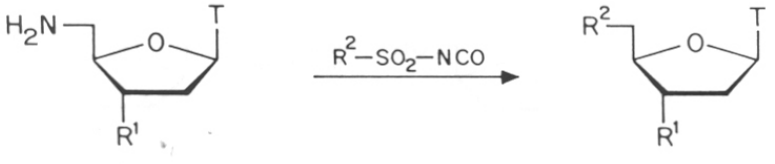
Scheme-1·20



44 45

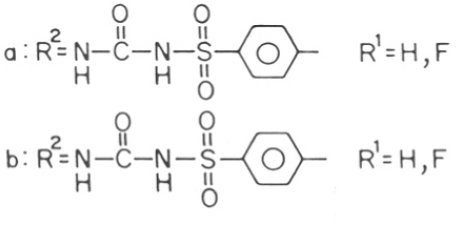
(i) PPh_3/HCO_2COCH_3 (ii) LiN_3 / DMF (iii) TsCl / Py

Scheme-1·21

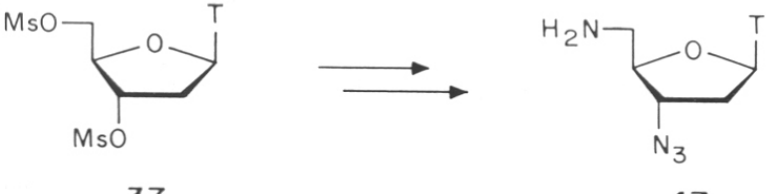


6 a-b 46 a-b

a : R^1 = OH
b : R^1 = F



Scheme-1·22



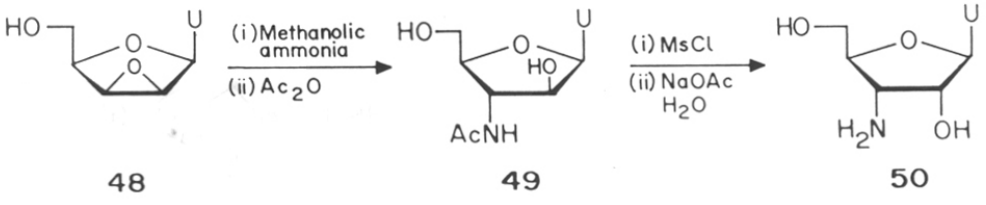
37 47

Nucleoside triphosphate isosteres of 5'-deoxy-5'-{[(toluenesulphonyl)-amino]carbonylamino}thymidine **46a** and its 3'-fluro-derivative **46b** were prepared[34] from 5'-aminothymidine **6a** and 3'-fluro-5'-aminothymidine **6b** (**Scheme-1.21**). Secrist and coworkers reported[35] the synthesis and biological properties of 5'-amino-3'-azidothymidine **47**; compound **47** was obtained from 2',3'-di-O-mesyl-thymidine **37** (**Scheme-1.22**).

1.3. Synthesis and biological properties of 3'-deoxy-3'-aminonucleosides

The first synthesis of 3'-amino-3'-deoxy-*ara*-uridine **49** was achieved[36] by opening of the anhydro-bridge of 2',3'-O-*lyxo*-anhydrouridine **48** with methanolic ammonia. The structure of the product **49** was confirmed by converting it to 3'-amino-3'-deoxyuridine **50** (**Scheme-1.23**).

Scheme-1·23

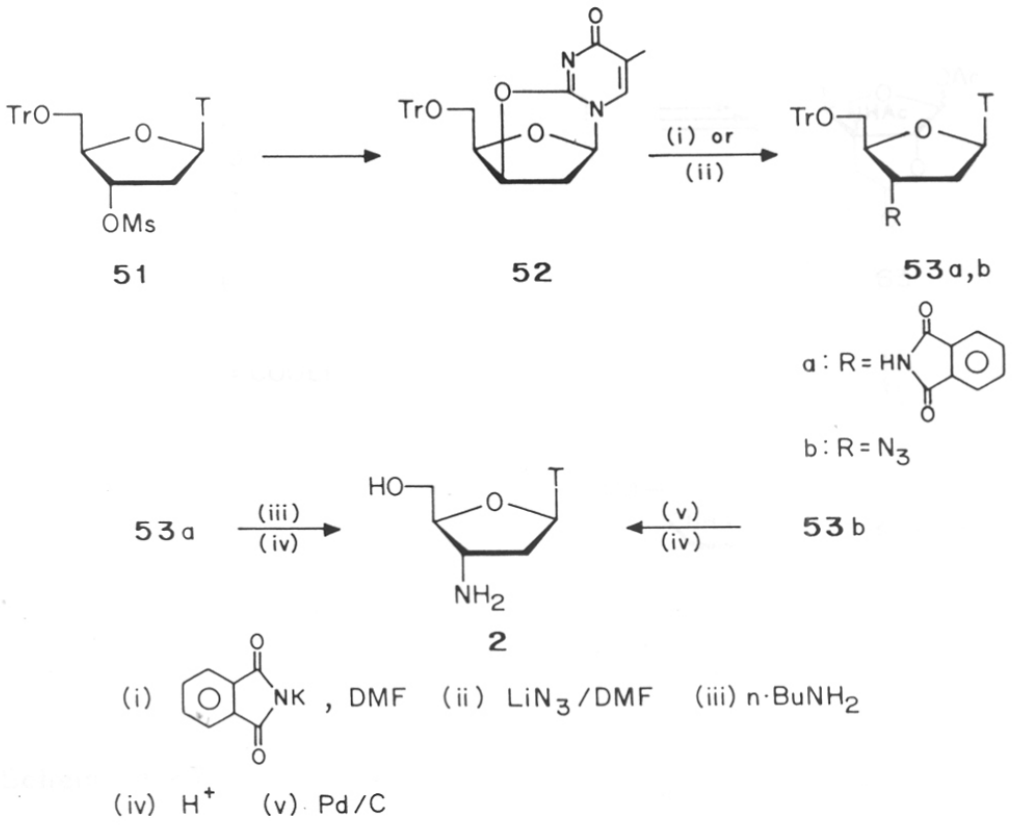


48 49 50

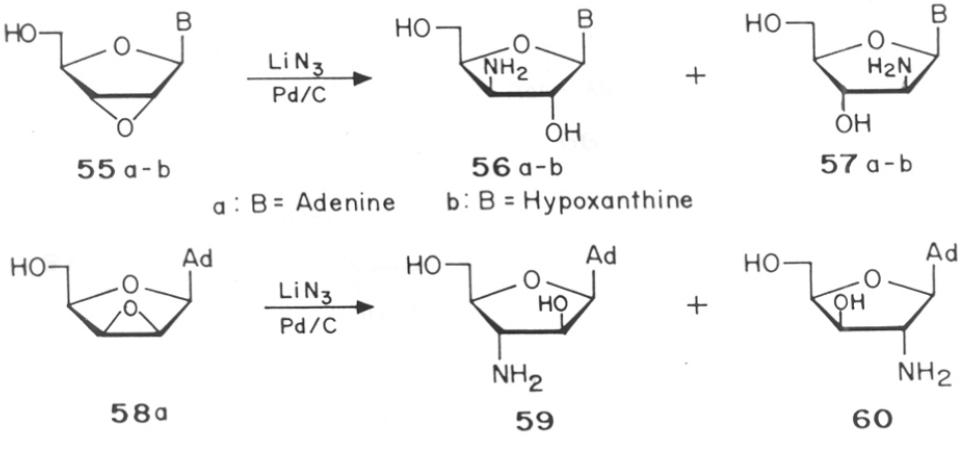
2',3'-Dideoxy-3'-aminothymidine **2** was first synthesised[37] by Miller and coworkers. 3'-O-Anhydrothymidine **52** or 5'-O-trityl-3'- deoxy-3'-O-mesylthymidine **51** was treated with potassium phthalimide in DMF to produce 3'-phthalimido-derivative **53a** which on further treatment with n-butylamine afforded 3'-aminothymidine **2**. Horwitz and coworkers later synthesised[12] compound **2** by opening of 2,3'-O-anhydrothymidine **52** with azide followed by catalytic reduction (**Scheme-1.24**). 2',3'-Dideoxy-3'-aminothymidine **2** was found to have potent inhibitory activity against the replication of both murinesarcoma-180 and L1210 cells in *in vitro* and *in vivo* studies.

Robins and coworkers described[38] the opening of 2',3'-O-*ribo*-anhydroadenosine **55** by azide; the resulting products on catalytic reduction afforded 3'-amino-3'-deoxy-β-D-*xylo*-furanosyladenine **56a** and **57a**. 3'-Amino-3'-deoxy-β-D-*xylo* (and *ara*)-furanosyl- inosine **56b** and **57b** were synthesised[39] from 2',3'-O-*ribo*-anhydro-inosine

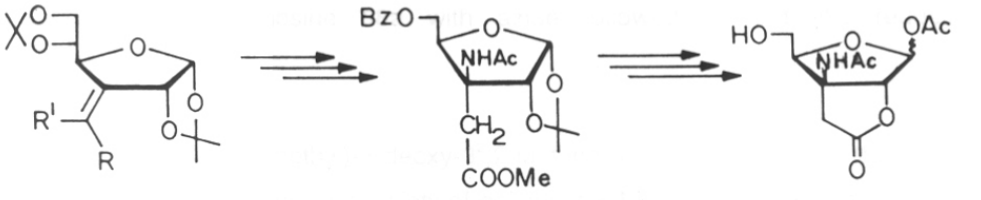
Scheme-1·24



Scheme-1·25



Scheme - 1·26



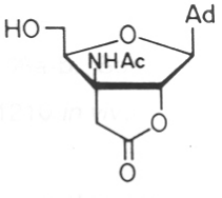
61 a–b

a : R = COOEt R^1 = H

b : R = H , R^1 = COOEt

62

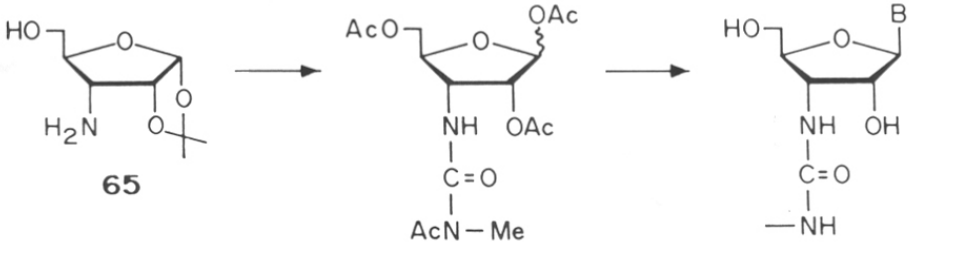
63



+ α-ISOMER

64

Scheme - 1·27



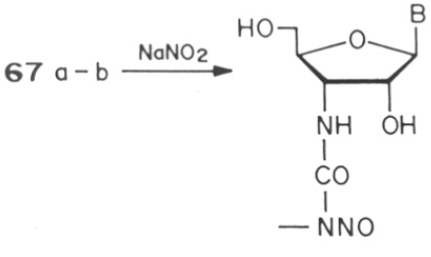
65

66

67 a–b

a : B = Adenine

b : B = Uracil



68 a–b

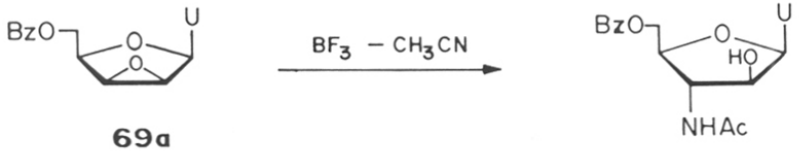
55b following the same route. In 1970, Martinez and coworkers reported[40] the synthesis of 3'-amino-3'-deoxy-*ara*- adenosine **59** and 2'-amino-2'-deoxy-*xylo*-adenosine **60** by opening of 2',3'-O-*lyxo*-anhydro-adenosine **58a** with azide followed by catalytic reduction (**Scheme-1.25**).

9-[3-Acetamido-3-C-(carboxymethyl)-3-deoxy-3^2,2-lactone-α (and β)-D-*xylo* -furanosyl]-adenine analogues of the nucleoside moiety of polyoxine **64** have been synthesised[41] from carbohydrate derivatives using the sequence **61->62->63->64 (Scheme-1.26)**.

3-Deoxy-3-(3-methylureido)-β-D-*ribo*furanosyl derivatives of adenine and uracil **67a** and **67b** respectively were obtained[42] from 3-deoxy-1,2-D-isopropylidine- (3-methylureido)-α-D-furanoside **65** (**Scheme-1.27**). Nitrosoation of the compounds **67a-b** gave the corresponding 3-methyl-3-nitrosoureido nucleosides **68a-b**. Some of these derivatives showed mild cytotoxicity or activity against leukemia L1210 *in vivo*.

The direct introduction of acetamide group at 3'-position of nucleoside of epoxides have been reported[43] by Fox and coworkers. Suitably protected derivative of 2',3'-O-anhydro-*lyxo*uridine **69a** was opened by acetonitrile in presence of BF_3-etherate complex to give 3'-acetamidio-3'-deoxy-*ara*-uridine **70** (**Scheme-1.28**).

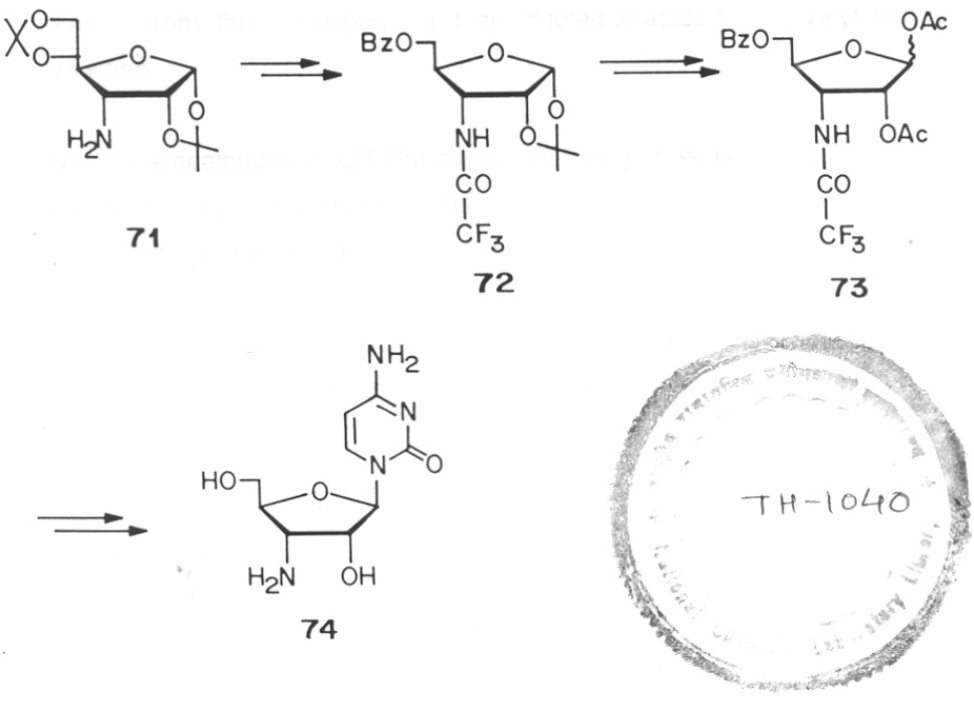
Scheme - 1.28



69a **70**

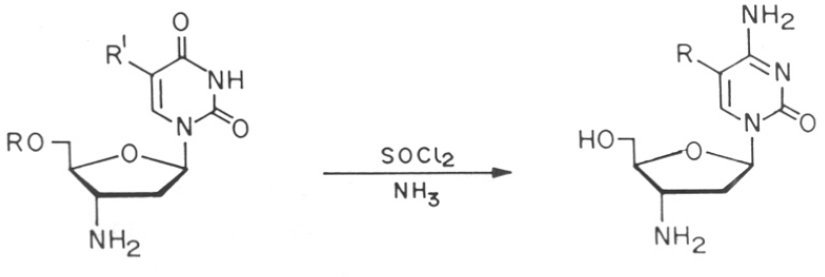
In 1981, 3'-deoxy-3'-aminocytidine **74** was synthesised[44] from 1,2:5,6-di-O-isopropylidine-3-amino-3-deoxy-α-D-allofuranose **71** (**Scheme-1.29**). 3'-Deoxy-3'-aminocytidine **74** showed activity against mouse leukemia L5178 cells. The synthesis and biological properties of 2',3'-dideoxy-3'-aminocytidine **76a** was also reported[45] in the literature. Synthesis of compound **76a** was achieved by the direct chlorination of 2',3'-dideoxy-3'-aminouridine **75a**

Scheme - 1·29



71 72 73 74

Scheme - 1·30



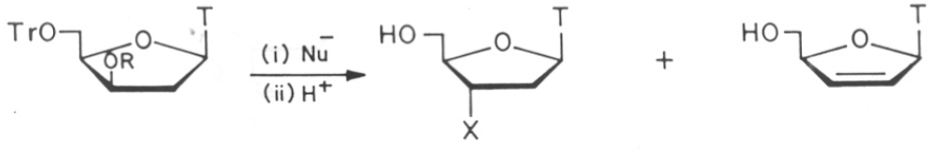
75 a–c
a : R' = H
b : R' = F
c : R' = I

76 a–c
a : R = H
b : R = F
c : R = I

at C-4 position using thionylchloride followed by methanolic ammonia treatment (**Scheme-1.30**). Compound **76a** was found to exhibit potent cytotoxic activity against both L1210 and S-180 cells *in vitro*. This also showed antitumor activity against L1210 tumor bearing mice. 5-Flouro- and 5-iodo- substituted-3'-amino-2'-deoxy-cytidines **76b and 76c** were obtained from the corresponding 5-substituted-3'-azido-2'-deoxy-cytidine under catalytic reduction.

Chemically reactive analogues of AZT **78a-d** and their biological evaluation against HIV have been reported[46] by Scheriber. The direct displacement reactions of 1-(5-O-trityl-3-O-trifulromethanesulphonyl-2-deoxy-*xylo*furanosyl)- thymine **77** with nucleophiles such as hydroxylamine, cyanide, thiocyanide and isothiocyanide were reported (**Scheme-1.31**). However all these nucleophilic displacement reactions produced compound **79** as the side product in varying yields.

Scheme - 1.31



77

R = SO_2CF_3

78 a-d

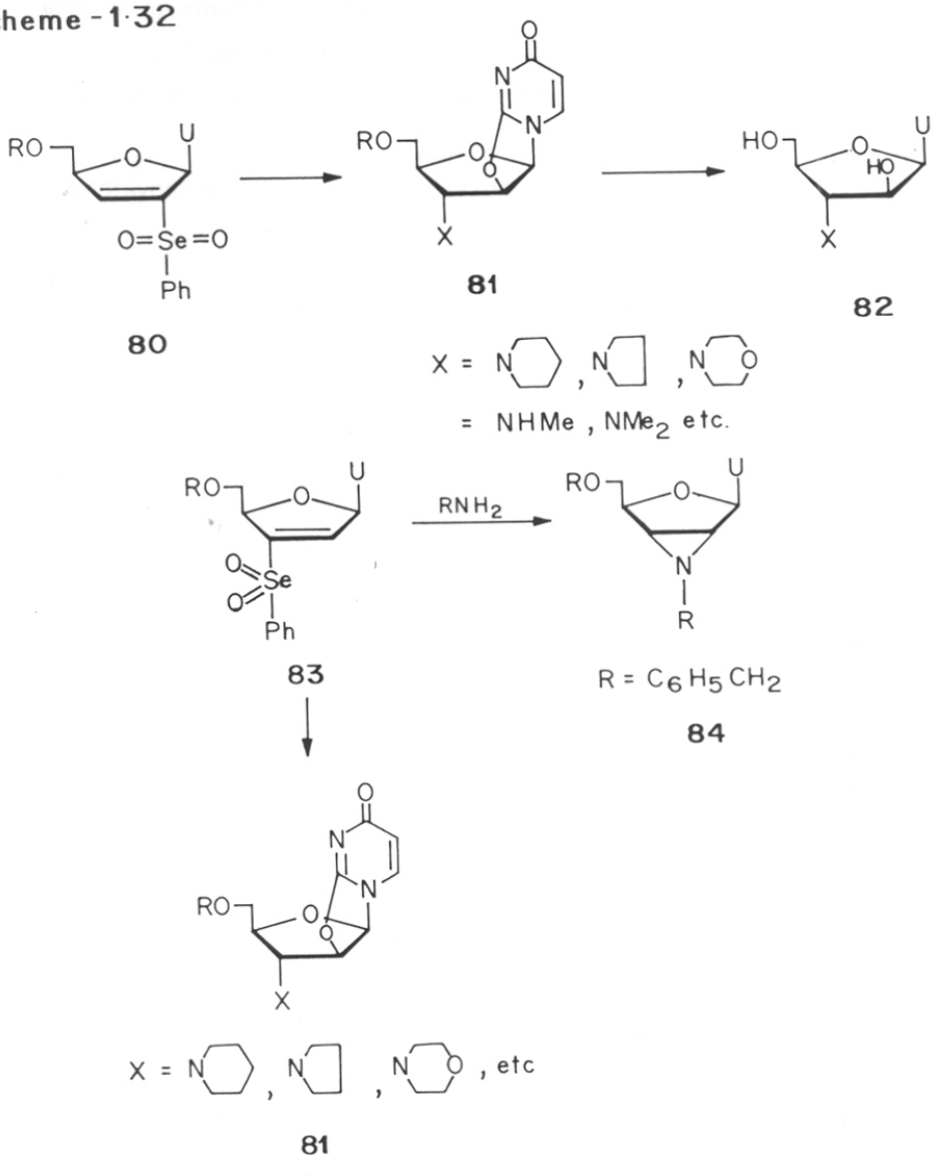
a : X = NHOH
b : X = CN
c : X = SCN
d : X = NCS

79

In 1989, Chattopadhyaya and coworkers reported[47] the Michael addition reactions of 1-(5-O-trityl-2',3'-dideoxy-2'- phenylselenonyl-β-D -*glycero*- pent-2-enofuranosyl)- uracil **80** with variety of amino- nucleophiles. As a result, various 3'-(dialkyl)amino-2,2'-O-anhydrouridines **81** and 3'-amino-3'-deoxy-*ara*-uridines **82** were synthesised. Nucleophilic attack at 3'-site of the nucleosides followed by intramolecular displacement of the phenylselenonyl group produced aziridinium derivative; in case of secondary amines this aziridinium ion intermediate was ultimately opened by C-2 oxygen to give 3'-amino-2,2'-O-anhydrouridine **81**. The same results were obtained[48] by reacting

2',3'-eno-furanosyl-2'-phenylselenonyluridine **83** with amines. It was also reported that the synthesis of 2',3'-dideoxy-2',3'-epiminouridines **84** could be achieved using this phenylselenone derivatives **83** (**Scheme-1.32**).

Scheme -1.32



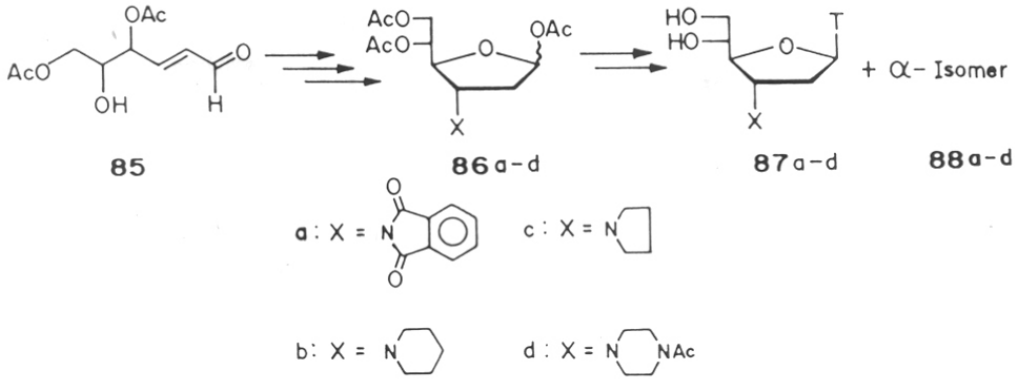
Pederson and coworkers reported[49] the convenient synthesis of 3'-amino-3'-deoxythymidine derivatives **87a** from carbohydrate derivative of α, β -unsaturated aldehyde **85.** Compound **85** on reaction with pthalimide in presence of DBU followed by acetylation afforded 3-pthalimido-5,1-O-diacetyl-2-deoxy-D-ribose **86**. Compound **86** was then coupled with thymine to produce anomeric mixture **87a** and **88a**. Anomers were separated and the pthalimido group was deprotected by treatment with methylamine in ethanol. Using the same methodology 3'-deoxy-3'-piperidino, pyrrolidino, N-acetylpiperazino- 2'-deoxythymidine derivatives **87b-d** were obtained[50] **(Scheme-1.33)**.

The efficient synthesis of 3'-amino-3'-deoxyadenosine **91** from adenosine has been reported[51] by Robins and coworkers. The 5'-O-*tert*-butyldiphenylsilyl- 2',3'-*lyxo*-O-anhydroadenosine **55** was opened by dimethylboron bromide. The resulting bromohydrine derivative was converted to N-benzylcarbamate **89** using benzylisocyanate; cyclisation of **89** afforded compound **90.** The deprotection of compound **90** produced 3'-amino-3'-deoxyadenosine **91** **(Scheme-1.34).**

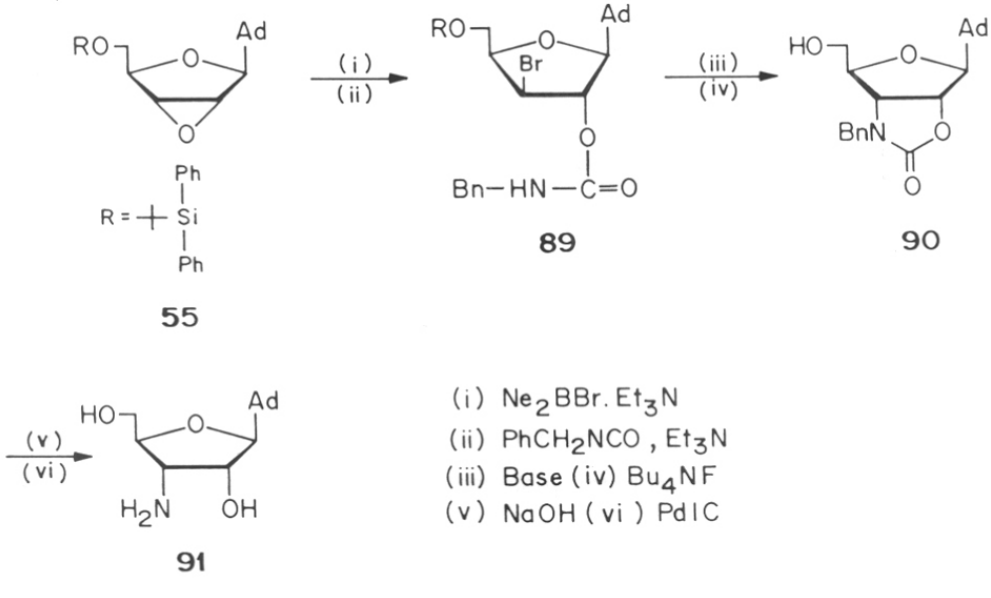
3'-N-(Pyrrol-1-yl)- and 3'-N-(1,2,4-triazolyl)-3'-deoxythymidine **92a** and **92b** were synthesised[52] by cyclisation of 3'-aminothymidine **2** with 2,5-dimethoxytetrahyrofuran and dimethylformamide azine hydrochloride respectively. In addition, various 2'-deoxy-2'-substituted and 3'-deoxy- 3'-substituted pyrrol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl thymidines were prepared. 2',3'-*Lyxo*-O-anhydrothymidine **93** was treated with sodium salt of pyrrol, imidazole and 1,2,4-triazole in DMSO. The resulting compounds **94a-c** and **95a-c** were deoxygenated to generate compounds **96a-c** and **97a-c** respectively in very poor yields **(Scheme-1.35)**. Among all these compounds, 3'-pyrrol-1-yl-3'-deoxythymidine **96a** showed marginal anti-HIV activity.

Synthesis of 3'-isocyano and 3'-isothiocyano-2',3'-dideoxyuridine have been reported[54]. The 5'-protected-3'-azidothymidine **1b** was converted to 3'-N-formamide using triphenylphosphine and aceticformicanhydride. Dehydration of 3'-N-formamide afforded 3'-isocyano-2'-deoxythymidine **98**. None of these compounds showed significant anti-HIV activity. In another development[55], 3'-isocyanothymidine **98** and 3'-isothiocyano-2'-deoxythymidine **78d** were obtained from 3'-amino-3'-deoxythymidine **2**. Compound **2** on treatment with carbondisulphide/DCC in pyridine produced compound **78d**.

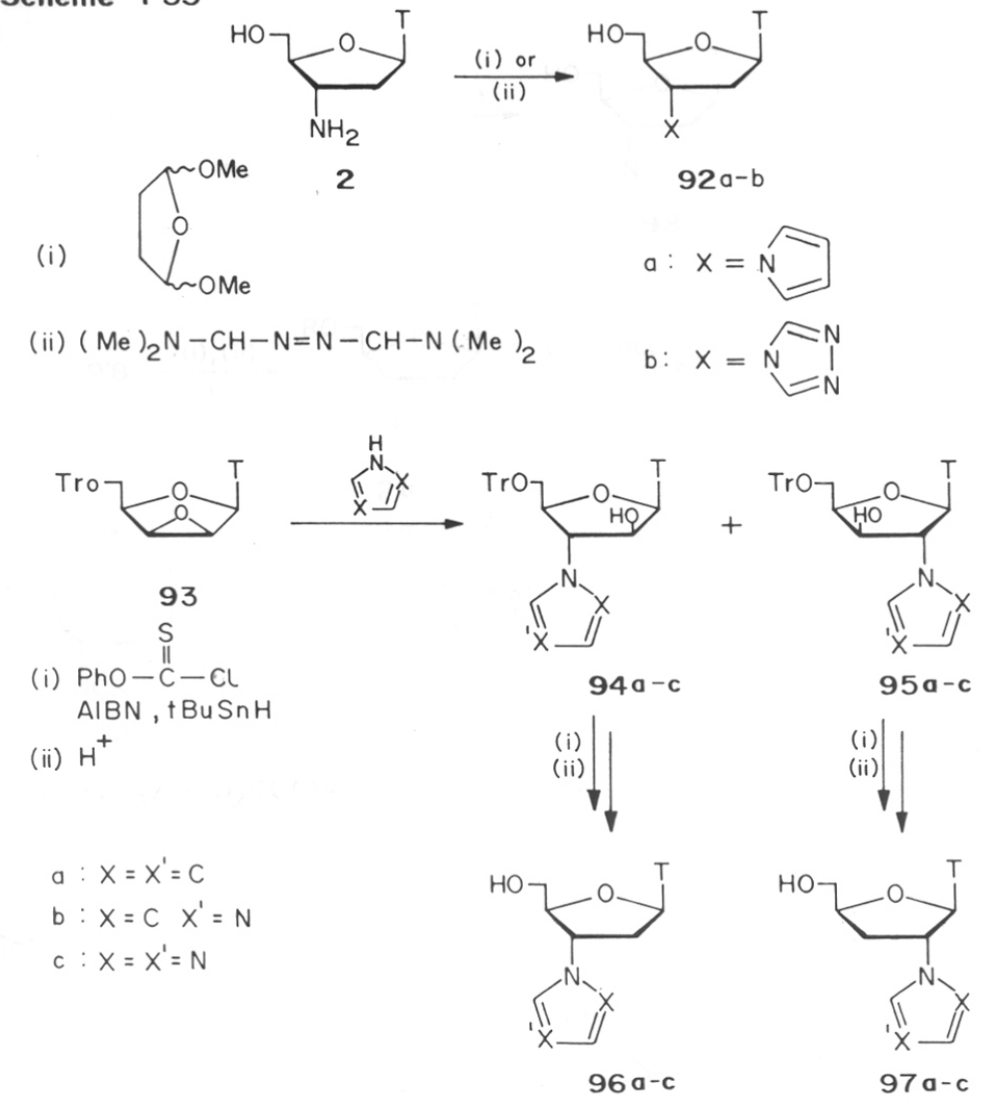
Scheme - 1·33



Scheme - 1·34

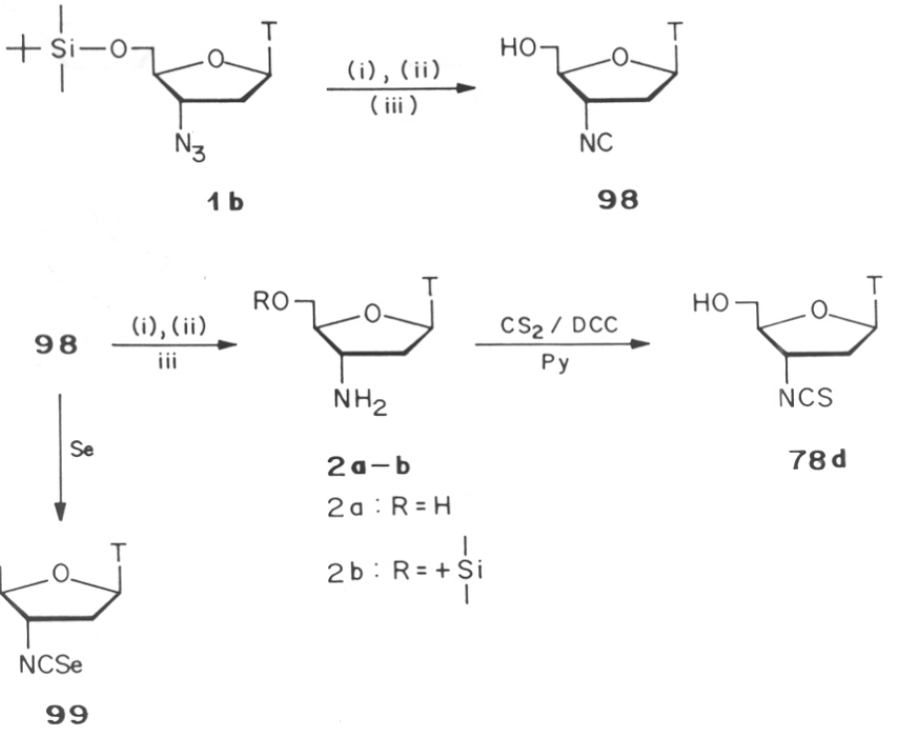


Scheme-1·35



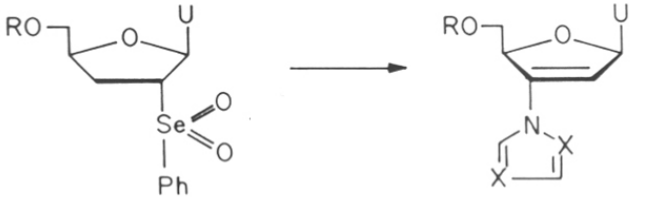
3'-Amino-3'-deoxythymidine **2** was treated with aceticformicanhydride/triphenylphosphine to give 3'-formamide derivative; it was then dehydrated to compound **98** using triethylamine. 3'-Isoseleno-3'-deoxythymidine **99** was also obtained by heating compound **98** with selenium metal in pyridine (**Scheme-1.36**). None of these compounds showed any significant anti-HIV

Scheme - 1·36



(i) PPh_3 / HCO_2COCH_3 (ii) $POCl_3$ $[(CH_3)_3CH]_2NH$

Scheme - 1·37



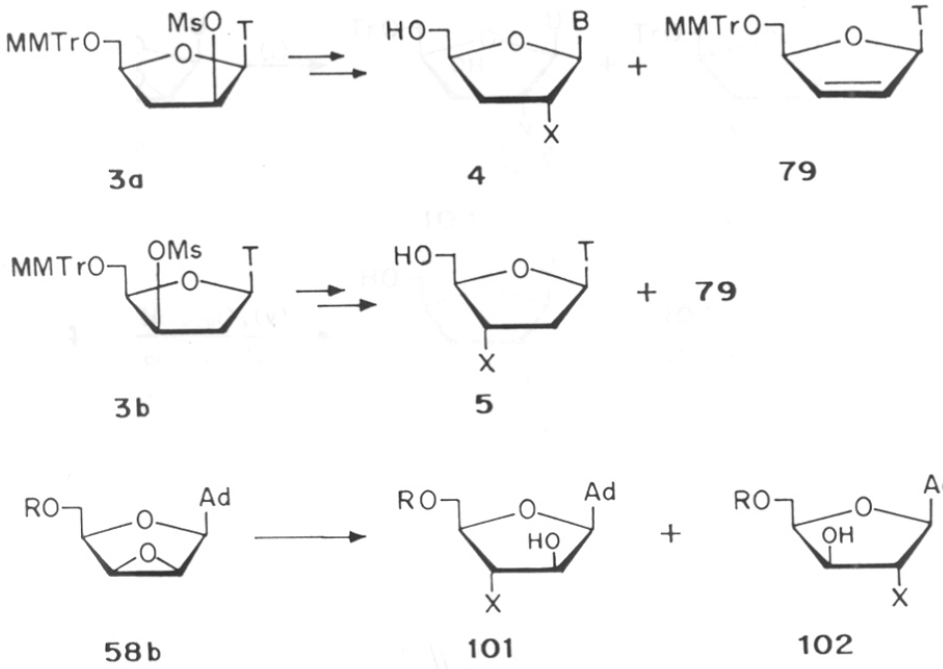
80

100 a–b

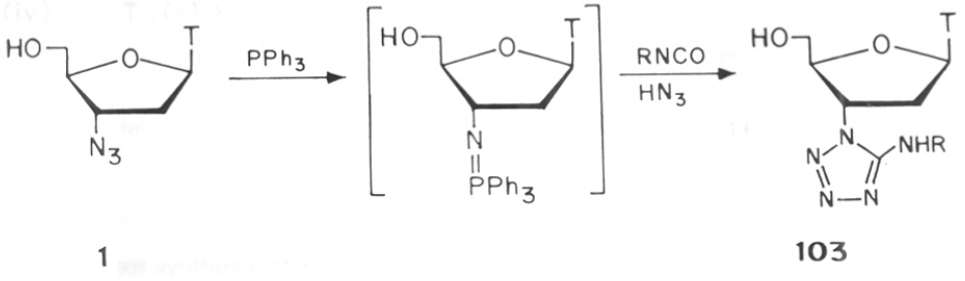
a : X = 'X = N

b : X = C 'X = N

Scheme-1·38



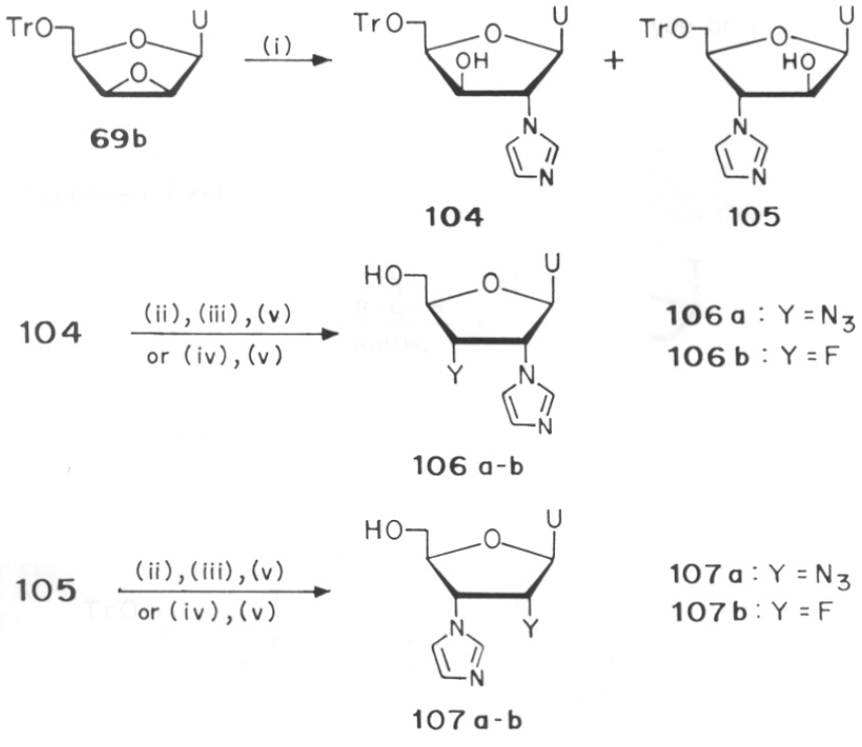
Scheme 1·39



activity. It was also reported[48] that 2',3'-dideoxy-3'-eno pentofuranosyl- 2'-phenylselenonyl-uridine **80** on reaction with triazole and imidazole produced 3'-triazolyl and 3'-imidazolyl-2',3'-dideoxy-2'-eno- pentofuranosyl-uridine **100a** and **100b** (**Scheme-1.37**).

5'-Protected-2',3'-O-*lyxo*-anhydro-adenosine **58b** was treated with various primary and secondary amines to yield 2'-amino- and 3'- aminonucleosides **101** and **102**. The direct

Scheme-1·40



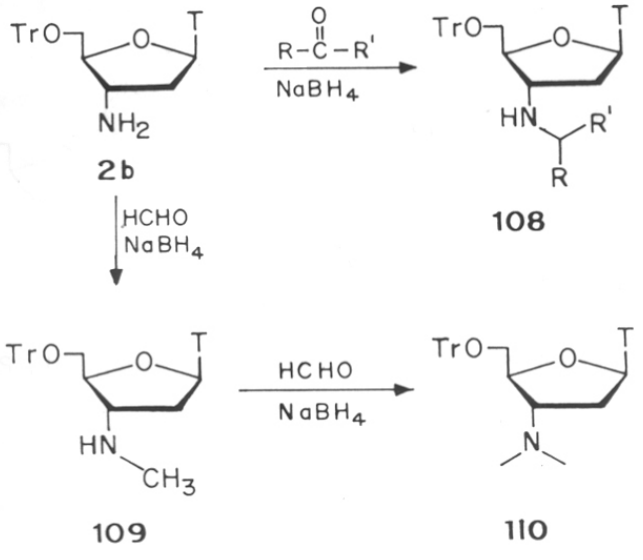
displacement reactions of compounds **3a** and **3b** with amines produced compounds **4** and **5** respectively[9] (**Scheme-1.38**).

The one pot synthesis of 3'-(5-amino-1,2,3,4- tetrazolyl-1-yl)-3-deoxythymidine **103** was reported[55]. 3'-Azido-3'-deoxythymidine **1** on treatment with PPh_3/THF and RNCO/HN_3 in toluene produced the carbodiimide intermediate which underwent cycloaddition reaction with hydrazoic acid to give compounds **103** (**Scheme-1.39**).

5'-O-Trityl-2',3'-O-anhydro-*lyxo*-uridine **69b** was opened by imidazole, pyrazole, and 1,2,4-triazole[56]. The resulting 2'-substituted-2'-deoxy-*xylo*- or 3'-substituted-3'-deoxy-*ara*-derivatives **104** and **105** were functionalised further to produce

2',3'-disubstituted-2',3'-dideoxy-uridines **106a-b** and **107a-b** (**Scheme-1.40**). 3'-Alkylamino-3'-deoxythymidines **108-110** were synthesised[57] by condencing 3'-amino-3'-deoxythymidine **9** with appropriate aldehyde or ketone followed by sodium borohydride reduction (**Scheme-1.41**).

Scheme - **1·41**

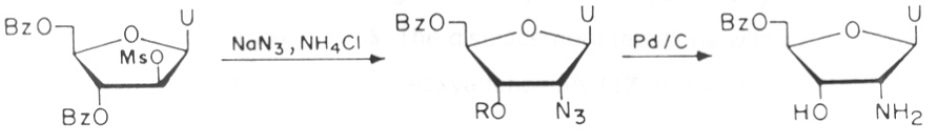


1.4. Synthesis and biological properties of 2'- deoxy-2'-aminonucleosides

2'-Deoxy-2'-aminonucleosides could be prepared[58] by the introduction of azide at the 2'-position followed by reduction. 1-(3,5-O-Dibenzoyl-2-O-mesyl-β-D-*ara*-furanosyl)- uracil **111** was treated with a mixture of sodium azide and ammonium chloride (3:2) at elevated temperature. Two products, 1-(2-azido-2-deoxy-3,5-O-dibenzoyl-β-D-*ribo*furanosyl)- uracil **112a** and 1-(2-azido-2-deoxy-5-O-benzoyl-β-D-*ribo*furanosyl)- uracil **112b** were isolated and catalytically reduced to the corresponding 2'-aminonucleoside **113** (**Scheme-1.42**).

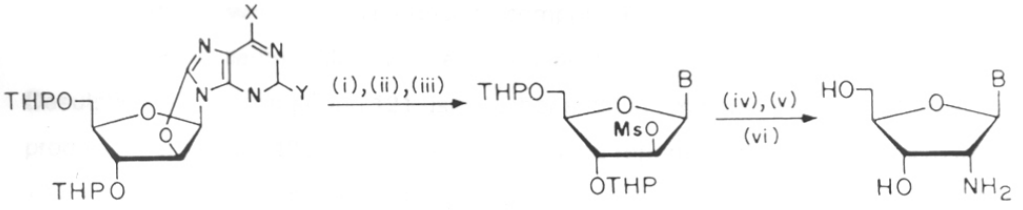
Ikehara and coworkers reported[59] the total synthesis of an antibiotic 2'-amino-2'-deoxyadenosine **117** and 2'-amino-2'-deoxyguanosine **118**. The 5',3'-tetrahyrofuran protected- 8,2'-O-anhydroadenosine **114a** and guanosine **114b** were

Scheme-1·42



111 — 112 a : R = Bz; 112 b : R = H — 113

Scheme-1·43



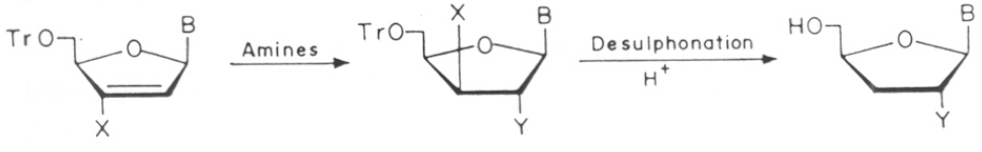
114a : X = NH_2 , Y = H
114 b : X = OH , Y = NH_2

115 : B = Adenine
116 : B = Guanine

117 : B = Adenine
118 : B = Guanine

(i) H_2S ; (ii) Raney Nickel ; (iii) Ms Cl / Py ; (iv) N_3^- ; (v) Pd/C ; (vi) H^+

Scheme-1·44



119 : X = Tol SO_2
B = U, Ad

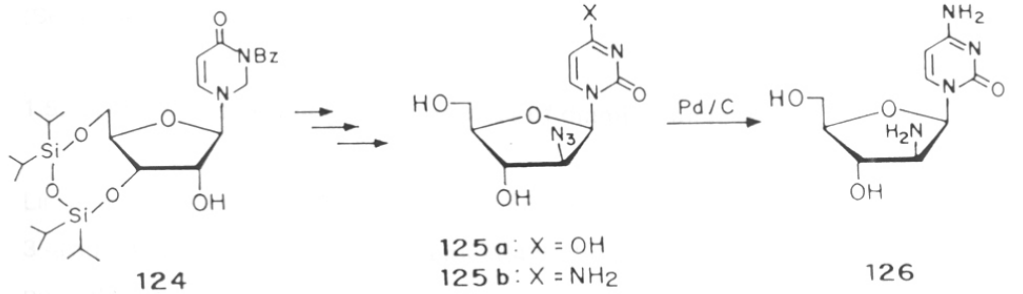
120 : X = CN , B = U

121 : X = Tol SO_2, B = U, Ad
Y = Various Amines

122 : X = CN , B = U
Y = Various Amines

123
Y = Various Amines

Scheme-1·45



124

125 a : X = OH
125 b : X = NH_2

126

reacted with hydrogen sulphide. The resulting 8-mercapto derivatives were dethiolated using Raney nickel and mesylated to generate 1-(3,5-tetrahydrofuranyl-2-O-mesyl-*ara*-furanosyl)-adenine **115** and guanine **116**. The displacement reactions with azide followed by catalytic reduction afforded 2'-amino-2'-deoxyadenosine **117** and 2'-amino-2'-deoxyguanosine **118** respectively (**Scheme-1.43**).

Chattopadhyaya and coworkers reported[60,61] the synthesis of 2'-alkylamino- and 2'-dialkylamino- nucleosides by using Michael addition reactions. Vinyl sulphone nucleoside **119** on treatment with amines produced[60] compounds **121**. Nucleophilic attack took place at the α-side of 2'-centre. Most of the amino nucleophiles gave exclusively trans adduct. Desulphonation of compound **121** using either sodium amalgum or magnesium in methanol produced compound **123** in poor yield. It was also reported[61] that 2',3'-ene-3'-nitrile-uridine **120** on reaction with amines produced 2',3'-dideoxy-2'-alkylamino-3'-nitrile-*xylo*-uridine **122** (**Scheme-1.44**).

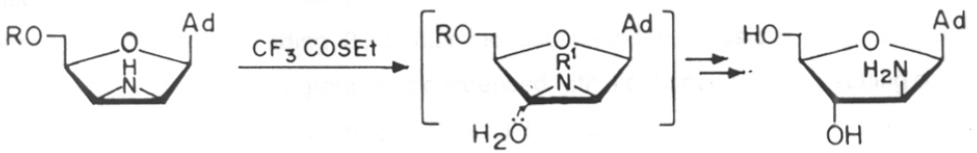
1-{3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)- β-D-*ribo*-furanosyl -3N-benzoyl)- uracil **124** was converted to its 2'-azido derivative **125a** by reacting with sodium azide under Mitsunobu conditions. Compound **125** was further converted to 1-(2-azido-2-deoxy-β-D-*ara*-furanosyl)-cytosine **125b**. The catalytic reduction of compound **125b** produced[62,63] the corresponding 1-(2-amino-2-deoxy-β-D-*ara*-furanosyl)-cytosine **126** (**Scheme-1.45**).

Robins and coworkers synthesised[64] 1-(2-amino-2-deoxy-β-D-*ara*-furanosyl)-adenine **129** by nucleophilic opening of 2',3'-aziridine-nucleosides **127** with excess of ethyltrifluoroacetate in warm DMF. Deprotection of ring opened product using 4N aqueous potassium hydroxide containing ethanol afforded 1-(2-amino-2-deoxy-β-D-*ara*-furanosyl)-adenine **129** (**Scheme-1.46**).

1.5. Synthesis and biological properties of diaminonucleosides

Lin and coworkers were the first to synthesise 5',3',-dideoxy-diaminothymidine **130** from 3'-azido-3'-deoxythymidine **1** (**Scheme-1.47**); the compound **130** showed neither antiviral nor antineoplastic activities[65].

Scheme - 1·46

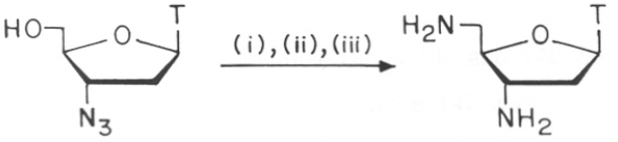


127 **128** **129**

R = $C_4H_9(C_6H_5)_2Si$

$R^1 = CF_3CO$

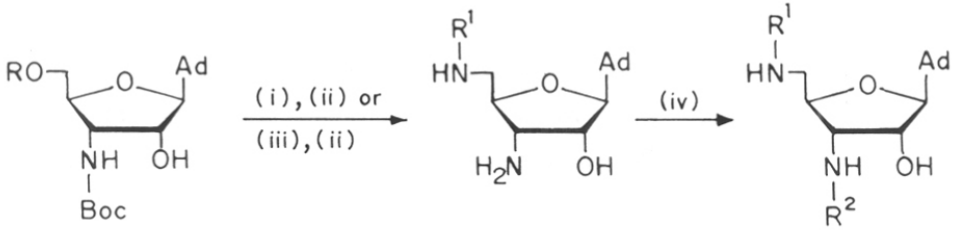
Scheme - 1·47



1 **130**

(i) TsCl / Py (ii) LiN_3 (iii) Pd / C

Scheme - **1·48**



131: R = H

132: R = Ts

133: R^1 = H

134: $R^1 = PhCH_2$

135: $R^1 = (CH_2)_7CH_3$

136: $R^1 = R^2 = PhCH_2$

(i) NH_3 / Dowex H^+/NH_3 ,(ii) CF_3COOH , (iii) R^1NH_2

(iv) C_6H_5CHO / $NaBH_4$

Synthesis of 3',5'-dialkylamino-3',5'-dideoxyadenosine **136** was reported[66]. The protected 3'-amino derivative **131** was converted to its 5'-tosylate nucleoside **132**. The direct displacement reaction of compound **132** with ammonia, benzylamine and n-octylamine produced the corresponding 3', 5'-diamino substituted nucleosides **133**, **134** and **135** respectively. The 5'-amino group was condenced with aldehyde and the resulting schiff base was reduced to give corresponding 3',5'-dialkyamino-3',5'-dideoxyadenosine **136** (**Scheme-1.48**).

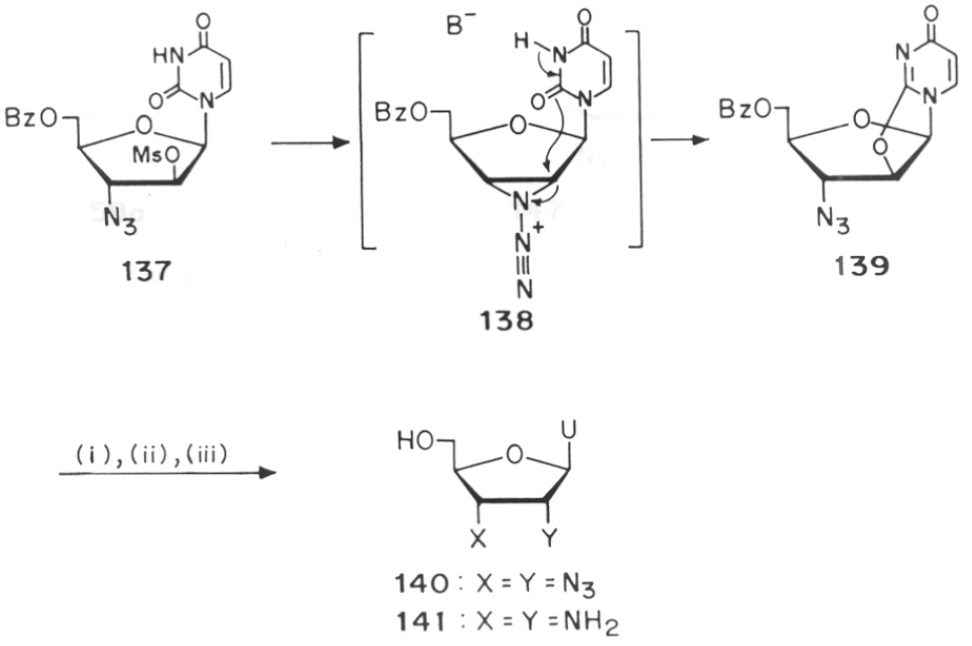
Sasaki and coworkers synthesised[67] 2',3'-dideoxy- 2',3'-diaminouridine **141** by reducing 2',3'-dideoxy-2',3'-diazidouridine **140** catalytically. Compound **137** was converted to 3'-azido-2,2'-O-anhydrouridine **139** through azidonium intermediate **138**. Compound **139** on treatment with sodium azide produced diazido- derivative **140** (**Scheme-1.49**).

3',5'-Dideoxy-3',5'-diamino-*ribo*-nucleosides **145** and **146** were synthesised[68] from xylose. 1,2-O-Isopropylidine-3,5-di-O-mesyl-D-xylose **142** was converted to its diazide derivative **143**. Compound **143** on treatment with acetic acid and acetic anhydride produced compound **144.** Compound **144** was coupled with nucleoside bases, thymine and uracil. The resulting diazidonucleosides were reduced to 3',5'-diamino-3',5'-dideoxynucleosides by using triphenylphosphine/ammonia/pyridine (**Scheme-1.50**).

Robins and coworkers[69] reported the synthesis of 2',3'-diamino-2',3'-dideoxyadenosine **148**. The 5'-O-silyl protected-*ara*-adenosine was converted to its 2',3'-O-anhydro-*lyxo*-adenosine **58a** using Mitsunobu reaction. This *lyxo*-epoxide was opened with azide and the resulting azido-alcohol was converted to its 2'-triflate derivative **147**. Further displacement reaction with azide produced 2',3'-diazido-nucleoside which was then reduced to 2',3'-diamino-2',3'-dideoxy-adenosine **148** catalytically (**Scheme-1.51**).

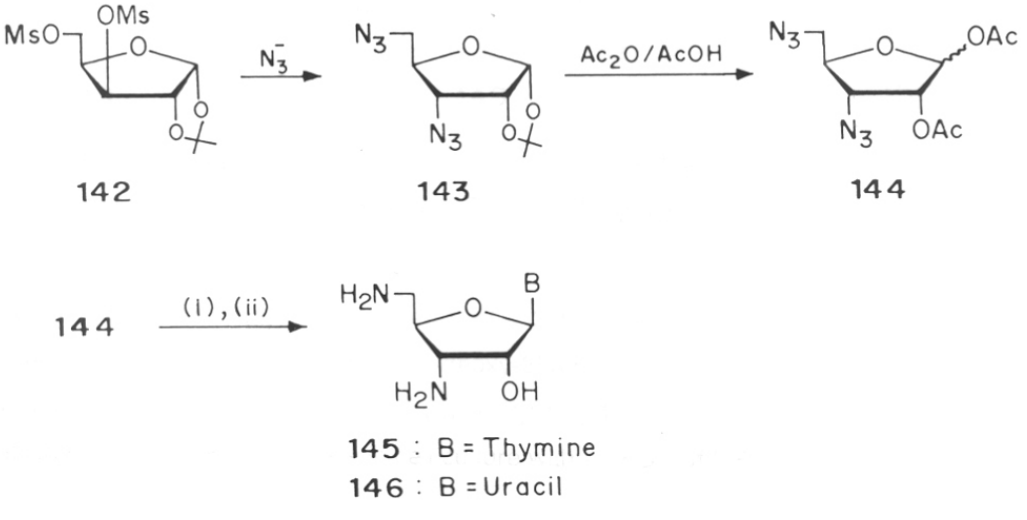
In 1992, Jandal and coworkers synthesised[70] water soluble ribonucleoside technetium chelate **150** and found it to inhibit ribonuclease U2. The synthesis of technetium complex involved four steps from 2',3'-dideoxy-2',3'-diamino-adenosine **148**. Compound **148** was converted to compound **149** which was metalated to **150** (**Scheme-1.52**).

Scheme - 1·49



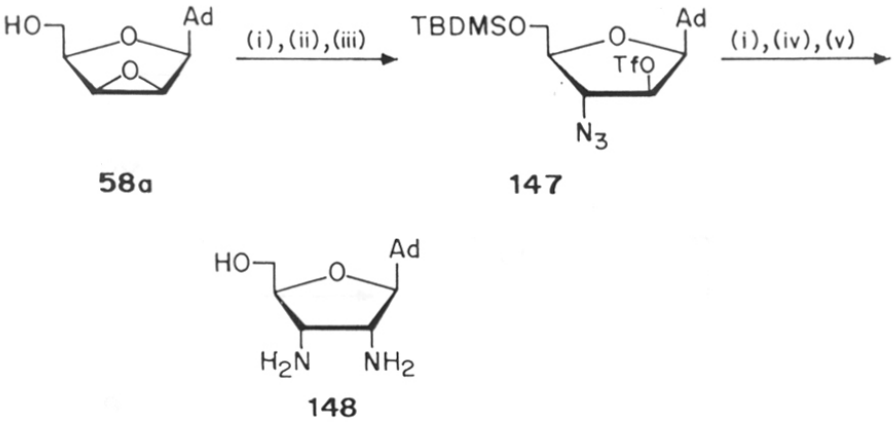
(i) LiN_3 (ii) Ammonia (iii) Pd/C

Scheme - 1·50



(i) Silylated Base / $SnCl_4$ / CH_3CN (ii) PPh_3 / Py / NH_3

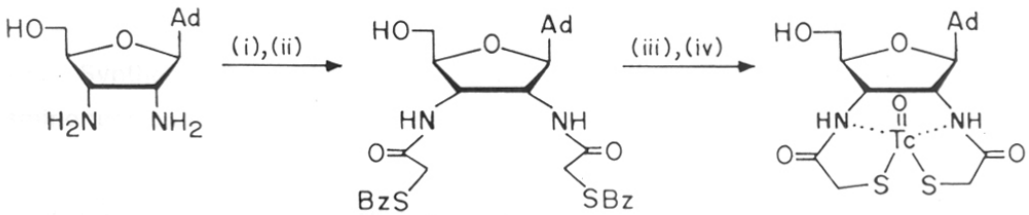
Scheme-1·51



58a 147 148

(i) LiN_3 (ii) TBDMSCl / imidazole (iii) CF_3SO_2Cl / DMAP (iv) $Bu_4N^+F^-$ (v) Pd/C

Scheme-1·52

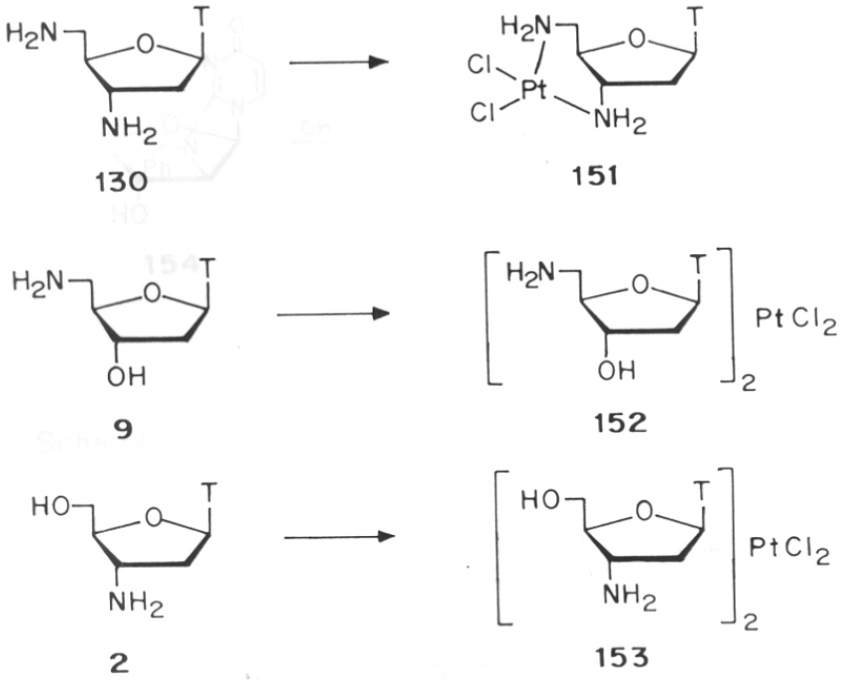


148 149 150

(i) 2 equ. $(ClCH_2CO)_2O$, CH_3CN, DMF (ii) $C_6H_5COS^-Na^+$, EtOH (iii) EtOH, NaOH (iv) 0·95 equ. Tc(VII), $Na_2S_2O_8$

Several platinum (II) complexes of 3',5'-dideoxy-3',5'-diaminothymidine **151**, 5'-deoxy-5'-aminothymidine **152** and 3'-deoxy-3'-aminothymidine **153** have been reported[71] (**Scheme-1.53**). (3'-Deoxy-3'-aminothymidine)$_2PtCl_2$ **153** proved to be a potent inhibitor of replication of murine L1210 cells in cell culture with an ED_{50} of 0.8μM.

Scheme-1·53

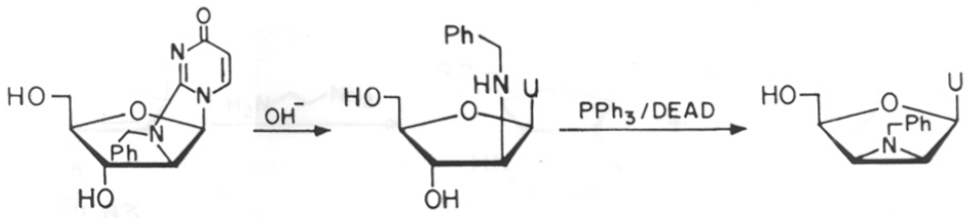


1.6. Synthesis and biological properties of 2',3'-dideoxy-2',3'-fused-cylic-aminonucleosides.

Minamoto and coworkers reported[72] the first synthesis of 2',3'-*lyxo*-epimino-2',3'-dideoxypyrimidine nucleoside **156**. 2'-Deoxy-2'-benzylamino-*ara*-uridine **155** was cyclised intramolecularly under Mitsunobu conditions to give 2',3'-dideoxy-2',3'-*lyxo*- epiminobenzyl-uridine **156**. Compound **155** was obtained by hydrolysing the 2,2'-N-benzylimino-*ara*-uridine **154** under basic conditions (**Scheme-1.54**).

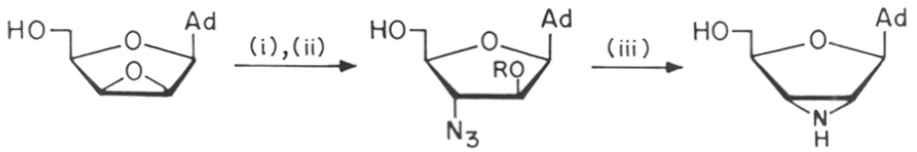
Synthesis of 2',3'-epiminopurine nucleosides was also reported[73]. Treatment of 9-(2,3-O-anhydro-β-D-*lyxo*-furanosyl)- adenine **58a** with sodium azide in hot DMF gave 9-(3-azido-3-deoxy-β-D-*ara*-furanosyl)- adenine **157a**. Selective protection of 5'-hydroxyl group using pivaloyl or tritylchloride and mesylation of 2'-hydroxyl produced compound **157b**. Compound **157b** was intramolecularly cyclised using hydrazine hydrate to give

Scheme-1·54



154 **155** **156**

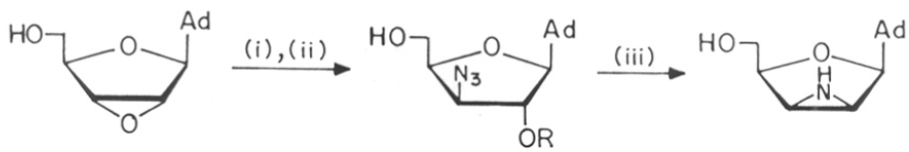
Scheme-1·55



58a **157a**: R = H
157b: R = Ts
158

(i) LiN_3 / DMF (ii) TsCl / Py (iii) H_2NNH_2 , Raney Nickel

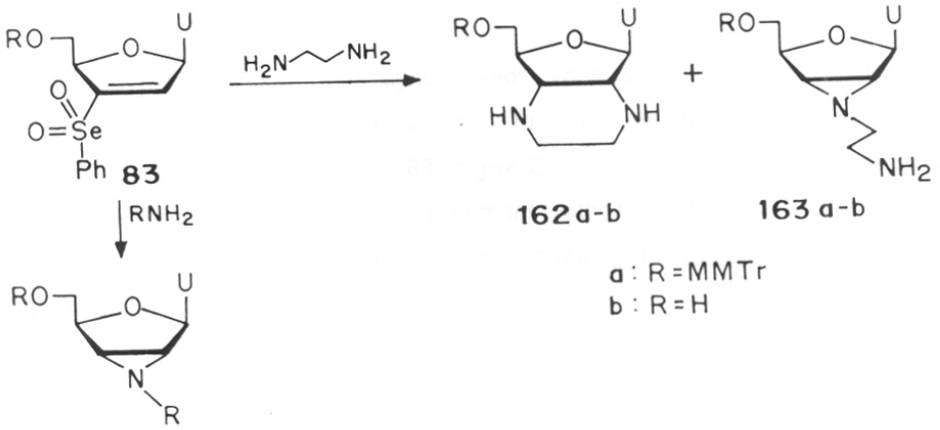
Scheme-1·56



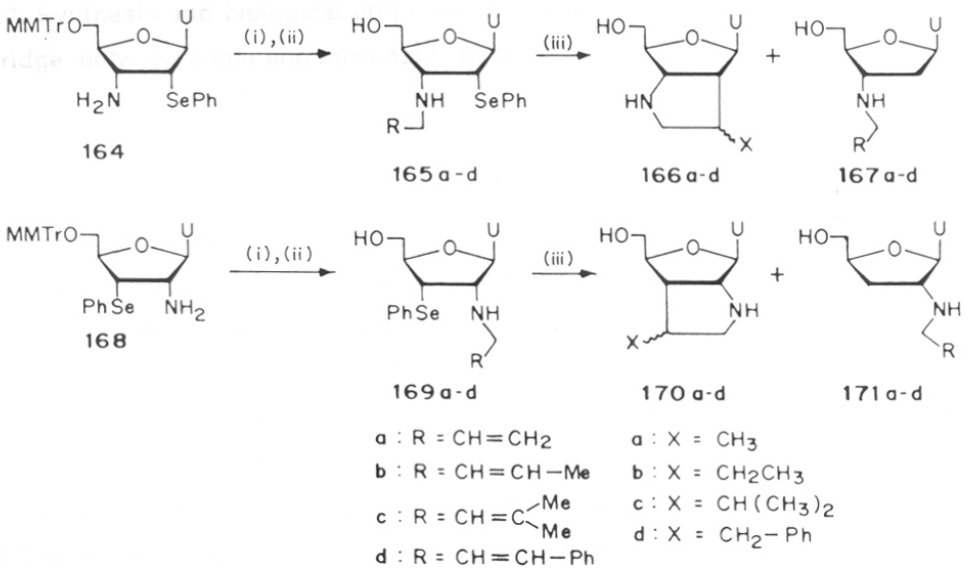
55a **159a**: R = H
159b: R = Ts
160

(i) LiN_3 / DMF (ii) TsCl / Py (iii) H_2NNH_2 , Raney Nickel

Scheme-1·57



Scheme-1·58



(i) RCHO 4Å molecular sives (ii) $NaCNBH_3$ 80% AcOH
(iii) nBu_3SnH, AIBN (Cat.)

9-(2,3-epimino-β-D-*ribo*-furanosyl)- adenine **158** (**Scheme-1.55**). The 9-(2,3-epimino-β-D-*lyxo*-furanosyl)- adenine **160** was prepared from 9-(2,3-O-anhydro-β-D-*ribo*-furanosyl)- adenine **55a** through compound **159** (**Scheme-1.56**).

Chattopadhyaya and coworkers synthesised[74] various 2',3'-epimino nucleosides using 2',3'-ene-3'-phenylselenone derivatives. Primary amines were reacted with 2',3'-ene-3'-phenylselenonyl-uridine **83** to give 2',3'-aziridinium nucleosides **161a-b.** Some diamines like, ethylenediamine on treatment with this phenylselenone **83** produced 2',3'-dideoxy-2',3'-N,N-ethylenediaminouridine **162a-b** and the epiminoderivative **163a-b** (**Scheme-1.57**).

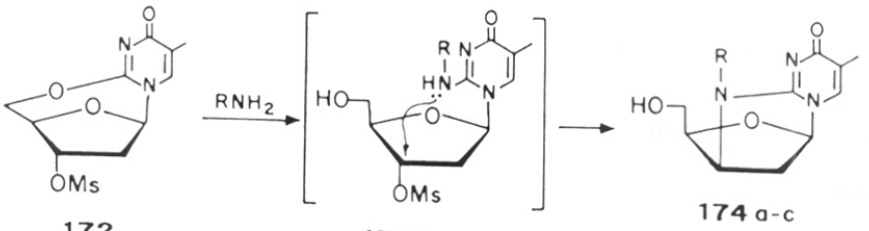
Synthesis of 2',3'-dideoxy-2',3'-*cis*-fused-pyrrolidino- β-D-*ribo*-furanosyl)- nucleosides **166a-d** and **170a-d** have also been described in literature[75]. This synthesis was achieved from 2'-alkyamino-3'-phenyselenyl **165a-d** and 3'-alkylamino-2'- phenylselenyl- uridine **169a-d** using free radical cyclisation. However this free radical cyclisation also afforded simple 3' and 2' -deoxygenated products **167a-d** and **171a-d** in minor amount (**Scheme-1.58**).

1.7. Synthesis and biological properties of nucleosides containing nitrogen (imino) bridge between sugar and nucleoside base.

Fox and coworkers reported[76] the first synthesis of 2,3'-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine **174a-c**. 2,5'-O-Anhydro-3'-O-mesylthymidine **172** was treated with liquid ammonia, methylamine and hydrazine to give the corresponding 2,3'-imino-1-(2-deoxy-β-D-*threo*- pentofuranosyl)- thymines **174a-c**. This reaction proceeded *via* isocytidine intermediates **173a-c** (**Scheme-1.59**).

8-Bromo-2'-O-triisopropylbenzenesulphonyladenosine **175** on treatment with ammonia or methylamine produced[77] the corresponding 8-aminosubstituted-2'-O-triisopropylbenzenesulphonyl- adenosine **176**; compound **176** was cyclised to afford 8,2'-imino- or methylimino-adenosine **177a-b** (**Scheme-1.60**). It was also reported that the 5'-O-benzoyl-3'-O- mesyl-2,2'-O-anhydro-uridine **178** on treatment[78] with ammonium azide generated *in situ*, produced 2,3'-imino-5'- O-benzoyl- β-D-*lyxo*-uridine **179** (**Scheme-1.61**).

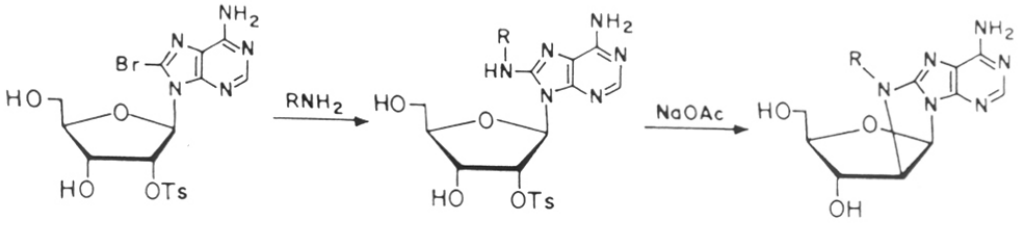
Scheme - 1·59



172 173 a-c 174 a-c

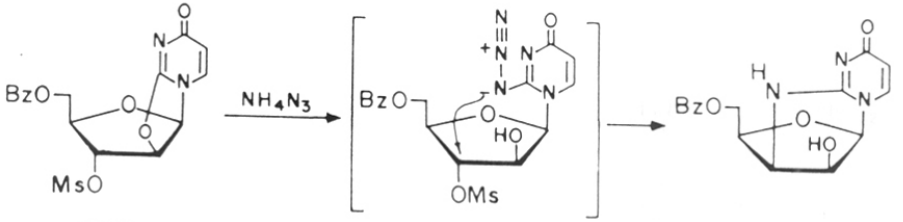
a : R = CH_3 ; b : R = H ; c : R = NH_2

Scheme - 1·60



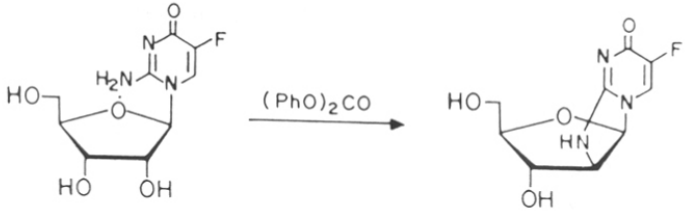
175 176 177a : R = H
177b : R = CH_3

Scheme - 1·61



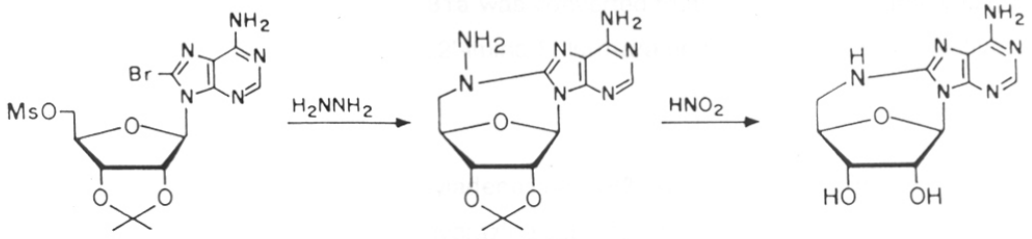
178 179

Scheme - 1·62



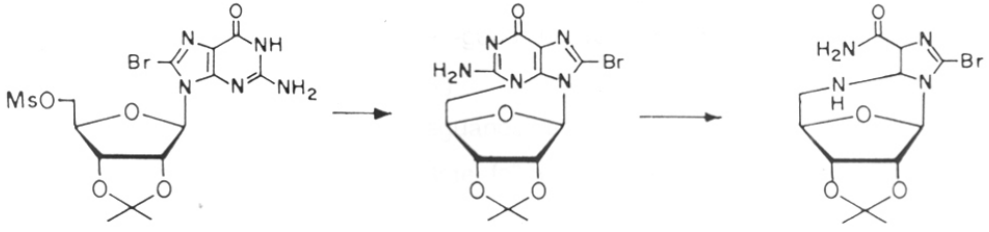
180 181

Scheme-1·63

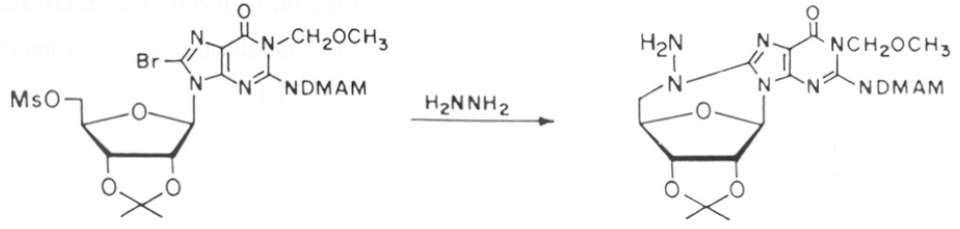


182 183 184

Scheme-1·64

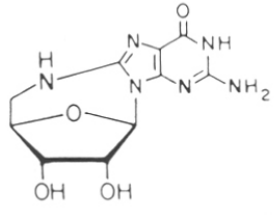


185 186 187



188 189

DMAM = Dimethylamino methylidino



190

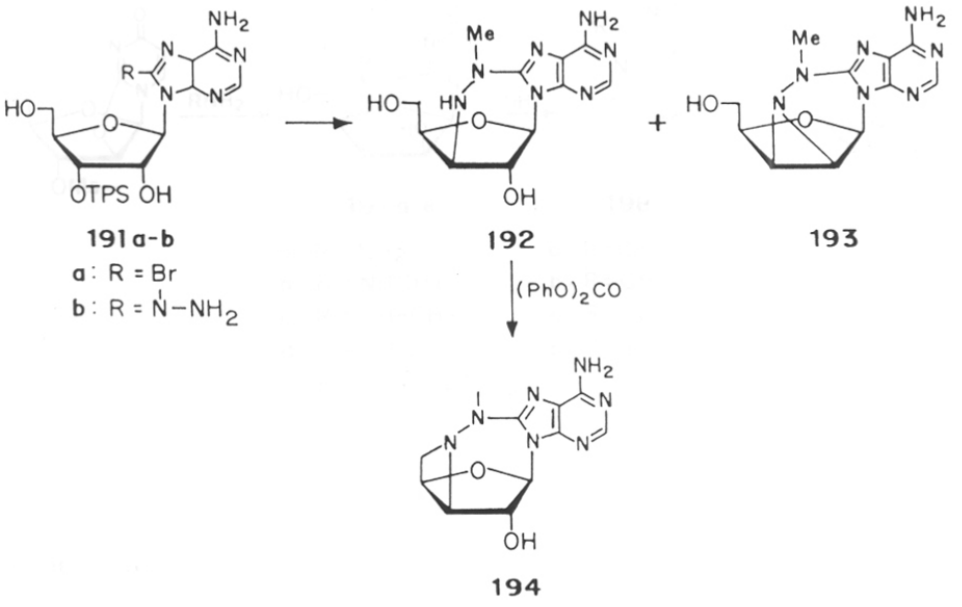
5-Fluro-*iso*cytidine **180** was cyclised intramolecularly using diphenylcarbonate and the resulting 2,2'-imino-5-fluro-*ara*-uridine **181a** was converted to its 2,2'-imino-5-fluro-cytidine **181b** (**Scheme-1.62**). None of these 2,2'-imino-5-fluro-*ara*-uridine or cytidine derivatives showed any antitumor activity[79].

8-Bromo-2',3'-O-isopropylidine-5-O-mesyladenosine **182** was reacted with anhydrous hydrazine in ethanol and the resulting 8-hydrazine substituted compound cyclised to give the corresponding 8,5'-aminoimino-adenosine **183** derivative. Interestingly, compound **183** was converted to 8,5'-iminoinosine **184** by treatment with nitrous acid[80] (**Scheme-1.63**). The same reactions in case of guanosine derivative **185**, produced 3-N,5'-cyclised product **186** and 5-N,5'-cylonucleoside of 4-carboxyhydrazido-5-amino-2-bromo-imidazole **187**. To exclude this 3-N,5'-cyclisation, 2-N-dimethylaminomethylidine- 1N-methoxymethylene, 8-bromo-2',3'-O-isopropylidine-5-O-mesyl-gunosine **188** was prepared[81] and treated with hydrazine under forcing conditions to produce 8,5'-aminoimino-N1-methoxymethylidineguanosine **189**. Compound **189** was oxidised with sodium metaperiodate and sodium nitrite followed by acidic deprotection to generate 8,5'-imino-1N-methoxymethylidine- guanosine **190** (**Scheme-1.64**).

8-Bromo-3'-O-(2,4,6-triisopropylphenylsulphonyl)- adenosine **191a** on treatment with methylhydrazine produced 8,3'-N(α-methylhydrazo)-9- [3'-deoxy-β-D-*xylo*-furanosyl]-purines **191b** and 9-[2',3'-[(methylamino)epimino]-2',3'-dideoxy-β-D-*lyxo*-furanosyl]-adenine- 8,N-cyclonucleoside **193**[82]. The compound **191b** on further treatment with diphenylcarbonate produced 9-[3',5'-[(N-methylamino) azetidino]-3',5'-dideoxy- β-D-*xylo*-furanosyl]- adenine-8,N-cyclonucleoside **194** (**Scheme-1.65**). The 2',3'-O-isopropylidine derivatives of 8-methylamino or benzylamino purines **195** on reaction with excess of diphenyl carbonate produced 8,5'-substituted iminocyclonucleosides derivatives **196**. The same conversion was also carried[83] out by using different reagents like, N,N'-carbonylimidazole and triphenylphosphine/diethylazodicarboxlate (**Scheme-1.66**).

Minamoto and coworkers reported the synthesis[84] and basic hydrolysis[85] of various N-substituted derivatives of 2,3'-imino-1-(3-deoxy-β-D-*lyxo*- furanosyl]- uracil **197a-e**. 2,2'-O-Anhydro-1-(5-O-benzoyl-3-O- mesyl-β-D-*ara*-furanosyl]- uracil on treatment with excess of amines in presence of acetic acid in DMF produced **197a-e**. The alkaline hydrolysis

Scheme-1·65



191a-b

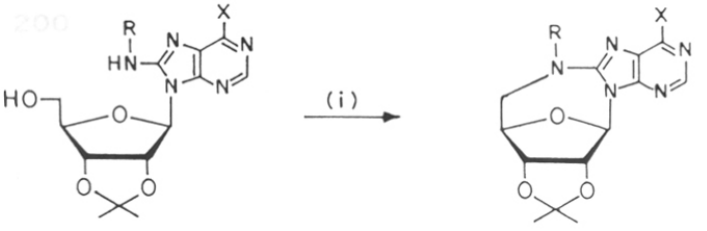
a: R = Br

b: R = $\overset{|}{N}-NH_2$

192 **193**

194

Scheme-1·66



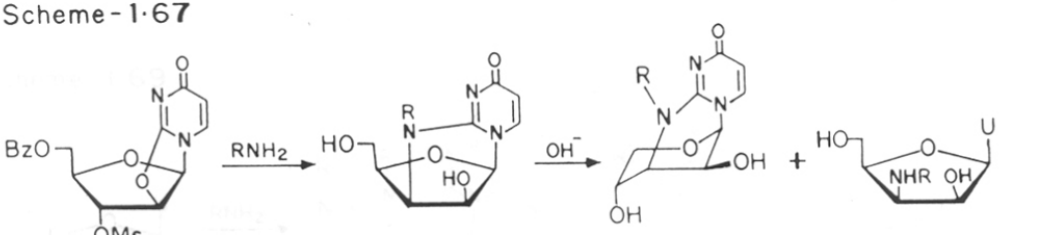
195 **196**

R : Me, $PhCH_2$

X : OH, NH_2

(i) $(PhO)_2CO$ or PPh_3 / DEAD

Scheme-1·67



197a-e

a : R = NH_2
b : R = $NHCH_3$
c : R = CH_2CH_3
d : R = C_6H_5
e : R = (p-OCH_3)C_6H_4

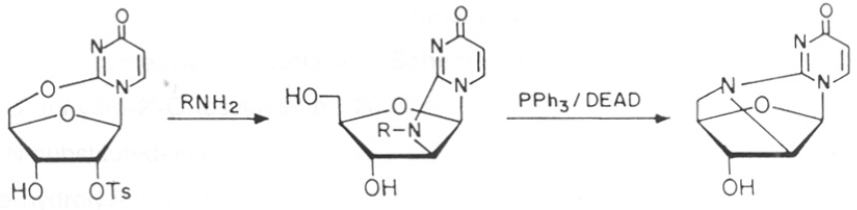
198a-d

a : R = CH_3NH
b : R = CH_2CH_3
c : R = C_6H_5
b : R = (p-OCH_3)C_6H_4

199a-b

a : R = Ph
b : R = (p-OCH_3)C_6H_4

Scheme-1·68

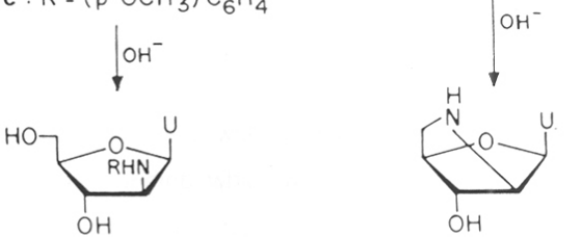


200

201a-c

a : R = H
b : R = Ph
c : R = (p-OCH_3)C_6H_4

202

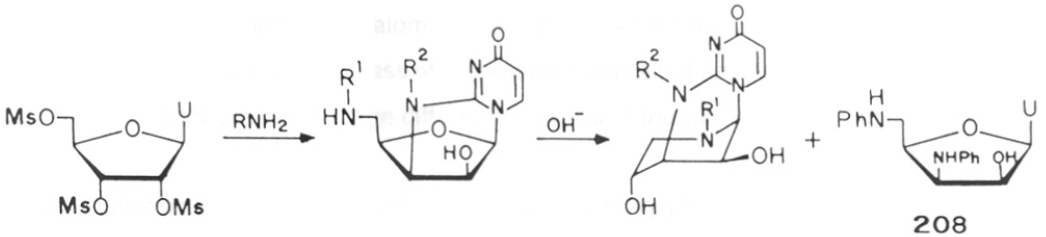


203b-c

b : R = C_6H_5
c : R = (p-OCH_3)C_6H_4

204

Scheme-1·69



205 206 a-c 207 a-c 208

a : $R^1 = R^2 = Me$
b : $R^1 = H$, $R^2 = Me$
c : $R^1 = R^2 = Ph$

of compounds **197a-e** with 6N sodium hydroxide and ethanol (1:1) produced the corresponding 2,3'-imino-bridged *lyxo*pyranosyl isomers **198a-d** as well as 3'-"up" arylamino furanosyl nucleosides **199a-b** (**Scheme-1.67**). It was also reported[86] that 2,5'-O-anhydro-2'-O-tosyluridine **200** on treatment with various amines afforded 2,2'-N-substituted- imino-1-(2'-deoxy-β-D-*ara*-furanosyl)- uracil **201a-c**. Compounds **201b-c** were hydrolysed under basic conditions to give 2'-deoxy-2'-arylamino-*ara*-uridine **203b-c**. 2,2'-Imino-1-(2-deoxy-β-D-*ara*-furanosyl)- uracil **201a** on the other hand, was converted[87] to tricyclic analogue of 5'-N-anhydro-2,2'- imino-1-(2,5-dideoxy-β-D-ara-furanosyl)- uracil **202** under Mitsunobu conditions (**Scheme-1.68**). Compound **202** was hydrolysed[87] under basic conditions to give 1-(2,5-N-anhydro-5-amino- 2,5-dideoxy-β- D-*ara*-furanosyl)- uracil **204**.

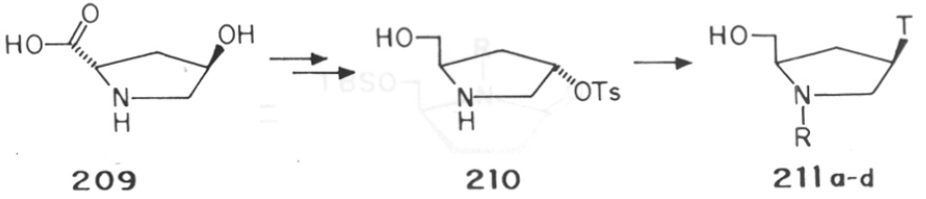
2',3',5'-O-Trimesyluridine **205** on treatment with various primary amines produced[88] 5'-O-mesyl-2,3'-iminosubstituted-*lyxo*- uridine which was further functionalised by amine to give compounds **206a-c**. Under basic conditions, 2,3'-alkylimino derivatives **206a-b** were hydrolysed to give 2,3'-iminobridged- piperidino-pyranosyl-nucleosides **207a-b** while, 2,3'-arylimino or anilino derivatives **206c** gave C-2 fission product of 3',5'-dianilino-3',5'-dideoxy-*lyxo*-uridine **208** as well as 2,3'-N-anilino- piperidinopyranosyl- nucleoside derivative **207c** (**Scheme-1.69**).

1.8. Synthesis and biological properties of nucleosides with nitrogen in the pentose ring (*aza*-nucleosides)

Incorporation of nitrogen atom into the furanose ring provided various 2',3'-dideoxynucleosides. This class of nucleosides are called *aza*-nucleosides. The nitrogen atom has been introduced in three different positions of the pentose ring so far.

3'-*Aza*-nucleosides were prepared[89] from trans-4-hydroxy proline **209**. Compound **209** was converted to the prolinol **210** with the inversion of both chiral centers. Coupling reaction with nucleosides bases produced 3'-aza nucleoside **211a**. The further modification was also carried at 3'-nitrogen position to obtain a series of AZT related *aza*-nucleosides **211b-d** (**Scheme-1.70**). The corresponding purine nucleosides were also reported[90,91] in the literature.

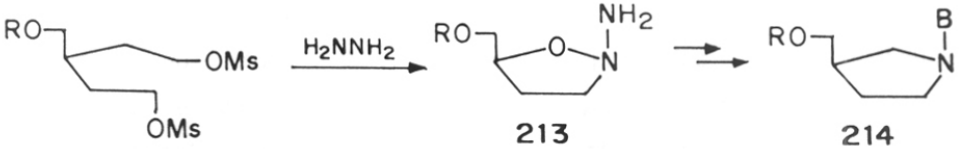
Scheme-1·70



Another group of modified *aza*-nucleosides involved linkage of the pyrrolidine ring to the nucleoside base *via*, the nitrogen atom. This kind of nucleosides were synthesised[92,93] from 1-amino-pyrrolidine **213**. The desired starting material **213** was obtained by reacting corresponding dimesylate **212** with hydrazine. The nucleoside base thymine, uracil, and cytosine were built on the 1-aminogroup to give *aza*-nucleosides **214** (**Scheme-1.71**).

In another development[94-95], the nitrogen atom was substituted for the oxygen atom of the dideoxyribose moiety. Synthesis of 4'-*aza*-uridine **216** from N-Boc-protected(S)-

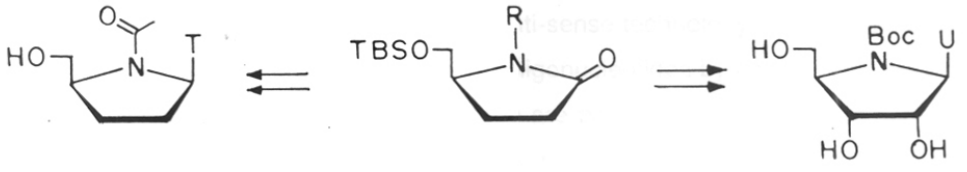
Scheme-1·71



212 213 214

B= T, U, C

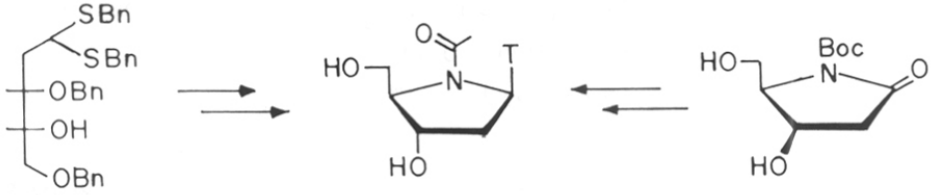
Scheme-1·72



217 215 a-b 216

a : R = BoC
b R = $COCH_3$

Scheme-1·73



218 219 220

5-hydroxymethyl-2-pyrrolidione **215a** was reported[94]. N-Acetyl-4'-aza-2',3'-dideoxythymidine **217** was also obtained[95] from N-acetyl- (S)-5-O-*t*butyldimethylsilyl-hydroxymethyl-2-pyrrolidione **215b** (**Scheme-1.72**).

In order to study the biophysical properties of 4'-*aza*-nucleosides, 4'-N-acetyl-2'-deoxy-*aza*thymidine **219** was synthesised[96], and incorporated into oligonucleotides[97]. The thirteen step synthesis of 4'-N-acetyl-*aza*thymidine **219** from deoxyribose derivative **218** was reported by Huang and coworkers[96]. Compound **219** was also synthesised[97] from prolinol derivative **220** (**Scheme-1.73**). Incorporation of *aza*-thymidine **219** in to oligonucleotides caused destabilisation of the DNA/RNA duplex as compared to unmodified duplex.

1.9. Synthesis and biological properties of dinucleotides or oligonucleotides containing nonphosphate nitrogen backbone (Fig-1.1)

Recently, in the rapidly developing area of anti-sense technology, several research groups have replaced the phosphate backbones of oligonucleotides by amino, amido, sulphamido, urea etc. linkages where the nitrogen atoms are part of the carbohydrate moieties of the nucleosides. Some of these oligonucleotides were more resistant towards nucleases and had shown comparable or higher melting temperatures (T_m).

Mesmaeker and coworkers reported[98-103] eight anionic and achiral, amide linkage between dinucleotides **L.1-L.8 (Fig-1.1)**. Among them linkage **L.3** was the best as it showed favorable melting temperature (T_m) and good resistance towards nucleases[100]. In addition, Mesmaeker and coworkers synthesised urea **L.9** (Ref.104), carbamates **L.10** (Ref.105) linked dinucleotides, incorporated them into oligonucleotides and studied their biophysical properties. Herdewijn and coworker[106] introduced the thiourea **L.11** linkage between the nucleosides. Kutter and Just reported[107] the synthesis of carbamate linked dimeric nucleotides **L.12** whereas tri, tetrameric carbamate linked nucleotides were synthesised by Agrawal and successfully incorporated into the oligonucleotides[108]. These oligomers were shown to enhance the nuclease resistance with only slight destabilisation of the duplexes.

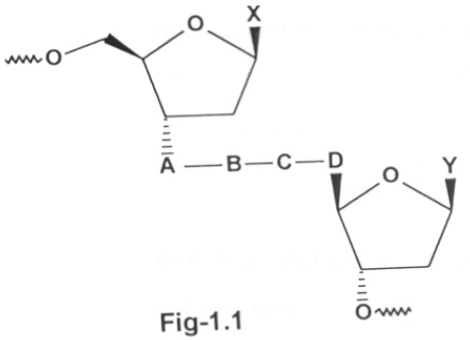


Fig-1.1

Table-1.1

No:	Nature of Linkage	X	Y	A-B-C-D
L.1.	Amide	T	T	$NRCOCH_2CH_2$
L.2.	,,	T	T	CH_2CH_2NHCO
L.3.	,,	T	T	$CH_2CONHCH_2$
L.4.	,,	C	T	$CH_2CONHCH_2$
L.5.	,,	A	G	$CH_2CONHCH_2$
L.6.	,,	G	T	$CH_2CONHCH_2$
L.7.	,,	T	T	$CH_2NHCOCH_2$
L.8.	,,	T	T	$CONHCH_2CH_2$
L.9.	Urea	T	T	$NRCONRCH_2$
L.10.	Carbamate	T	T	$OCONRCH_2$
L.11.	Thiourea	T	T	$NHCSNHCH_2$
L.12.	Carbamate	T	T	$NRCOOCH_2$
L.13.	Amine	T	T	$NHCH_2CH_2CH_2$
L.14.	,,	T	T	$CH_2NRCH_2CH_2$
L.15.	,,	T	T	$CH_2CH_2NRCH_2$
L.16.	,,	T	T	$CH_2CH_2NHCH_2$
L.17.	,,	T	T	Piprazine-CH_2
L.18.	Oxyamide	T	T	O-NHCO
L.19.	Carboxyamide	T	T	OCH_2CH_2NHCO
L.20.	Glyamide	T	T	$NHCOCH_2NHCO$
L.21.	Oxime	T	T	$CH{=}N\text{-}OCH_2$
L.22.	Methyleneimino	T	T	CH_2NHOCH_2
L.23.	,,	T	T	$CH_2N(CH_3)OCH_2$
L.24.	,,	C	C	$CH_2N(CH_3)OCH_2$
L.25.	,,	A	C	$CH_2N(CH_3)OCH_2$
L.26.	,,	G	C	$CH_2N(CH_3)OCH_2$
L.27.	,,	T	T	$CH_2N(CH_3)N(CH_3)CH_2$
L.28.	,,	T	T	$CH_2ON(CH_3)CH_2$
L.29.	,,	T	T	$ON(CH_3)CH_2CH_2$
L.30.	Guanidine	T	T	NH-C(=N-CN)-$NHCH_2$
L.31.	,,	T	C,A	NH-C(=N-CN)-$NHCH_2$
L.32.	,,	T	T	NH-C(=NR)-CH_2
L.33.	Sulphonamide	T	T	$NHSO2CH_2CH_2$
L.34.	Sulphamoyl	T	T	OSO_2NHRCH_2

It was believed that amino linkage would be partially protanated at physiological pH and could assist in cellular uptake. The electrostatic and hydration factors between protonated nitrogen atom in the amino linkage and the anionic phosphate of the complimentary strand were expected to further increase in thermal stability of these duplexes. Therefore, various amino-linkages **L.13-L.17** were introduced[108-111] and their biological properties were studied.

Most of the researchers in this field reported the four atom modification at dinucleotide level. However few reports have appeared on five atom modification at dimer level. Peterson and coworkers sythesised[110] amino-4 linkage **L.16** and along with an interesting[111] cyclic amino-5 linkage **L.17** (piperazino). Both are 5 atom linked backbones unlike the natural phosphate linkages which is a four atom one. Oxyamido linked dimer T*T **L.18** was prepared and shown to hybridise to complimentary DNA (Ref.112). The five atom linker carboxamide **L.19** was synthesised[112] and it was shown that the oligonucleotides containing this carboxamide linked units destabilised the duplex by 2-4°C. Varma and coworkers have reported[113] the synthesis of five atom glycyl-amide linked dimer **L.20**.

A variety of nitrogen containing backbones have been synthesised[114] by a group of scientists from ISIS pharmaceutical Ltd. These included oxime **L-21**, methyleneimino, methylene(methylimino), methylene(dimethylhydrazo), methylenenoxy(methylimino) and hydroxy (methyliminomethylene) **L.22-L.29** linkages[115-117]. Biophysical properties of the oligomers containing these modifications were studied. Herdewijn and coworkers synthesised[118-120] oligothymidilate containing thymidine dimers with a variety of guanidine linkages **L.30-L.32**. Among them, the N-methylsulphonyl guanidine linkage **L.32** showed intresting biophysical properties. Widlanski and coworkers reported[121] the synthesis and biophysical properties of sulphonamide linked dinucleosides **L.33**. Sulphamoyl linked dinucleosides **L.34** were also reported in the literature[122].

1.10. Aminonucleoside antibiotics and their biological properties.

Various naturally occuring antibiotics contain aminosugar modified nucleoside units. Since various reviews are available in this area[123,124], we will briefly highligt the core structures of such nucleoside antibiotics.

3'-Aminoacyl- analog of nucleosides were reported[125] by Iwamoto and coworkers;. Antibiotic FR-900403 (**Fig-1.2**) was produced by a fungus kermia.SP.F-19849. It was shown[126] to be a 3'-aminoacyladenosine derivative related to chryscandin. The 3'-amino group was linked with alloisoleucine. This antibiotic exhibited specific antimicrobial activity against *candida albicans*.

Few 4'-aminoacyl-4'-deoxy pyranosyl cytosines were reported[127] as Blasticidin S (**Fig-1.3**). Two other groups[128,129] have isolated 5-hydroxymethyl leucyl blasticidin S. It was found to have anti-inflammatory activity in the reverse passive Arthus reaction and the adjuvant arthritic rate at doses ranging between 1-10mg/kg and 0.3-0.6mg/kg respectively[130]. 5-Hydroxymethyl Blasticidin S was isolated from the culture filtrate of *streptomyces setonii* together with blasticidin S and 16-deethyllindanomycin[131].

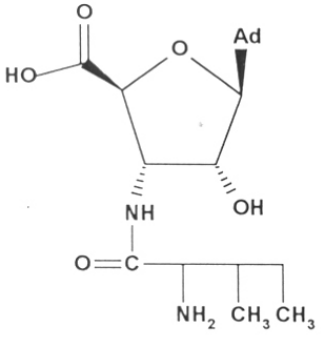
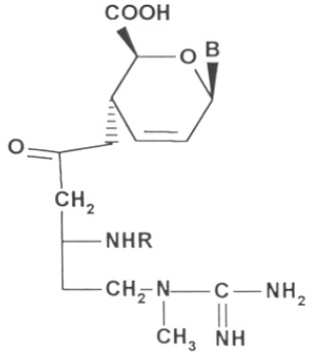


Fig-1.2

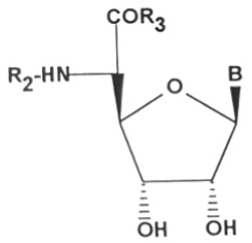


B= Cytosine, 5-Hydroxymethyl cytosine

R= H, Leucyl

Fig-1.3

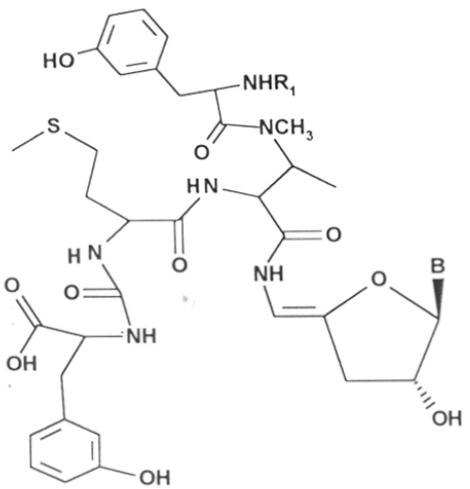
Various Nikkomycins (neopolyoxins) (**Fig-1.4**) were reported by different groups[123,132,133]. These Nikkomycins are a group of peptidyl nucleosides structurally and biologically related to polyoxins which are inhibitors of chitin synthetase of the fungal cell wall. Mureidomycins A-D (**Fig-1.5**) are peptidyl nucleosides produced by *streptomyces flavidovirenes*[134]. The planar structures were deduced from all spectrocopic analysis and degradation studies[135].



B= Uracil, Thymine

R_2=L-Tyrosine , R_3= OH or Glutamate

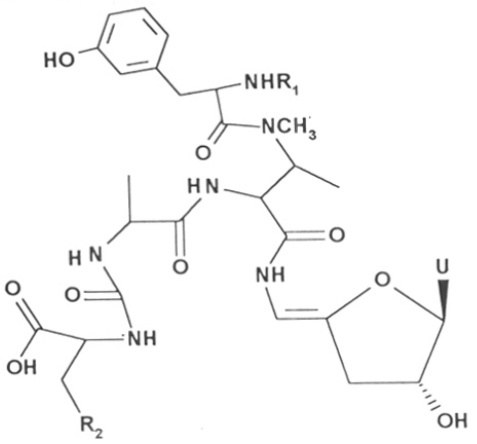
Fig-1.4



R_1= H, Glycyl

B= 5,6-Dihydrouracil, 5,6- Cyclopropyl uracil

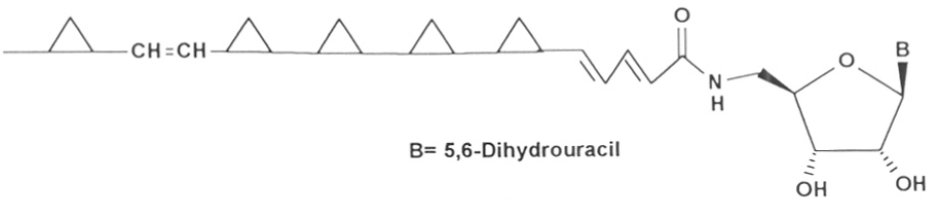
Fig-1.5



R_1= Alanyl, H, Glycyl

R_2= Indol-3-yl, Phenyl, m-hydroxyphenyl

Fig-1.6



B= 5,6-Dihydrouracil

Fig-1.7

Mureidomycins A and C contains uracil while dihydrouracil is the component of B and D. Pacidamycins (**Fig-1.6**) produced by streptomyces coeruleorubidus were also described in literature[136].

Antibiotic T.R-900848 (**Fig-1.7**) was discovered[137] by Fujisawa and coworkers. The structure was shown to be 5'-amino-5'-deoxy-5,6-dihydrouridine with an unsaturated fatty acid having unprecedented four serial and one isolated cyclopropane rings. It showed highly specific activity against *filamentous fungi* at concentrations of 0.005-0.5μg/ml, suppressing the growth of aspergillus niger, mucor rouxianus, penicillium pullium pullulans, aureobasidium pullulans, trichopytons spcies fusarium oxysporum and scherosinia arachidins.

1.11. References

1. *Carbohydrate Chemistry*; Ferrier, R.J. Senior Reporter; **Vol. 1-23**, The Royal Society of Chemistry, Cambridge.
2. Horton, D.; Wander, J.D.; In *The Carbohydrates: Chemistry and Biochemistry;* Pigman, W.; Horton, D.; Wander, J.D.; Eds. **1980**, Vol 1B, pp 643-760, Academic Press, New York.
3. Review: a) Fox, J.J.; *Pure Appl. Chem.*, **1969**, 18, 223-55. b) Mofatt, J.G. In *Nucleoside Analogues: Chemistry, Biology and Medical Applications*; Walker, R.T.; De Clercq, E.; Ecstein, F. Eds.; Plenum Press, New York, **1979**, pp 71-164.
4. Mitsuya, H.; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Nusinoff-Lehrman, S.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S. *Proc. Natl. Acad. Sci. USA*, **1985**, 82, 7096-100.
5. For a review, see: a) Huryn, D.M.; Okabe, M. *Chem. Rev.* **1992**, 92, 1745-68. b) De Clercq, E. *Antiviral Res.*, **1989**, 12, 1-20. c) De Clercq, E. *Aids Research and Human Retroviruses*, **1992**, 8, 119-34.
6. Balzarini, J.; *Pharm World Sci.*; **1994**, 16, 113-26.
7. Cheng, Y.-C.; Dutschman, G. E.; Bastow, K. F.; Sarnyadharan, M. G.; Ting, R. Y. C.; J. Biol. Chem.; 1987, 262, 2187-9.
8. Motawia, M. S.; Pedersen, E. B.; Nielsen, C. M.; *Arch. Pharm.*; **1990**, 323, 971-5.
9. Vial, J.M.; Johansson, N.G.; Vrang, L.; Chattopadhyaya, J. *J. Antivir. Chem. Chemother.*, **1990**, 1, 183-202.
10. Shealy, Y.F.; O'Dell, C.A.; Shannon, W.M.; Arnett, G. *J. Med. Chem.*, **1986**, 29, 483-8.
11. Lin, T-S.; Neenan, J.P.; Cheng, Y-C.; Prusoff, W.H.; Ward, D.C. *J. Med. Chem.*, **1976**, 19, 495-8.
12. Horwitz, J. P.; Tomson, J. A.; Urbanski, J. A.; Chua, J.; *J. Org. Chem*; **1964**, 29, 2076-8.
13. Neenan, J.P.; W. Rohde, W. *J. Med. Chem.*, **1973**, 16, 580-1.
14. Cheng, Y.C.; Prusoff, W.H. *Biochemistry*, **1974**, 13, 1179-85.
15. Cheng, Y.C. Prusoff, W.H. *Biochemistry*, **1973**, 12, 2612-9.
16. Hampton, A.; Bayer, M.; Gupta, V.S.; Chu, S. Y; *J. Med. Chem.*, **1968**, 11, 1227-32.
17. Schimidt, R. R.; Schloz, U.; Schwille, D.; *Chem. Ber.* **1968**, 101, 590-4.
18. Hampton, A.; Kappler, F.; Chawla, R. R.; *J. Med. Chem.*, **1979**, 11, 621-31.

19. Baker, J. J., Mellish, P.; Riddle, C.; Somerville, A. R.; Tittensor, J. R.; *J. Med. Chem.*, **1974**, 17, 764-6.
20. Baker, J. J., Mian, A. M.; Tittensor, J. R.; *Tetrahedron*. **1974**, 30, 2939-42.
21. Robins, M. J.; Simon, L. N.; Stout, M. G.; Ivanovics, G. A.; Schweizer, M. P.; Rousseau, R. J.; Robins, R. K.; Secrist III, J.A.*; J. Am. Chem. Soc.*, **1971**, 93, 1474-80.
22. Murayama, A.; Jastorff, B.; Cramer, F.; Gettler, H.; *J. Org. Chem.*, **1971**, 20, 3029-33
23. Mitsunobu, O.; Takizawa, S.; Morimato, H.; *J. Am. Chem. Soc.*, **1976**, 98, 7858-9.
24. Secrist III, J.A.;Winter, Jr. W. J.; *J. Am. Chem. Soc.*, **1977**, 100, 2554-5.
25. Adachi, T.;Yamada, Y.; Inoue, I.; Saneyoshi, M.; *Carbohydr. Res.*, **1979**, 73, 113-24
26. Adachi, T.; Arai, Y.; Inoue, I.; Saneyoshi, M.; *Carbohydr. Res.*, **1980**, 78, 67-77
27. Davies, L. C.; *Nucleosides. Nucleotides.*, **1985**, 4, 395-400.
28. Elliott, R.D.; Brockman, R. W.; Montgomery, J.A.; *J. Med. Chem.*, **1987**, 29, 1052-6.
29. Secrist III, J.A.; *Nucleosides. Nucleotides.*, **1987**, 6, 73-83.
30. Elliott, R. D.; Montgomery, J. A.; Riordan, J. M.; *J. Org. Chem.*, **1987**, 52, 2892-6.
31. Casara, P.; Marchal, P. Wagner, J. Danzin, C.; *J. Am. Chem. Soc.*, **1989**, 111, 9111-3.
32. Talebian, A. H.; Schein, P. S.; Green, D. C.; *Nucleosides. Nucleotides.*, **1990**, 5, 721-30.
33. Hiebl, J.; Zbrial, E.; Balzarini, J.; De Clercq, E. *J. Med. Chem.*, **1991**, 34, 1426-30.
34. Bjorsne, M.; Classon, B.; Kvarnstrom, I.; Samuelsson, B.; *Nucleosides. Nucleotides.*, **1993**, 12, 529-36.
35. Reynolds, R. C.; Crooks, P. A.; Parker, W. B.; Maddry, J. A.; Montgomery, J. A.; Secrist III, J. A.; *J. Biopharm. Sci.*, **1991**, 2, 195-203.
36. Codington, J. F.; Fecher, R.; Fox, J. J.; *J. Org. Chem.*, **1962**, 27, 163-7.
37. Miller, N.; Fox, J. J.; *J. Org. Chem.*, **1964**, 29, 1772-6.
38. Martinez, A. P.; Calkins, D. F,; Reist, E. J.; Lee, W. W.; Goodman, L.; *J. Heterocycl. Chem.*, **1970**, 713-4.
39. Robins, M. J.; Fouron, Y.; Mengel, R.; *J. Org. Chem.*, **1974**, 39, 1564-70.
40. Lichtenthaler, F. W.; Kitahara, K.; Strobel, K.; *Synthesis.*, **1974**, 860-2.
41. Rosenthal, A.; Ratcliffe, M.; *Carbohydr. Res.*, **1978**, 60, 39-49.
42. Montgomery, J. A.; Thomas, H. J.; *J. Med. Chem.*, **1979**, 22, 1109-13.
43. Reichman, U.; Hollenberg, D. H.; Chu, C. K.; Watanabe, K. A.; Fox, J. J.; *J. Org. Chem.*, **1976**, 41, 2042-3.
44. Saneyoshi, M.; Nishizaka, H.; Katoh, N.; *Chem. Pharm. Bull.*, **1981**, 29, 2769-75.
45. Lin, T-S.; Gao, Y-S.; Mancini, W. R.; *J. Med. Chem.*, **1983**, 26, 1691-6.

46. Schreiber, S. L.; Ikemoto, N.; *Tetrahedron. Lett.*, **1988**, 26, 3211-4.
47. Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J.; *Tetrahedron.*, **1991**, 47, 3431-50.
48. Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopadhyaya, J.; *Tetrahedron.*, **1993**, 49, 10133-56.
49. Motawia, M. S.; Wengel, J.; Abdel-Megid, A. E.-S.; Pedersen, E. B.; *Synthesis.*, **1989**, 384-7.
50. Wengel, J.; Pedersen, E. B.; Vestergaard, B. F.; *Synthesis.*, **1992**, 319-22.
51. Samano, M. C.; Robins, M. J.; *Tetrahedron Lett.*, **1989**, 30, 2329-32.
52. Wigerinck, P.; Aerchot, A. V.; Janssen, G.; Claes, P.; Balzarini, J.; Clarcq, E. De.; *J. Med. Chem.*, **1990**, 33, 868-73.
53. Hiebl, J.; Zbrial, E.; Balzarini, J.; De Clercq, E.; *J. Med. Chem.*, **1990**, 33, 845-8.
54. Matsuda, A.; Satoh, M.; Ueda, T.; Machida, H.; Sasaki, T.; *Nucleosides. Nucleotides.*, **1990**, 9, 587-97.
55. Habich, D.; *Synthesis.*, **1992**, 358-60.
56. Ariza, X.; Garces, J.; Vilarrasa, J.; *Tetrahedron Lett.*, **1992**, 28, 4069-72.
57. Celewicz, L.; Urjasz, W.; Golankiewicz, K.; *Nucleosides. Nucleotides.*, **1993**, 12, 951-66.
58. Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M . B.; *J. Org. Chem.*, **1976**, 41, 3138-43.
59. Ikehara, M.; Maruyama, T.; Miki, H.; *Tetrahedron Lett.* **1976**, 49, 4485- 8.
60. Wu, J.-C.; Chattopadhyaya, J.; *Tetrahedron.*, **1989,** 45, 855-62.
61. Wu, J.-C.; Chattopadhyaya, J.; *Tetrahedron.*, **1989,** 45, 5407-22.
62. Matsuda, A.; Yasuoka,J.; Sasaki, T.; Ueda,T.; *J. Med. Chem.*, **1991**, 34, 999-1002.
63. Matsuda, A.; Yasuoka,J.; Ueda,T.; *Chem. pharm. Bull.*, **1989**, 37, 1659-61.
64. Robins, M. J.; Hawrelak, S. D.; *Tetrahedron Lett.* **1978**, 51, 3653-6.
65. Lin, T-S.; Prusoff, W.H.; *J. Med. Chem.*, **1978**, 21, 109-11.
66. Morr, M.; Ernst,L.; *Chem.Ber.* **1979**, 112, 2815-28.
67. Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M . B.; *J. Org. Chem.*, **1976**, 41, 3138-43.
68. Ozols, A. M.; Azhayev, A. V.; Krayevsky, A. A.; Ushakov, A. S.; Gnuchev, N. V.; Gottikh, B.P.; *Synthesis.*, **1980,** 559-61.
69. Jack Chen, Y.-C.; Hansske, F.; Janda, K. D.; Robins, M. J.; *J. Org. Chem.*, **1991**, 56, 3410-13.
70. Jack Chen, Y.-C.; Janda, K. D.; *J. Am. Chem. Soc.*, **1992**, 114, 1488-9
71. Lin, T-S.; Zhou, R-X.; Scanlon, K. J.; Brubaker, W. F.; Lee, J. J. S.; Woods,K.; Humphreys, C.; Prusoff, W. H.; *J. Med. Chem.*, **1986**, 29, 681-6.

72. Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M.; *J. Org. Chem.*, **1976**, 41, 3138-43.
73. Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefert, J-M.; Mengel. R.; *J. Org. Chem.*, **1979**, 44, 1317-22.
74. Tong, W.; Wu, J.-C.; Sandstrom, A.; Chattopadhyaya, J.; *Tetrahedron.*, **1990**, 46, 3037-60.
75. Xi, Z.; Glemarec, C.; Chattopadhyaya, J.; *Tetrahedron.*, **1993**, 49, 7525-46.
76. Doerr, I. L.; Cushley, R. J.; Fox, J. J.; *J. Org. Chem.*, **1968**, 33, 1592-9.
77. Kaneko, M.; Shimizu, B.; *Tetrahedron. Lett.*, **1971**, 33, 3113-6.
78. Sasaki, T.; Minamoto, K.; Sugiura, T.; *J. Org. Chem.*, **1975**, 40, 3498-502.
79. Cook, A. F.; *J. Med. Chem.*, **1977**, 20, 344-8.
80. Sasaki, T.; Minamoto, K.; Itoh, H.; *J. Org. Chem.*, **1978**, 33, 2320-5.
81. Sasaki, T.; Minamoto, K.; Itoh, H.; *Tetrahedron.*, **1980**, 36, 3509-15.
82. Sasaki, T.; Minamoto, K.; Yamashita, S.; Fujiki, Y.; *J. Org. Chem.*, **1982**, 47, 4465-70.
83. Sasaki, T.; Minamoto, K.; Fujiki, Y.; *Chem. Lett.*, **1983**, 1017-20.
84. Minamoto, K.; Tanaka, T.; Azuma, K.; Suzuki, N.; Eguchi, S.; Kadoya, S.; Hirota, T.; *J. Org. Chem.*, **1986**, 51, 4417-24.
85. Minamoto, K.; Azuma, K.; Fujiwara, N.; Eguchi, S.; Hirota, T.; Kadoya, S.; *J. Org. Chem.*, **1989**, 54, 4543-9.
86. Minamoto, K.; Azuma, K.; Tanaka, T.; Iwasaki, H.; Eguchi, S.; Kadoya, S.; Moroi, R.; *J. Chem. Soc. Perkin Trans. I.*, **1988**, 2955-61.
87. Minamoto, K.; Azuma, K.; Hoshino, Y.; Eguchi, S.; *Chem. Lett.*, **1989**, 825-8.
88. Minamoto, K.; Fujiwara, N.; Hoshino, Y.; Hamano, Y.; Eguchi, S.; Hirota, T.; Moroi, R.; *J. Chem. Soc. Perkin Trans. I.*, **1990**, 3027-33.
89. Ng, K.-M.E.; Orgel,L.E.; *J. Med. Chem.*, **1989**, 32, 1754-7.
90. Peterson, M. L.; Vince,R.; *J. Med. Chem.*, **1991**, 34, 2787-97.
91. a) Kaspersen, F. M.; Pandit,U.K.; *J. Chem. Soc. Perkin Trans. I.*, **1975**, 1617-25; b) Kaspersen, F. M.; Pandit,U.K.; *J. Chem. Soc. Perkin Trans. I.*, **1975**, 1798-802.
92. Hardnden, M. R.; Jarvest, R. L.; *Tetrahedron. Lett.*, **1991**, 32, 3863-6.
93. Hardnden, M. R.; Jarvest, R. L.; *J. Chem. Soc. Perkin Trans. I.*, **1991**, 2073-9.
94. Altmann, K.-H.; *Tetrahedron. Lett.*, **1993**, 34, 7721-4.
95. Rassu, G.; Pinna, L.; Spann, P.; Ulgheri, F.; Casiraghi, G.; *Tetrahedron. Lett.*, **1994**, 35, 4019-22.
96. Huang, B.; Chen, B.; Hui,Y.; *Synthesis;* **1993**, 769-71.

97. Altmann,K.-H.; Freier, S.M.; Pieler. U.; Winkler,T.; *Angew. Chem. Int. Ed. Engl.;* **1994**, 33, 1654-7.

98. Lebreton, J.; De Mesmaeker A.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M.; *Tetrahedron lett.;* **1993,** 34, 6383-6.

99. De Mesmaeker A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M.; *Synlett.*; **1993**, 733-6.

100. De Mesmaeker A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Fritsch, V.; Wolf, R. M.; Freier, S. M.; *Angew. Chem. Int. Ed. Engl.*; **1994**, 33, 226-9.

101. Lebreton, J.; Waldner, A.; Lesueur, C.; De Mesmaeker A.; *Synlett.*; **1994**, 137-9.

102. Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; De Mesmaeker A.; *Tetrahedron lett.;* **1994,** 35, 5225-8.

103. De Mesmaeker A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 873-8.

104. Waldner, A.; De Mesmaeker A.; Lebreton, J.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 405-8.

105. Vandeendrissche, F.; Van Aerschot, A.; Voortmans. M.; Janssen, G.; Busson, R.; Van Overbeke, A.; Van Den Bossche, W.; Hoogmartens, J.; Herdewijn, P.; *J. Chem. Soc.*; **1993**, 1567-75.

106. Kutterer, K. M. K.; Just, G.; *Bioorg. Med. Chem. Lett.*; **1994**, 3, 435-8.

107. Habus, I.; Temsamani, J.; Agrawal, S.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 1065-70.

108. Saha, A. K.; Schairer, W.; Waychunas, C.; Prasad, C. V. C.; Sardaro, M.; Upson, D. A.; Kruse., L.I.; *Tetrahedron lett.;* **1993,** 34, 6017-20.

109. De Mesmaeker A.; Waldner, A.; Sanghvi, Y. S.; Lebreton, J.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 395-8.

110. Caulfield, T. J.; Prasad, C. V. C.; Prouty, C. P.; Saha, A. K.; Sardaro, M.; Schairer, D. W. C.; *Bioorg. Med. Chem. Lett.*; **1993**, 3, 2771-6.

111. Petersen, G. V.; Wengel, J.; *Tetrahedron.*; **1995**, 51, 2145-54.

112. Chur, A.; Holst, B.; Dahl, O.; Valentin-Hansen, P.; Pedersen, E. B.; *Nucleic Acids Res.;* **1993,** 32, 729-31.

113. Varma, R. S.; *Synlett.;* **1993,** 621-37.

114. Burgess, K.; Gibbs, R. A.; Metzker, M. L.; Raghavachari, R.; *J. Chem. Soc.* Chem. Commun.; **1994**, 915-6.

115. a) Sanghvi Y. S.; Cook, P. D.; *In Nucleosides And Nucleotides as Antitumor and Antiviral Agents;* Chu, C. K.; Baker, D. C.; Eds.; Plenum Press: Newyork 1993; pp.311-24. b). Vasseur, J-J.; Debart,F.; Sanghvi, Y. S.; Cook, P. D.; *J. Am. Chem. Soc.*, **1992**, 114, 4006-7. c.) Debart, F.; Vasseur, J-J.; Sanghvi, Y. S.; Cook, P. D.; *Tetrahedron. Lett.*, **1992**, 33, 2645-8.

116. Sanghvi, Y. S.; Vasseur,J.-J.; Debart, F.; Cook,P. D.; *Collect. Czech. Chem. Commun.* Special Issue **1993,** 58, 158-62

117. Sanghvi, Y. S.; Cook, P. D.; *Eds. Carbohydrate Modifications in Antisense Research.;* American Chemical Society, Washington, DC **1994**, pp 1-22.

118. Vandeendrissche, F.; Voortmans. M.; Hoogmartens, J.; Van Aerschot, A.; Herdewijn, P.; *Bioorg. Med. Chem. Lett.*; **1993**, 3, 193-8.

119. Pannecouque, C.; Schepers, G.; Rozenski, J.; Van Aerschot, A.; Claes, P.; Herdewijn, P.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 1203-6.

120. Pannecouque, C.; Vandeendrissche, F.; Rozenski, J.; Janssen. G.; Busson, R.; Van Aerschot, A.; Claes, P.; Herdewijn, P.; *Tetrahedron.*; **1994**, 50, 7231-46.

121. McElroy, E. B.; Bandaru, R.; Haund, J.; Widlanski,T. S.; *Bioorg. Med. Chem. Lett.*; **1994**, 4, 1071-6.

122. Dewynter, G.; Montero, J-L.; *Acad. Sci.;* **1992**, 315, 1675-82.

123. Isono, K.; *Pharmac. Ther.;* **1991**, 269-86.

124. Isono, K.; *J. Antibiotics.*, **1988**, 41, 1711-39.

125. Iwamoto, T.; Fujie, A.; Tsurumi, Y.; Nitta, K; Hashimoto, S.; Okuhara.; *J. Antibiotics.*, **1990,** 43, 1183-5.

126. Yamasita, M.; Kawai, Y.; Uchida, I.; Komori, T.; Kohsaka, M.; Imanaka, H.; Sakane, K. Setoi,H.; Teraji, T.; *J. Antibiotics.*, **1984**, 37, 1284-93.

127. Prabhakaran, P. C.; Woo, N.-T.; Yorgey, P. S.; Gould, S. J.; *J. Am. Chem. Soc.;* **1988**, 110, 5785-91.

128. Cooper, R.; Conover, M.; Patel, M.; *J. Antibiotics.*, 1988, 41, 123-5.

129. Dellweg, H.; Kurz, J.; Pfluger, W.;Schedel, M.; Bobis, G.; Wunsche, C.; *J. Antibiotics.*, **1988**, 41, 1145-7.

130. Gullo, V.; Conover, M.; Cooper, R.; Federbush, C.; Horan, A. C.; Kung, T.; Marquez, J.; Patel, M.; Watnick, A.; *J. Antibiotics.*, **1988**, 41, 20-4.

131. Larsen, S. H.; Berry, D. M.; Paschal, J. W.; Gillium, J. M.;*J. Antibiotics.*, **1989**, 42, 470-1.

132. Rathmann, R.; Konig, W.A.; Schmalle, H.; Carlsson,G.; Bosch, R.; Hagenmaierr, H.; Winter, W.; *Liebigs Ann. Chem.* **1984**, 1216-29.

133. Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima. T.; Miyazawa, T.;Jenkins, E. E.; McCloskey, J. A.; *Tetrahedron.*, **1982**, 38, 1599-608.

134. Inukai,M.; Isono,F.; Takahashi. S.; Enokita, R.; Sakaida, Y.; Haneishi, T.; *J. Antibiotics.*, **1989**, 42, 662-6.

135. Isono, F.; Inukai,M.; Takahashi. S.; Haneishi, T.; *J. Antibiotics.*, **1989**, 42, 667-73.

136. Chen, R. H.; Buko, A. M.; Whittern, D. N.; Mcalpine, J. B.; *J. Antibiotics.*, **1989**, 42, 512-20.

137. Yoshida, M.; Ezaki.M.; Hashimoto, M.; Shigematsu,N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K.; *J. Antibiotics.*, **1990**, 43, 748-54.

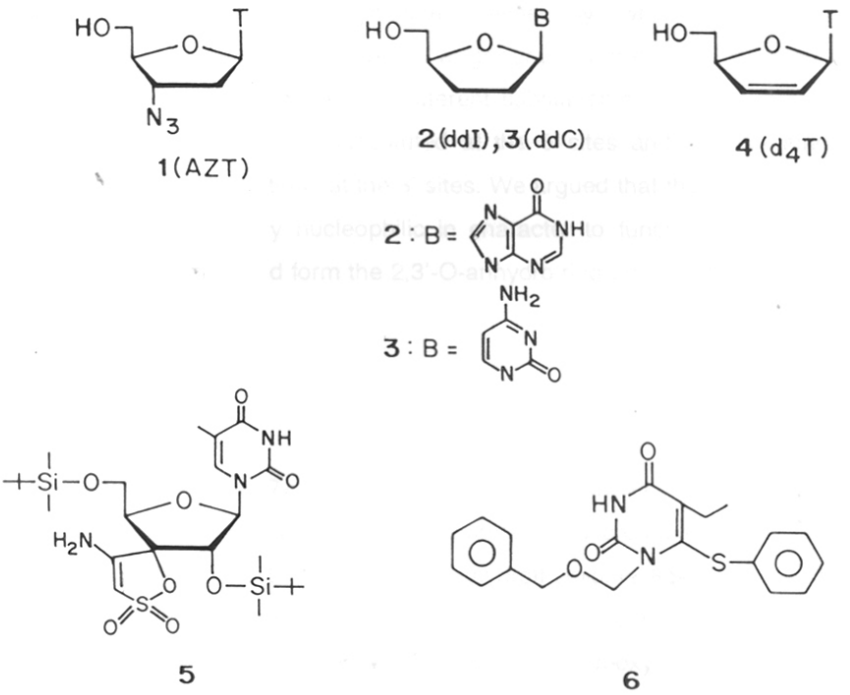
CHAPTER-II

Reactions of 3',5'-Di-O-mesylthymidine with Secondary Amines

2.1. Introduction

Since the discovery of the anti-HIV activity of 3'-deoxy-3'-azidothymidine **1** (AZT)[1], enormous progress has been made in the synthesis of new 3'-deoxy-3'-substitutedthymidines due to urgent need for better therapeutic agents. As a result, in addition to **1** (AZT), three more nucleosides, such as, 2',3'-dideoxyionosine **2** (ddI)[2], 2',3'-dideoxycytidine **3** (ddC)[2], and 2',3'-dideoxy-2',3'-didehydrothymidine **4** (d_4T)[3,4] were approved for the treatment of AIDS.

Fig - 2·1



In general, all these modified nucleosides need to be phosphorylated through three consecutive steps to their triphosphate forms before they can interact at the HIV reverse transcriptase level[5]. Therefore, attempts in recent years are aimed at designing new modified nucleosides with 5'-free hydroxyl groups[6,7]. Interestingly, however, Miyasaka and co-workers have shown[8] that a modified nucleoside having no free primary hydroxyl group, i.e. a

nucleoside which can not be phosphorylated, inhibits HIV-1 more efficiently than the corresponding nucleoside with free hydroxyl group; compound **5** and related derivatives interact, as such, noncompetitively, with a specific allosteric binding site of HIV-1 reverse transcriptase[9]. It has been also reported[9] that another modified nucleoside, compound **6** (**Fig-2.1**) with no free hydroxyl group, selectively inhibited HIV-1. The last few reports coupled with the literature on the synthesise and biological studies of 3',5'-dihetero- substituted nucleosides mentioned in Chapter-I (**Schemes-I.20** and **1.22**) warrants the synthesis of 3',5'-dideoxy-3',5'-disubstituted- thymidine nucleosides.

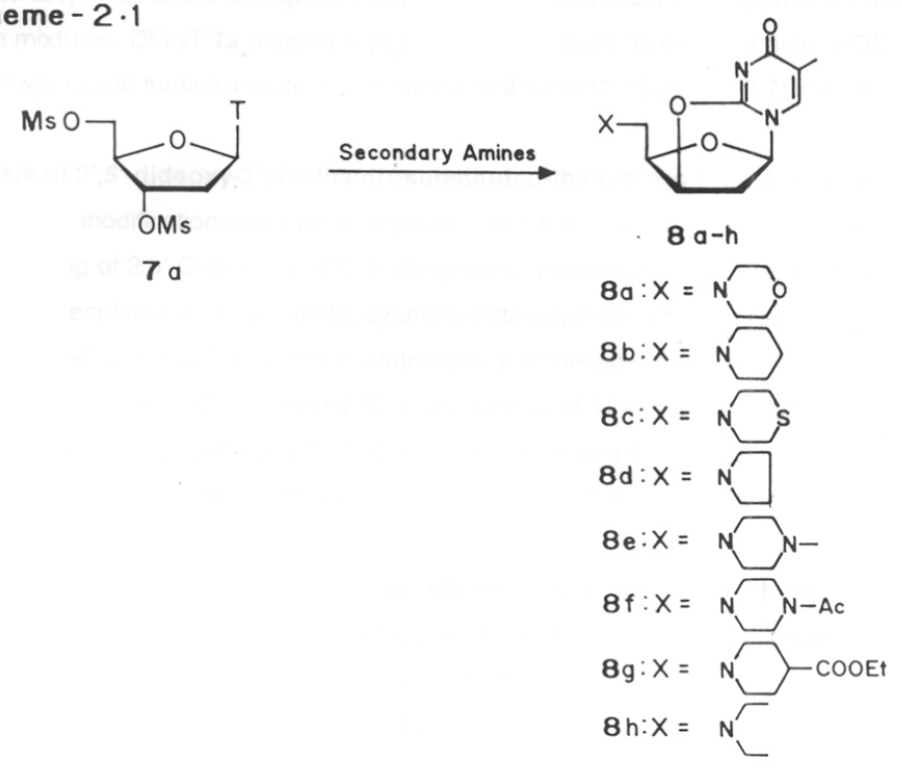
There are very few reports on the synthesis[10-12], and antiviral properties[10,11] of 3',5'-dideoxy-3',5'-disubstituted thymidines, especially when 3'- and 5'-sites are heterosubstituted. In order to develop a general methodology for the synthesis of 5'-deoxy-5'-alkylaminothymidines with different substituents at the 3'-sites, we set out to identify versatile intermediates substituted at the 5'-sites and suitably functionalised to undergo further transformations at the 3'-sites. We argued that the ideal reagent should be both basic and moderately nucleophilic in character to functionalise the 5'-end of the derivatives of thymidine and form the 2,3'-O-anhydro ring but should stop short of opening the anhydro ring.

2.2. Present work

3',5'-Di-O-mesylthymidine **7a** (DMST)[13] on treatment with secondary amines underwent a hitherto unknown "one-pot-two-steps" transformation to produce a new class of modified nucleosides 5'-alkylamino-5'-deoxy-2,3'-O-anhydrothymidine **8a-h**. To show the usefulness of these derivatives **8a-h** in synthesis of 3',5'-dideoxy-3',5'-disubtituted nucleosides, compounds **8a** and **8b** were further transformed to 3',5'-dideoxy-5'-alkylamino-3'-substituted-thymidines **9-13**.

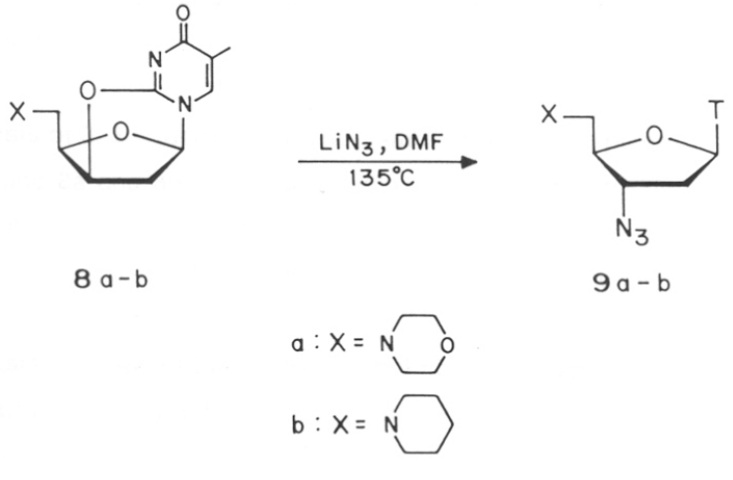
General method for the synthesis of 5'-deoxy-5'-alkylamino-2,3'-O-anhydrothymidines 8a-h: DMST **7a** was reacted with neat morpholine, piperidine, thiomorpholine, and pyrrolidine at room temperature or at 50-60°C to produce compounds **8a-d** respectively. Other bifunctionalised cyclic amines such as N-methylpiperazine, N-acetylpiperazine and ethyl *iso*nipecotate reacted with DMST in a similar fashion to produce compounds **8e-g** respectively

Scheme - 2·1



7 a

Scheme-2·2



8 a-b

9 a-b

(**Scheme-2.1**). In all cases (except for thiomorpholine) the products precipitated out from the reaction mixtures. DMST **7a** reacted with acyclic amine such as diethyl amine in DMF at a much slower rate to furnish a mixture of compounds **8h** and **17** (**Scheme-2.7**) in a ratio 1.4:1.

Synthesis of 3',5'-dideoxy-3',5'-diheterosubstituted-thymidines 9-13: As reported in the literature[14,15a], modification could be incorporated at the 3'-position of thymidine derivatives by the opening of 2,3'-O-anyhdro bridge using nucleophiles such as azide, thiophenol etc; however nucleophiles like thiocyanate, cyanide, isothiocyanide were not reactive enough to open the 2,3'-O-anhydro bridge. For the introduction of the latter class of nucleophiles at the 3'-position, compound **12** (**Scheme-2.5**) in its mesylated form would be an ideal starting material[15b]. In order to synthesise 3',5'-dideoxy-3'-substituted-5'-morpholino and piperidino thymidines, compounds **8a** and **8b** were subjected to four different reaction conditions.

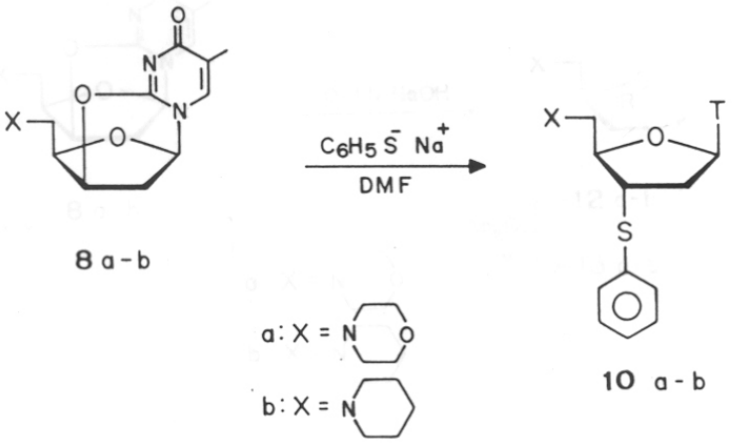
Synthesis of 3',5'-dideoxy-3'-azido-5'-morpholino- and piperidino- thymidines 9a-b: Compound **8a** and **8b** on reaction with lithium azide in DMF at 135°C produced anhydro ring opened products, 3',5'-dideoxy-3'-azido-5'-morpholino- thymidine **9a** and 3',5'-dideoxy-3'-azido-5'-piperidino- thymidine **9b** respectively (**Scheme-2.2**).

Synthesis of 3',5'-dideoxy-3'-S-thiophenyl-5'-morpholino- and piperidino- thymidines 10a-b: Compound **8a** and **8b** on reaction with sodium salt of thiophenol in DMF at 135°C produced anhydro ring opened products 3',5'-dideoxy-3'-S- thiophenyl-5'-morpholino-thymidine **10a** and 3',5'-dideoxy-3'-S- thiophenyl-5'-piperidino- thymidine **10b** respectively (**Scheme-2.3**).

Synthesis of 3',5'-dideoxy-2',3'-ene-5'-morpholino- and piperidino- thymidines 11a-b: Compound **8a** and **8b** on treatment with potassium*tert*-butoxide in DMSO underwent an elimination reaction to produce 3',5'-dideoxy-2', 3'-ene-5'-morpholino-thymidine **11a** and 3',5'-dideoxy-2', 3'-ene-5'-piperidino- thymidine **11b** respectively (**Scheme-2.4**).

Synthesis of 1-(2,5-dideoxy-5-morpholino- (and piperidino) -3-O-acetyl-β-D-*threo*-pentofuranosyl)-thymines 13a-b : Compound **8a** and **8b** were treated with 0.1N sodium hydroxide to produce 2,3'-O-anhdyro ring opened products **12a** and **12b** respectively (**Scheme-2.5**). Due to the polar nature of these compounds, **12a** and **12b** were acetylated

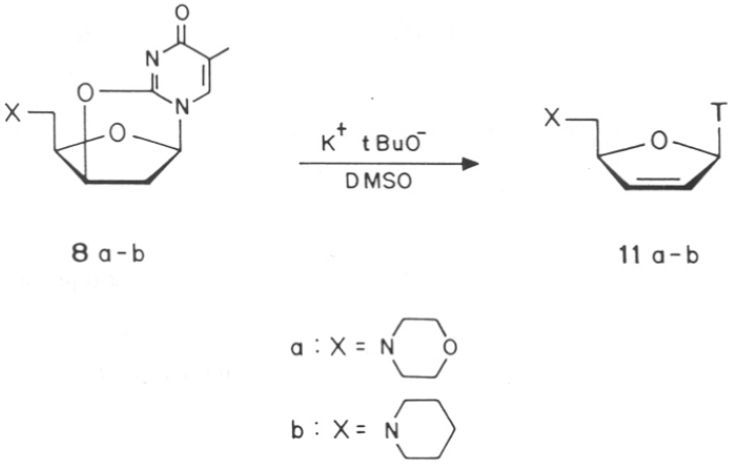
Scheme-2·3



8 a-b

10 a-b

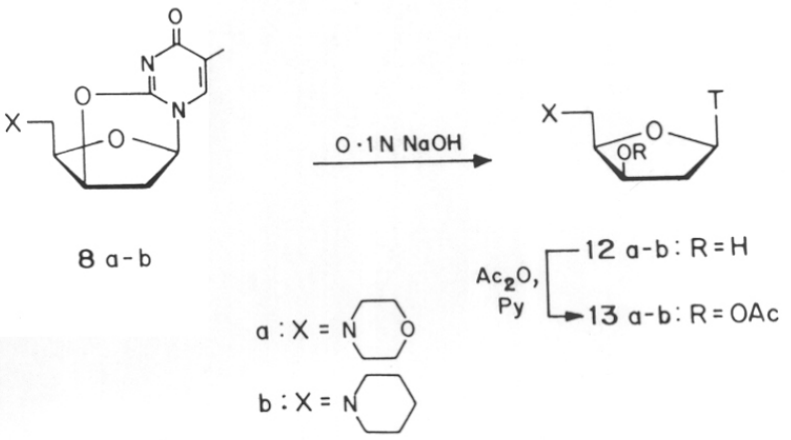
Scheme-2·4



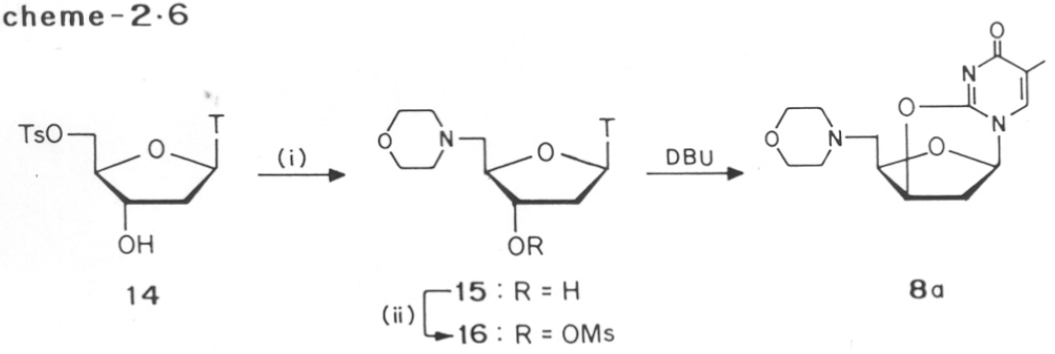
8 a-b

11 a-b

Scheme - 2·5



Scheme-2·6



to the corresponding products **13a** and **13b** respectively. By introducing mesyl group at 3'-position instead of acetyl group, one could achieve the synthesis of various 3'-substituted nuclesides such as, 3'-cyano-, 3'-thiocyano- and 3'-isothiocayano- derivatives[15b].

2.3. Structural assignment

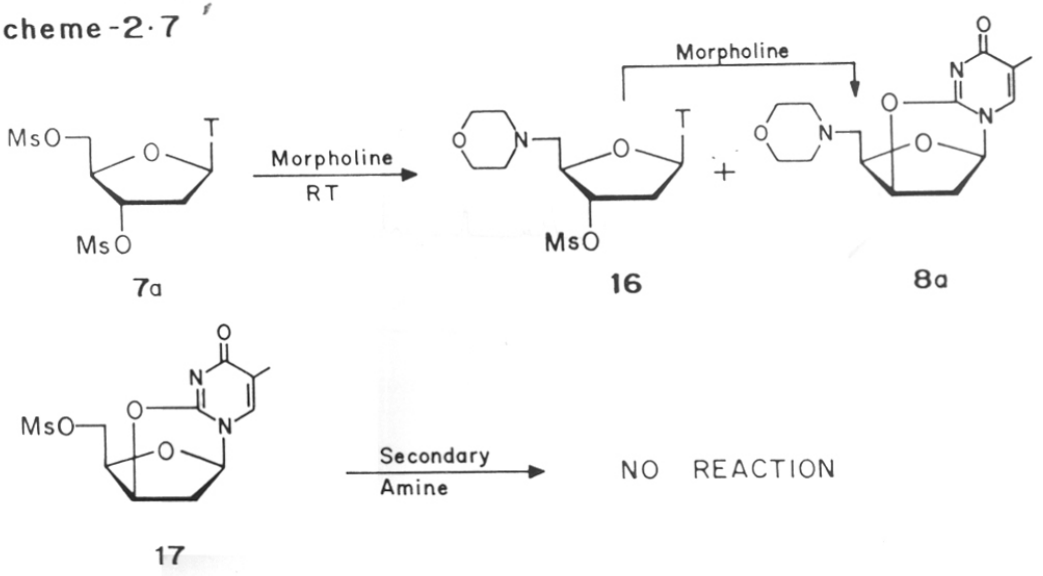
Structural assignment of compounds 8a-h: In order to establish the structures of the

Table - 2.1

Compound No: (Solvent)	H-1' $J_{H-1',H-2'}$	H-3'	H-4'
17 ($DMSO-d_6$)	5.82 (d)	5.28 (bs)	4.4-4.38 (m)
8a ($CDCl_3$)	5.58 (d) 3.8 Hz	5.19 (bs)	4.43 (septet)
8b ($CDCl_3$)	5.52 (d) 3.8 Hz	5.14 (bs)	4.37 (septet)
8c ($CDCl_3$)	5.52 (d) 3.8 Hz	5.17 (bs)	4.36 (sextet)
8d ($DMSO-d_6$)	5.77 (d) 3.8 Hz	5.2 (bs)	4.3 (sextet)
8e ($CDCl_3$)	5.52 (d) 3.7 Hz	5.11 (bs)	4.34 (septet)
8f ($CDCl_3$)	5.58(d) 3.7 Hz	5.22 (bs)	4.37 (m)
8g ($CDCl_3$)	5.52(d) 3.8 Hz	5.17 (bs)	4.38 (septet)
8h ($CDCl_3$)	5.5 (d) 3.8 Hz	5.15 (bs)	4.28 (sextet)

Structural assignment of compounds 9a and 9b: The IR spectrum of azido derivatives **9a** and **9b** showed sharp peaks at 2100 cm^{-1} corresponding to azide frequency. ^1H NMR of compounds **9a** and **9b** showed triplets around 6 ppm for H-1' protons which corresponded to the anhydro ring opened product. The H-3' and H-4' protons of compounds **9a** and **9b** resonated at @ 4.1 and 3.9 as multiplet. In ^{13}C NMR spectrum, compounds **9a** and **9b** showed

Scheme-2·7



products **8a-h** unambiguously compound **8a**, as a representative example, was synthesised through an independent route. 5'-O-Tosylthymidine **14** (ref.16), on reaction with morpholine at room temperature was converted to compound **15** which on treatment with methanesulphonyl chloride in pyridine produced 3'-O-mesyl-5'-N-morpholino-5'-deoxythymidine **16**. Compound **16** on reaction with DBU furnished compound **8a** in good overall yield (**Scheme-2.6**).

The ^{1}H-NMR of compounds **8a-h** were consistent with the structures assigned. The H-1' resonance appeared around 5.52-5.77 ppm as a doublet showing small coupling constant ($J_{1',2'}$= @ 3.8 Hz) and the H-3' resonance appeared around 5.11-5.22 ppm as broad singlet which were consistent with the literature[17] values for compound **17a**. In case of all the compounds the H-4' signal appeared either as sextet or septet (**Table-2.1**). The carbon signals were assigned on the basis of HET-COSY for the morpholino- and the diethylamino-derivatives **8a** and **8h** respectively (**Fig-2.2** and **2.3**). In ^{13}C spectrum, C-1' carbon appeared at 87-89 ppm for all anhydro- compounds **8a-h**. Similarly C-4'-and C-3' carbon signals appeared around 84 and 77-80 ppm respectively. The carbon signals of the rest of the carbons were consistent with structure assigned. In mass spectrum, all 5'-alklyamino-2,3'-O-anhydro derivatives produced corresponding amine+5'CH_2 peak as the base peak along with molecular ion peak.

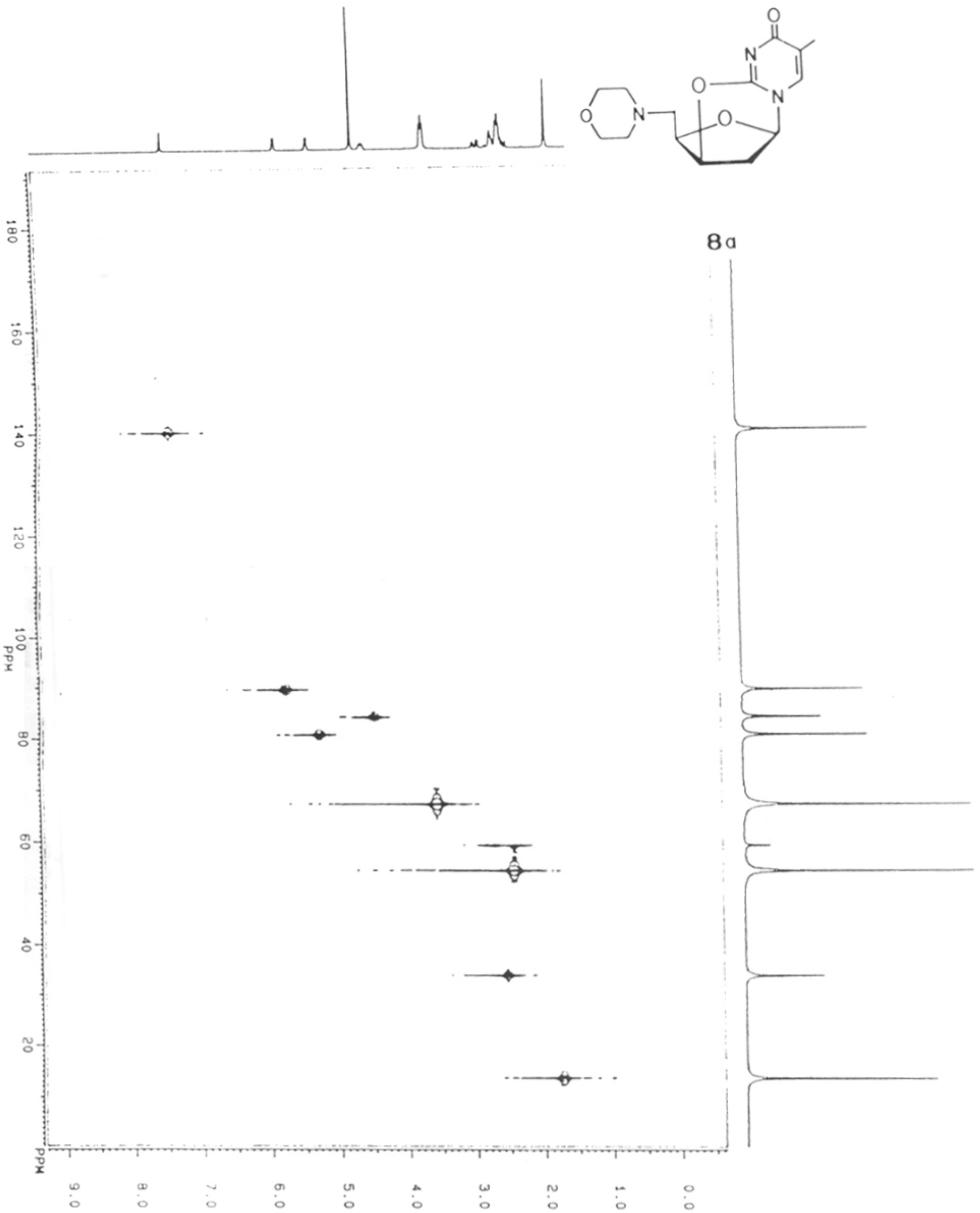

8a
PPM
PPM
180
160
140
120
100
80
60
40
20
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig-2.2

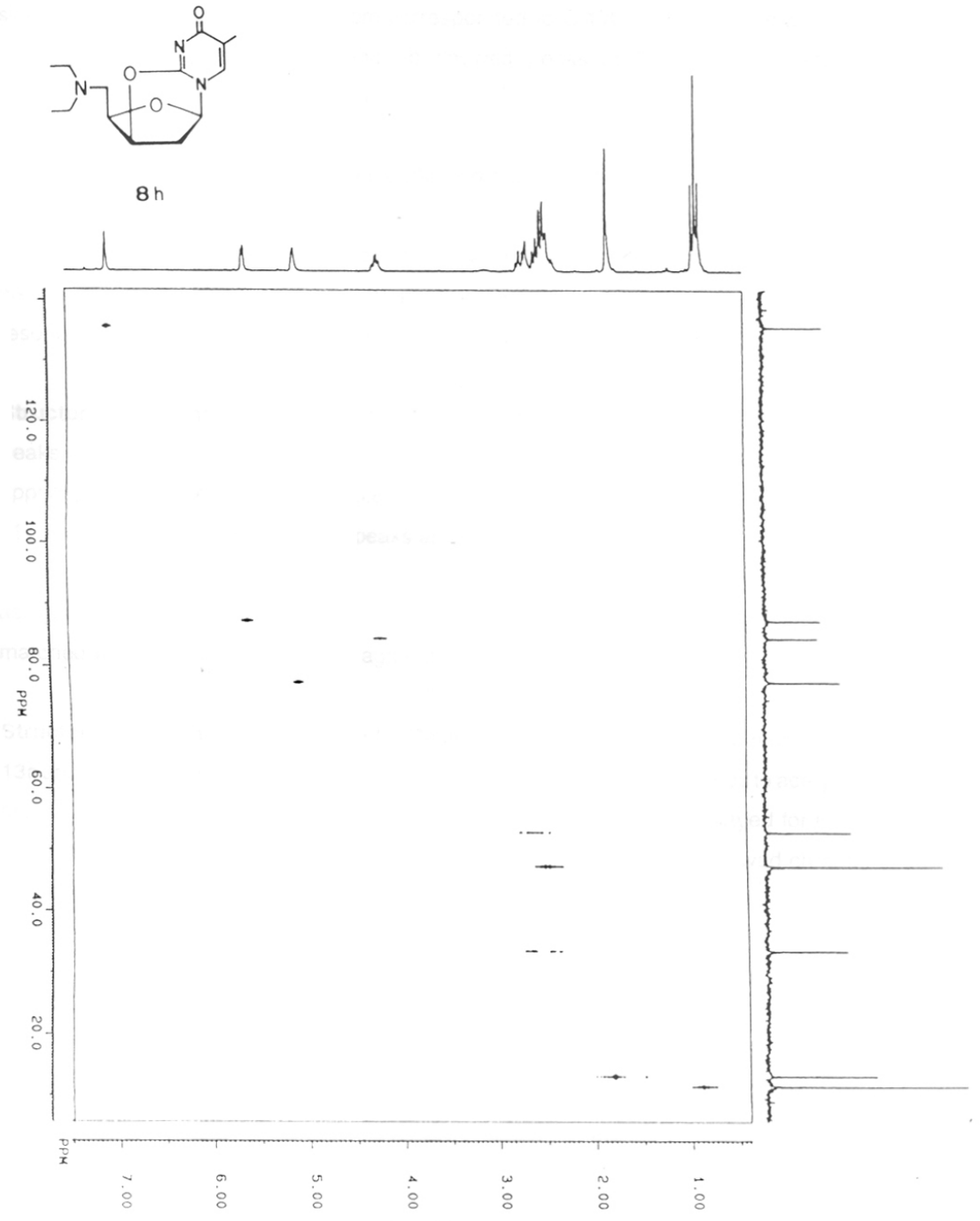


Fig-2.3

signals at around 85 / 81 and 62 ppm corresponded to C-1'/C-4' and C-3' respectively. In mass spectrum, compounds **9a** and **9b** showed peaks at 292 and 290 respectively corresponding to molecular ion-N_3 fragment.

Structural assignment of compounds 10a and 10b: In ^{1}H NMR, compounds **10a** and **10b** showed peaks at around 6 (dd or t) for H-1', 3.5 (m) for H-3' and 4.0 (m) for H-4'. The aromatic protons resonated around 7.5 as multiplet. ^{13}C NMR spectra of the compounds **10a** and **10b** displayed peaks at 85.1 and 83 for C-1' and C-4' respectively. All other carbons and protons resonated at the characteristic frequencies.

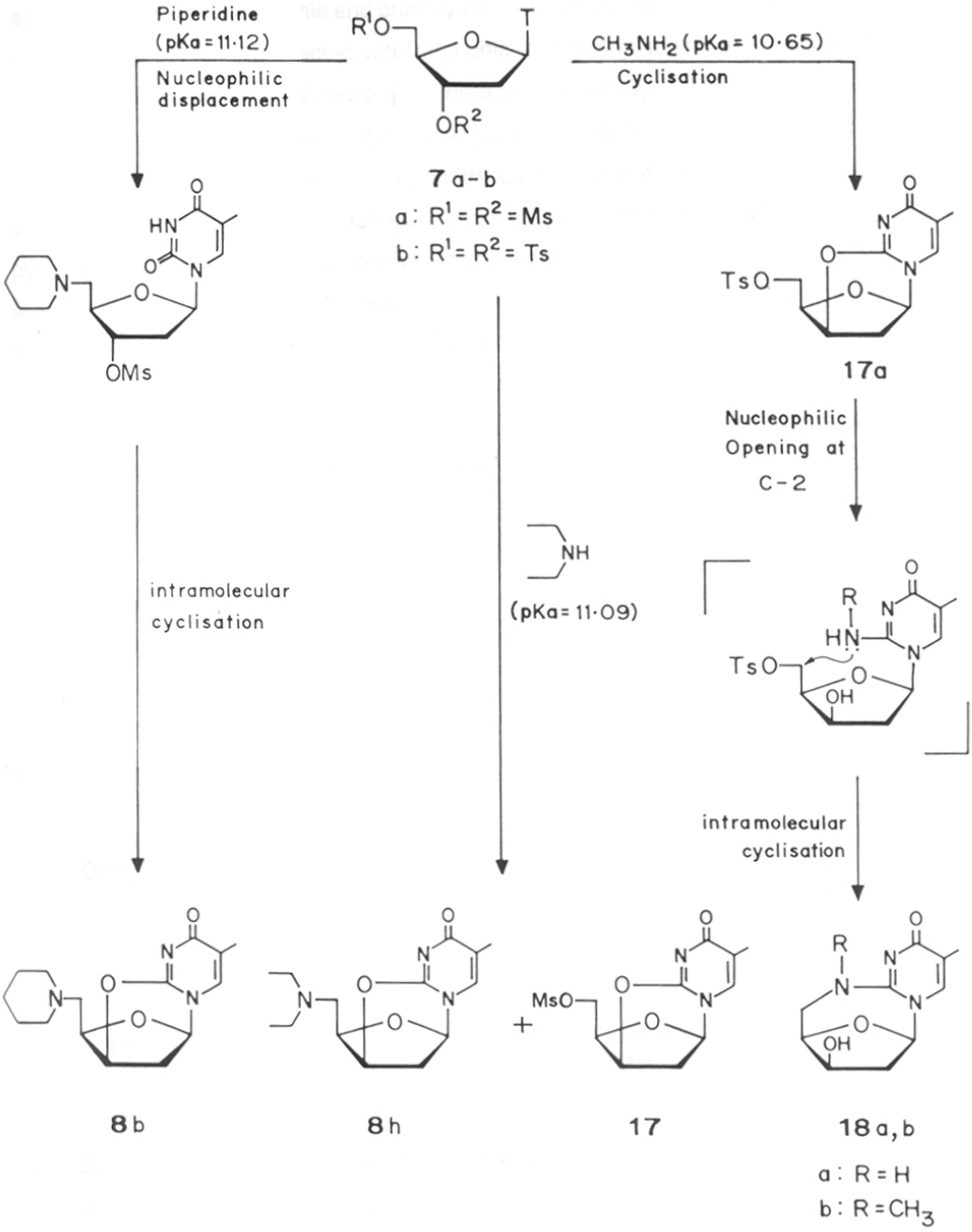
Structural assignment of compounds 11a and 11b: The ^{1}H NMR of compounds displayed peaks at 7.0 as multiplet which corresponded to H-1' proton. The H-3' and H-2' protons appeared as mutiplet at @6.3 and 5.8 ppm respectively. ^{13}C NMR spectrum of compounds **11a** and **11b** showed characteristic peaks around 90 ppm for C-1', 125 for C-2' and 135 for C-6 and C-3'. Position of the rest of the protons and carbons were consistent with the structure assigned. In mass spectrum, compounds **11a** and **11b** produced both peaks at 206 which matched with molecular ion-amine fragments.

Structural assignment of compounds 13a and 13b: The ^{1}H NMR spectrum of compounds **13a** and **13b** showed sharp singlet peak at around 2.1 ppm which corresponds to acetyl-methyl group. In addition, mutiplet peaks at @6.2, 5.4 and 4.32 ppm were displayed for H-1', H-3' and H-4' respectively. ^{13}C NMR spectrum of compounds **13a** and **13b** showed chracteristic peaks at @169 ppm for $OCOCH_3$. The signals corresponding to C-1'/C-4'/C-3' were displayed around 83/79/73ppm.

2.4. Discussion

The mechanism of conversion of DMST **7a** to compound **8a-h** was believed to involve formation of compound **16** by nucleophilic displacement of the 5'-O-mesyl group of DMST, followed by anhydro ring formation. In fact, if the reaction mixture of DMST **7a** and morpholine was not heated at 50°C the major product isolated was compound **16** (**Scheme-2.7**). Prior formation of compound **17** was also ruled out by the fact that unreacted starting material was recovered when **17** was reacted with morpholine at 50°C (**Scheme-2.7**). It was assumed that

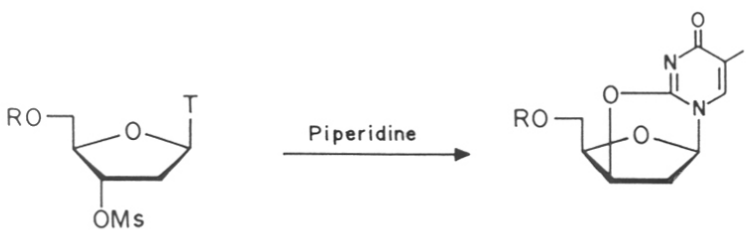
Scheme-2·8


Piperidine
(pKa = 11·12)
Nucleophilic
displacement
CH_3NH_2 (pKa = 10·65)
Cyclisation
7 a-b
a: $R^1 = R^2$ = Ms
b: $R^1 = R^2$ = Ts
17a
Nucleophilic
Opening at
C-2
intramolecular
cyclisation
NH
(pKa = 11·09)
intramolecular
cyclisation
8b
8h
17
18 a, b
a: R = H
b: R = CH_3

the same mechanism was operating in case of all the reported compounds **8a-h**. The mechanism of conversion of DMST **7a** to compounds **8a-h** should be contrasted with the reported reactions[17] of ammonia and primary amines with 3',5'-di-O-tosylthymidine **7b** (DTST **Scheme-2.8**)) ; DTST **7b** reacted with ammonia and methyl amine to produce 2,5'-imino- and 2,5'-(methylimino)-1- (2-deoxy-β-D-*threo*-pentofuranosyl)- thymines **18a** and **18b** respectively, *via* the formation of 2,3'-O-anhydro-5'-O-tosylthymidine **17a** and subsequent attack on C-2. The formation of compounds **8a-h** from the reactions of DMST **7a** and secondary amines was not obvious as it was expected that piperidine (pKa 11.123)[18] and pyrrolidine (pKa 11.27)[18], which were stronger amines than methylamine (pKa 10.657)[18] and ammonia (pKa 9.247)[18] should have produced the anhydro- compound **17** first, by abstracting the N-3 proton. In fact, as mentioned earlier, diethylamine (pKa 11.09)[18], a less nucleophilic amine because of its "flapping" ethyl groups, produced compound **17** alongside the desired product **8h**, in a ratio 1.4:1 (**Scheme-2.8**). It was highly probable that reactions of DMST ***7a*** and DTST ***7b*** with secondary and primary amines were controlled by the nucleophilicities of the amines and not by their basicities.

It should also be emphasised that the presence of an amino group at the 5'-position facilitated the anhydro ring formation. This conclusion corroborated from the fact that compounds **19**

Scheme - 2·9



19 : R = Tr
20: R = H

21 : R = Tr
22 : R = H

and **20** (ref. 13) required 104h and 140h respectively to get converted to compounds **21** (ref. 19) and **22** (ref. 20) when treated with neat piperidine at room temperature (**Scheme-2.9**); DMST **7a** was converted to compound **8b** under identical conditions within 70h. Whether the

tertiary amino group present at the 5'-end of the intermediate (compound of the structure such as **16**) abstracted the N-3 proton intramolecularly or altered its pKa through intramolecular H-bonding or through-space interactions[21], remains to be established.

2.5. Conclusion

We have demonstrated that DMST **7a** reacted with secondary amines to generate a new class of aminonucleosides **8a-h**, ready to undergo further transformations to compounds **9-13**; most of the amines used, irrespective of their basicities showed remarkable selectivity towards the 5'-substitution over the 2,3'-O-anhydro ring formation.

2.6. Experimental:

Melting points were uncorrected. All amines were purchased from Aldrich, U.S.A. and were used without further purification. Thymidine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS, solvent chloroform-d or dioxane (in case of D_2O) as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

Synthesis of 3',5'-di-O-mesylthymidine (DMST) 7a:

Compound **7a** was synthesised using reported procedure[13].

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-morpholino- thymidine 8a:

DMST **7a** (1mmol) was reacted with neat morpholine (5ml) at room temperature for 20h and then at 60°C for 40h. The reaction mixture was poured into ether and filtered. The residue was washed thoroughly with ether and was purified by column chromatography on basic alumina to yield compound **8a**. This reaction could also be carried out directly at 50°C for 50h.

Yield : 80%

M.P : 229°C (decomp)

^{1}H-NMR : ($CDCl_3$): δ 7.06 (d, 1.0 Hz, 1H) H-6; 5.58 (d, 3.8 Hz, 1H) H-1'; 5.19 (bs, 1H) H-3'; 4.44-4.37 (Sept, 1H) H-4'; 3.67 (m, 4H) H_2C-O-CH_2; 2.8-2.43 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.92 (d, 3H) 5-CH_3.

^{13}C-NMR : (D_2O): δ 175.9, C-4; 156.1, C-2; 140.0, C-6; 118.8, C-5; 89.4, C-1'; 84.0, C-4'; 80.6, C-3'; 67.2, H_2C-O-CH_2; 59.1, C-5'; 54.3, H_2C-N-CH_2; 3.8, C-2'; 13.6, CH_3.

Mass (EI) : 293 (M^+, 2%); 100 (Morpholino+CH_2, 100%)

Synthesis of compound 8a from 3'-O-mesyl-5'-deoxy-5'-N-morpholino-thymidine 16:

A solution of compound **16** (1.5mmol) and DBU (1.65mmol) in dichloromethane (20ml) was stirred for 6h at room temperature. The solvent was then removed under reduced pressure and the residue was purified on basic alumina column. The product thus obtained was similar in every respect with compound **8a**.

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-piperidino-thymidine 8b:

DMST **7a** (1mmol) was reacted with neat piperidine (5ml) at 50°C for 50h. The product was isolated and purified as described in case of compound **8a**

Yield : 85%

M.P : 223°C (decomp)

^{1}H-NMR : ($CDCl_3$): δ 6.99 (d, 1.0 Hz, 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.14 (bs, 1H) H-3'; 4.4-4.33 (Sept, 1H) H-4'; 2.78-2.39 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.91 (d, 3H) 5-CH_3; 1.6-1.39 (m, 6H) H_2C-CH_2-CH_2

^{13}C-NMR : ($CDCl_3$+DMSO-d_6): δ 170.6, C-4; 152.5, C-2; 135.0, C-6; 116.0, C-5; 86.1, C-1'; 82.4, C-4'; 76.8, C-3'; 57.4, C-5'; 53.7, H_2C-N-CH_2; 32.3, C-2'; 24.5 and 22.6 H_2C-CH_2-CH_2; 11.9, CH_3.

Mass (EI) : 291 (M^+, 2%); 98 (piperidino+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-thiomorpholino-thymidine 8c:

DMST **7a** (1mmol) was reacted with neat thiomorpholine (3ml) at room temperature for 17h and at 50°C for 48h. The reaction mixture was poured in ether and filtered. Saturated sodium bicarbonate solution was added to the residue and the mixture was stirred for 30min. The compound was then extrated with dichloromethane (3x15ml). Dichloromethane fractions were pooled together, dried on sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on a basic alumina column.

Yield : 76%

M.P : 233°C

^{1}H-NMR : ($CDCl_3$): δ 7.0 (s, 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.17 (bs, 1H) H-3'; 4.4-4.32 (sex, 1H) H-4'; 2.83-2.41 (m, 12H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2, H_2C-S-CH_2; 1.94 (s, 3H) 5-CH_3.

^{13}C-NMR : (D_2O): δ 175.8, C-4; 156.0, C-2; 139.9, C-6; 118.8, C-5; 89.3, C-1'; 84.2, C-4'; 80.6, C-3'; 59.1, C-5'; 55.5, H_2C-N-CH_2; 33.8, C-2'; 27.3, H_2C-S-CH_2; 13.5, CH_3.

Mass (EI) : 309 (M^+, 5%); 116 (thiomorpholino+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-pyrrolidino-thymidine 8d:

DMST **7a** (1mmol) was reacted with neat pyrrolidine (5ml) at room temperature for 72h. The product was isolated and purified as described in case of compound **8a**

Yield : 93%

M.P : 215°C

^{1}H-NMR : (DMSO-d_6): δ 7.55 (s, 1H) H-6; 5.77 (d, 1H) H-1'; 5.2 (bs, 1H) H-3'; 4.3 (sex, 1H) H-4'; 2.8-2.3 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.75-1.5 (m, 7H) 5-CH_3, H_2C-CH_2

^{13}C-NMR : (DMSO-d_6+$CDCl_3$): δ 170.9, C-4; 153.5, C-2; 136.5, C-6; 115.8, C-5; 86.6, C-1'; 83.7, C-4'; 77.5, C-3'; 55.1, C-5'; 54.0, H_2C-N-CH_2; 32.7, C-2'; 23.1 H_2C-CH_2; 12.8, CH_3.

Mass (EI) : 246 (M^+, 3%); 84 (pyrrolidino+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-(1-methylpiperazino)-thymidine 8e:

DMST **7a** (1mmol) was reacted with neat 1-methylpiperizine (3ml) at room temperature for 34h and at 50°C for 24h. The product was isolated and purified as described in case of compound **8a**.

Yield : 62%

M.P : 238°C

^{1}H-NMR : ($CDCl_3$): δ 6.98 (s, 1H) H-6; 5.52 (d, 3.7 Hz, 1H) H-1'; 5.11 (bs, 1H) H-3'; 4.34 (Sept, 1H) H-4'; 2.77-2.36 (m, 12H) H-2', H-2'', H-5', H-5'', $(H_2C$-N-$CH_2)_2$; 2.22 (s, 3H) N-CH_3; 1.87 (s, 3H) 5-CH_3.

^{13}C-NMR : ($CDCl_3$): δ 171.6, C-4; 153.4, C-2; 135.3, C-6; 118.0, C-5; 87.5, C-1'; 83.6, C-4'; 77.5, C-3'; 57.7, C-5'; 54.7 and 53.5, $(H_2C$-N-$CH_2)_2$; 45.7, N-CH_3; 33.5, C-2'; 13.1, CH_3

Mass (EI) : 306 (M^+, 25%); 113 (1-Methylpiperazino+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-(1-acetylpiperazino)-thymidine 8f:

DMST **7a** (1mmol) was reacted with neat 1-acetylpiperazine (3ml) at room temperature for 96h and at 50°C for 48h. The product was isolated and purified as described in case of compound **8a**.

Yield : 70%

M.P : 256°C

^{1}H-NMR : ($CDCl_3$): δ 7.55 (s, 1H) H-6; 5.58 (d, 1H) H-1'; 5.22 (bs, 1H) H-3'; 4.37 (m, 1H) H-4'; 2.75-2.3 (m, 12H) H-2', H-2'', H-5', H-5'', $(H_2C\text{-}N\text{-}CH_2)_2$; 1.95 (s, 3H) $NC(O)CH_3$; 1.75 (s, 3H) 5-CH_3

^{13}C-NMR : (D_2O): δ 175.8, acetyl CO; 173.4, C-4; 156.1, C-2; 139.9, C-6; 118.7, C-5; 89.3, C-1'; 84.2, C-4'; 80.5, C-3'; 58.3, C-5'; 53.8, 53.4, 46.8 and 42.2, $(H_2C\text{-}N\text{-}CH_2)_2$; 33.7, C-2'; 21.3, acetyl CH_3; 13.4, CH_3.

Mass (EI) : 334 (M^+, 3%); 141 (1-Acetylpiperazino+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-(ethyl *iso*nipecotatyl)-thymidine 8g:

DMST **7a** (1mmol) was reacted with neat ethyl *iso*nipecotate (3ml) at room temperature for 48h. The reaction mixture was poured in ether and filtered. Saturated sodium bicarbonate solution was added to the residue and the mixture was stirred for 30min. The compound was then extrated with dichloromethane (3x15ml). Dichloromethane fractions were pooled together, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column.

Yield : 66%

M.P : 230°C

^{1}H-NMR : ($CDCl_3$): δ 7.0 (d, 0.9 Hz 1H) H-6; 5.52 (d, 3.8 Hz, 1H) H-1'; 5.17 (bs, 1H) H-3'; 4.38 (Sept, 1H) H-4'; 4.13 (q, 2H) ethyl CH_2; 2.95-1.65 (m, 16H) H-2', H-2'', H-5', H-5'', $HC(H_2C\text{-}N\text{-}CH_2)_2$, 5-$CH_3$; 1.25 (t, 3H) ethyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 174.6, ester CO; 171.7, C-4; 153.4, C-2; 135.5, C-6; 117.7, C-5; 87.4, C-1'; 83.7, C-4'; 77.5, C-3'; 59.9 ethyl CH_2; 57.9, C-5'; 53.28 and 53.19, $H_2C\text{-}N\text{-}CH_2$; 40.4 and 27.9 $H_2C\text{-}CH\text{-}CH_2$; 33.4, C-2'; 13.9, ethyl CH_3; 12.9, CH_3

Mass (EI) : 363 (M^+, 3%); 170 (Ethylisonipecotatyl+CH_2, 100%)

Synthesis of 2,3'-O-anhydro-5'-deoxy-5'-N-diethylamino-thymidine 8h:

DMST **7a** (1mmol) was reacted with diethylamine (3ml) in DMF (2ml) at room temperature for 100h. The precipitate formed was filtered and it was found to be compound **17**. The filtrate was evaporated to dryness and was purified on a basic alumina column to produce the title compound.

Yield : 55%

M.P : 191°C

^{1}H-NMR : ($CDCl_3$): δ 6.97 (d, 1.1 Hz, 1H) H-6; 5.5 (d, 3.8 Hz, 1H) H-1'; 5.15 (bs, 1H) H-3'; 4.31-4.24 (sex, 1H) H-4'; 2.9-2.4 (m, 8H) H-2', H-2'', H-5', H-5'', $H_2C\text{-}N\text{-}CH_2$; 1.91 (d, 3H) 5-$CH_3$; 0.97 (t, 6H) ethyl $(CH_3)_2$.

^{13}C-NMR : ($CDCl_3$): δ 172.0, C-4; 153.7, C-2; 135.8, C-6; 117.9, C-5; 87.6, C-1'; 84.9, C-4'; 77.6, C-3'; 53.1, C-5'; 47.5, $H_2C\text{-}N\text{-}CH_2$; 33.7, C-2'; 13.3, CH_3; 11.7, ethyl $(CH_3)_2$

Mass (EI) : 279 (M^+, 1%); 86 (diethylamino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-3'-azido-5'-N-morpholino-thymidine 9a:

A mixture of compound **8a** (1mmol) and lithium azide (3mmol) in DMF (5ml) was heated at 140°C. After 4h the mixture was cooled and poured in water (10ml). The aqueous solution was extracted with ethyl acetate (3x15ml). Organic layers were pooled together and washed with water (3x10ml). Ethyl acetate solution was dried on sodium sulphate and filtered. The filtrate was evaporated to dryness. The white foam thus obtained, was purified on basic alumina column.

Yield : 62%

M.P : hygroscopic foam

I.R : $2100Cm^{-1}$

^{1}H-NMR : ($CDCl_3$): δ 9.87 (bs, 1H) H-3; 7.18 (s, 1H) H-6; 6.06 (t, 6.0 Hz and 6.7 Hz, 1H) H-1'; 4.12 (m, 1H) H-3'; 3.98 (m, 1H) H-4'; 3.76 (t, 4H) H_2C-O-CH_2; 2.83-2.32 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.95 (s, 3H) CH_3

^{13}C-NMR : ($CDCl_3$): δ 163.8, C-4; 150.4, C-2; 135.9, C-6; 111.6, C-5; 85.9/82.2, C-1'/C-4'; 67.1, H_2C-O-CH_2; 62.5, C-3'; 60.8, C-5'; 54.9, H_2C-N-CH_2; 37.5, C-2'; 12.7, CH_3.

Mass (EI) : 294 (M^+-N_3, 3%); 100 (morpholino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-3'-azido-5'-N-piperidino-thymidine 9b:

A mixture of compound **8b** (1mmol) and lithium azide (3mmol) in DMF (5ml) was heated at 140°C for 4h. The product was isolated and purified as described in case of compound **9a**

Yield : 70%

M.P : hygroscopic foam

I.R : $2100cm^{-1}$

^{1}H-NMR : ($CDCl_3$): δ 7.25 (s, 1H) H-6; 6.05 (t, 6.0 Hz and 6.7 Hz, 1H) H-1'; 4.11 (m, 1H) H-3'; 2.91 - 2.35 (m, 8H) H-4', H_2C-N-CH_2; H-2', H-2", H-5', H-5" ; 1.93 (s, 3H) CH_3; 1.71 - 1.14, H_2C-CH_2-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 164.4, C-4; 150.6, C-2; 136.2, C-6; 111.2, C-5; 85.6/81.3, C-1'/C-4'; 62.14, C-3'; 60.21, C-5'; 55.2, H_2C-N-CH_2; 37.0, C-2'; 25.2 and 23.6, H_2C-CH_2-CH_2; 12.5, CH_3.

Mass (EI) : 292 (M^+-N_3, 10%); 98 (morpholino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-3'-thiophenyl-5'-N-morpholino-thymidine 10a:

A mixture of compound **8a** (1mmol) and sodium thiophenolate (5mmol) in DMF (5ml) was heated at 60°C. After 16h the mixture was cooled and poured in water (10ml). The aqueous solution was extracted with dichloromethane (3x15ml). Organic layers were pooled together and washed with water (3x10ml). Dichloromethane solution was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column.

Yield : 54%

M.P : 43°C

^{1}H-NMR : ($CDCl_3$): δ 9.55 (bs, 1H) H-3; 7.51-7.25 (m, 6H) aromatic, H-6; 6.11 (dd, 6.7 Hz and 5.2 Hz, 1H) H-1'; 4.03 (m, 1H) H-4'; 3.72 (t, 4H) H_2C-O-CH_2; 3.54 (m, 1H) H-3'; 2.67-2.64 (m, 2H) and 2.61-2.40 (m, 6H) H-2', H-2", H-5', H-5", H_2C-N-CH_2; 1.95 (d, 1.2 Hz, 3H) CH_3

^{13}C-NMR : ($CDCl_3$): δ 164.1, C-4; 150.5, C-2; 135.6, C-6; 133.3, 133.0, 129.5, 128.4, aromatic; 111.2, C-5; 85.1/83.0, C-1'/C-4'; 66.9, H_2C-O-CH_2; 60.6, C-5'; 54.6, H_2C-N-CH_2; 46.9, C-3'; 39.3, C-2'; 12.8, CH_3.

Mass (EI) : 403(M^+, 10%); 294 (M^+-SPh, 20%); 100 (morpholino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-3'-thiophenyl-5'-N-piperidino-thymidine 10b:

A mixture of compound **8b** (1mmol) and sodium thiophenolate (5mmol) in DMF (5ml) was heated at 60°C for 16h. The product was isolated and purified as described in case of compound **10a**.

Yield : 65%

M.P : 65°C

^{1}H-NMR : ($CDCl_3$): δ 10.1 (bs, 1H) H-3; 7.61-7.30 (m, 6H) aromatic, H-6; 6.15 (t, 1H) H-1'; 4.05 (m, 1H) H-4'; 3.51 (m, 1H) H-3'; 2.82 - 2.3 (m, 8H) H_2C-N-CH_2, H-2', H-2'', H-5', H-5''; 1.93 (s, 3H) CH_3; 1.62 - 1.3 (m, 6H) H_2C-CH_2-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 164.4, C-4; 150.5, C-2; 135.5, C-6; 132.8, 132.6, 129.06, 127.76, aromatic; 110.7, C-5; 84.5/82.2, C-1'/C-4'; 60.29, C-5'; 54.97, H_2C-N-CH_2; 46.43, C-3'; 39.04, C-2'; 25.36 and 23.76, H_2C-CH_2-CH_2; 12.5, CH_3.

Mass (EI) : 98 (piperidino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-2'-ene-5'-N-morpholino-thymidine 11a:

A mixture of compound **8a** (1mmol) and potassium *tert*butoxide (2.2mmol) in DMSO (5ml) was stirred at room temperature. After 1h the mixture was poured in water (10ml). The aqueous solution was extracted with dichloromethane (3x15ml). Organic layers were pooled together

and washed with water (3x10ml). Dichloromethane solution was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified on basic alumina column.

Yield : 81%

M.P : 125°C

^{1}H-NMR : ($CDCl_3$): δ 7.15 (s, 1H) H-6; 7.02 (m, 1H) H-1'; 6.32 (m, 1H) H-3'; 5.82 (m, 1H) H-2'; 5.03 (m, 1H) H-4'; 3.74 (t, 4H) H_2C-O-CH_2; 2.63 (m, 6H) H-5', H-5'', H_2C-N-CH_2; 1.92 (d, 3H) CH_3.

^{13}C-NMR : ($CDCl_3$): δ 164.3, C-4; 151.0, C-2; 135.63/ 135.58, C-6/C-3'; 125.9, C-2'; 111.1 C-5; 90.1, C-1'; 84.0, C-4'; 66.6, H_2C-O-CH_2; 62.8, C-5'; 54.1, H_2C-N-CH_2; 12.6, CH_3

Mass (EI) : 206 (M^+-morpholino, 2%); 100 (morpholino+CH_2, 100%)

Synthesis of 3',5'-dideoxy-2'-ene-5'-N-piperidino-thymidine 11b:

A mixture of compound **8b** (1mmol) and potassium *tert*butoxide (2.2mmol) in DMSO (5ml) was stirred at room temperature for 1h. The product was isolated and purified as described in case of compound **11a**.

Yield : 70%

M.P : 120°C

^{1}H-NMR : ($CDCl_3$): δ 7.21 (s, 1H) H-6; 7.0 (m, 1H) H-1'; 6.35 (m, 1H) H-3'; 5.82 (m, 1H) H-2'; 5.01 (m, 1H) H-4'; 2.8 - 2.4 (m, 6H) H_2C-N-CH_2, H-5',H-5''; 1.92 (d, 3H) CH_3, 1.71 - 1.4 (m, 6H) H_2C-CH_2-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 164.3, C-4; 150.9, C-2; 135.65/135.45, C-6/C-3'; 125.3, C-2'; 110.6, C-5; 89.7, C-1'; 83.9, C-4'; 62.5, C-5'; 54.55, H_2C-N-CH_2; 25.66 and 23.6, H_2C-CH_2-CH_2; 12.17, CH_3

Mass (EI) : 206 (M^+-piperidino, 4%); 98 (piperidino+CH_2, 100%)

Synthesis of 1-(2,5-dideoxy-5-morpholino-3-O-acetyl-β-D-*threo*-pentofuranosyl)-thymine 13a:

Compound **8a** (1mmol) was reacted with aqueous sodium hydroxide solution (0.1N, 3ml) at room temperature. After 3h, the reaction mixture was neutralised with aqueous hydrochloric acid solution (0.1N). The solution was evaporated to dryness and the residual water was removed by coevaporation with pyridine (3x5ml). The residue was redissolved in pyridine (5ml) and acetic anhydride (5mmol) was added. After 2h the reaction mixture was poured into saturated sodium bicarbonate solution (15ml) and was extracted with dichloromethane (3x15ml). Dichloromethane solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained, was purified on a silica gel column.

Yield : 73%

M.P : 95°C

^{1}H-NMR : ($CDCl_3$): δ 7.43 (s, 1H) H-6; 6.26 (dd, 2.9 Hz and 8.0 Hz, 1H) H-1'; 5.41 (m, 1H) H-3'; 4.21 (m, 1H) H-4'; 3.75 (t, 4H) H_2C-O-CH_2; 2.85 - 2.49 (m, 7H) and 2.09 - 1.96 (m, 1H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 2.11 (s, 3H) acetate CH_3; 1.96 (s, 3H) CH_3

^{13}C-NMR : ($CDCl_3$): δ 169.1, acetyl CO; 163.6, C-4; 150.4, C-2; 135.1, C-6; 110.4, C-5; 83.7/79.9, C-1'/C-4'; 72.9, C-3'; 66.5, H_2C-O-CH_2; 57.1, C-5'; 53.9, H_2C-N-CH_2; 39.3, C-2'; 20.5, acetate CH_3; 12.4, CH_3.

Mass (EI) : 227 (M^+-thymine, 2%); 168 (M^+-thymine-OAc, 3%); 126 (thymine, 5%); 100 (morpholine+CH_2, 100%)

Synthesis of 1-(2,5-dideoxy-5-piperidino-3-O-acetyl-β-D-*threo*-pentofuranosyl)-thymine 13b:

Compound **8b** (1mmol) was reacted with aqueous sodium hydroxide solution (0.1N, 3ml) at room temperature. After 3h, the reaction mixture was neutralised with aqueous hydrochloric acid solution (0.1N). The product was acetylated and purified as described in case of compound **13a**.

Yield : 70%

M.P : 102°C

^{1}H-NMR : ($CDCl_3$): δ 7.45 (s, 1H) H-6; 6.25 (m, 1H) H-1'; 5.41 (m, 1H) H-3'; 4.32 (m, 1H) H-4'; 2.89 - 2.49 (m, 7H) and 2.09 - 1.96 (m, 1H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 2.11 (s, 3H) acetate CH_3; 1.81-1.42 (m, 6H) H_2C-CH_2-CH_2; 1.96 (s, 3H) CH_3

^{13}C-NMR : ($CDCl_3$): δ 169.3, acetyl CO; 164.2, C-4; 150.6, C-2; 135.4, C-6; 110.5, C-5; 83.9/79.2, C-1'/C-4'; 73.4, C-3'; 57.0, C-5'; 54.5, H_2C-N-CH_2; 39.3, C-2'; 30.6 and 24.7, H_2C-CH_2-CH_2; 20.8, acetate CH_3; 12.6, CH_3.

Mass (EI) : 292 (M^+-OAc, 10%); 98 (piperidino+CH_2, 100%)

Synthesis of 5'-O-tosylthymidine 14:

Compound **14** was synthesised using reported procedure[16].

Synthesis of 3'-O-Mesyl-5'-deoxy-5'-N-morpholino-thymidine 16:

5'-O-Tosylthymidine **14** (2mmol) was reacted with morpholine (neat, 5ml) at room

temperature. After 4d, the amine was removed under reduced pressure. The residue was passed through a basic alumina column. The appropriate fractions were collected and solvent was evaporated. The residue was dried by coevaporation with pyridine and was redissolved in the same solvent (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (10mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the solution was left at +4°C overnight. The mixture was then poured in saturated sodium bicarbonate solution (30ml) and was extracted with dichloromethane (3x20ml). Dichloromethane solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained, was purified on a silica gel column.

Yield : 88%

M.P : 130°C

^{1}H-NMR : ($CDCl_3$): δ 9.49 (bs, 1H) N-H; 7.21 (d, 0.9 Hz, 1H) H-6; 6.18 (t, 6.8 Hz, 1H) H-1'; 5.24 (m, 1H) H-3'; 4.31 (dd, 1H) H-4'; 3.75 (m, 4H) H_2C-O-CH_2; 3.14 (s, 3H) SO_2CH_3; 2.75-2.35 (m, 8H) H-2', H-2'', H-5', H-5'', H_2C-N-CH_2; 1.95 (d, 3H) 5-CH_3.

^{13}C-NMR : ($CDCl_3$): δ 164.1, C-4; 150.6, C-2; 135.6, C-6; 111.6, C-5; 85.6, C-1'; 81.5, C-4'; 79.9, C-3'; 66.9, H_2C-O-CH_2; 59.7, C-5'; 54.4, H_2C-N-CH_2; 38.6, SO_2CH_3; 37.5, C-2'; 12.7, 5-CH_3.

2.7. References

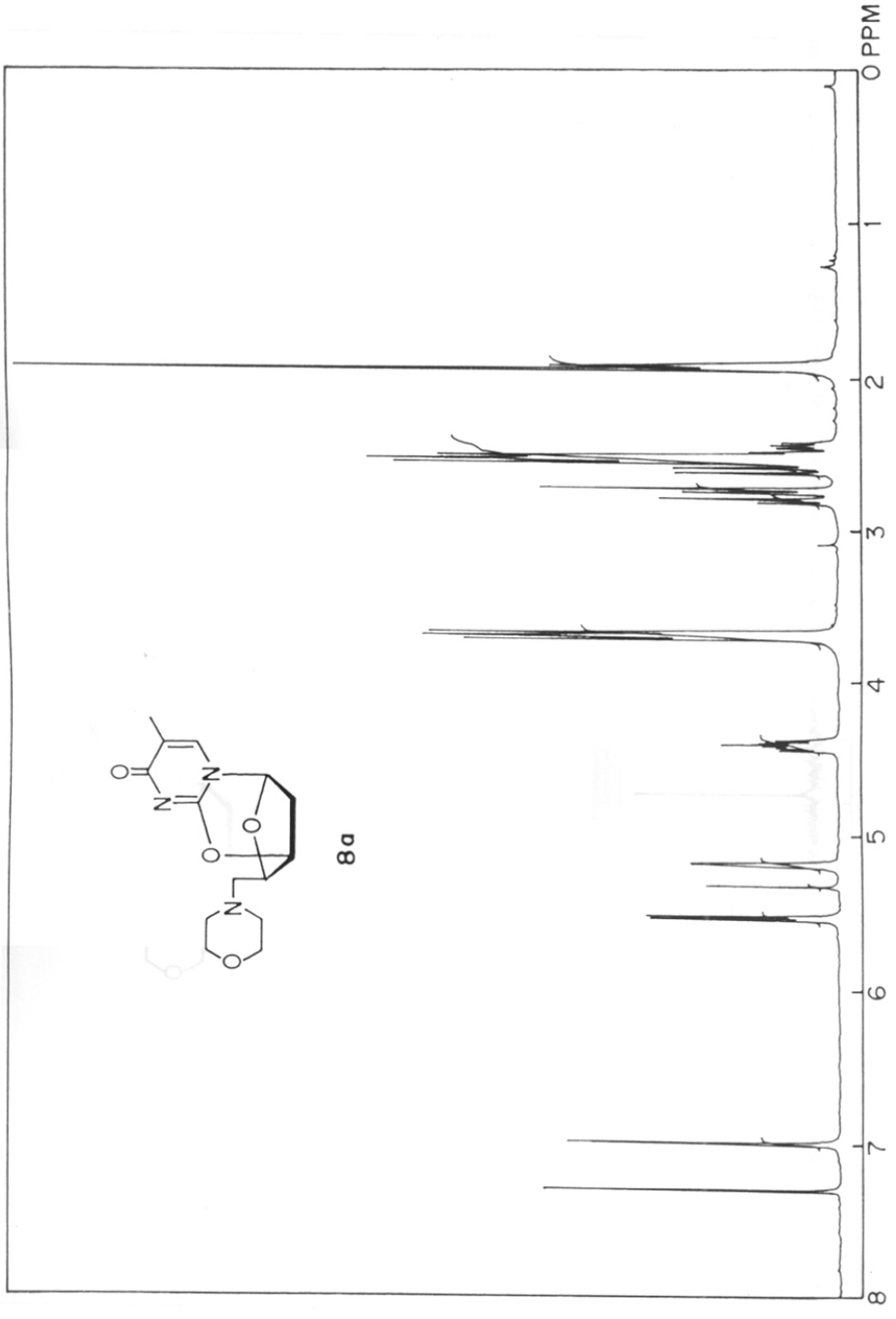
1. Mitsuya, H.; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Nusinoff-Lehrman, S.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S. *Proc. Natl. Acad. Sci. USA,* **1985**, 82, 7096-100.
2. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA,* **1986**, 83, 1911-5.
3. Balzarini, J.; Kang, G.-J.; Dalal, M.; Heredewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G.; *Mol. Pharmacol.,* **1987**, 32, 162-7
4. Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N.; *Antimicrob. Agents Chemother.,* **1987**, 31, 907-10.
5. For a review, see: Huryn, D.M.; Okabe, M. *Chem. Rev.* **1992**, 92, 1745-68 and the references cited therein.
6. Reynolds, R. C.; Crooks, P. A.; Parker, W. B.; Maddry, J. A.; Montgomery, J. A.; Secrist III, J. A.; *J. Biopharm. Sci.,* **1991**, 2, 195-203.
7. Review: a) De Clercq, E. *Antiviral Res.*, **1989**, 12, 1-20. b) De Clercq, E. *Aids Research and Human Retroviruses*, **1992**, 8, 119-34.
8. Tanaka, H.; Baba, M.; Saito, S.; Miyasaka, T.; Takashima, H.; Sekiya, K.; Ubasawa, M.; Nitta, I.; Walker, R.T.; Nakashima, H.; De Clercq, E. *J. Med. Chem.*, **1991**, 34, 1508-11.
9. Balzarini, J.; Perez-Perez, M-J.; San-Felix, A.; Schols, D.; Perno, C-F.; Vandamme, A-M.; Camarasa, M-J.; De Clercq, E. *Proc. Natl. Acad. Sci., USA*, **1992**, 89, 4392-6.
10. Hiebl, J.; Zbrial, E.; Balzarini, J.; De Clercq, E. *J. Med. Chem.*, **1991**, 34, 1426-30.
11. Crooks, P.A.; Reynolds, R.C.; Maddry, J.A.; Rathore, A.; Akhtar, M.S.; Montgomery, J.A.; Secrist III, J. A. *J. Org. Chem.*, **1992**, 57, 2830-5.
12. Reynolds, R. C.; Crooks, P. A.; Parker, W. B.; Maddry, J. A.; Montgomery, J. A.; Secrist III, J. A.; *J. Biopharm. Sci.,* **1991**, 2, 195-203.
13. Michelson, A.M.; Todd, A.R. *J. Chem. Soc.*, **1955**, 816-23.
14. Fox, J. J.; *Pure Appl. Chem;* **1969**, 18, 223-55.
15. a) Moffatt, J. G.; *In nucleoside Anologues: Chemistry, Biology And Medical Applications.;* Walker, R.T.; De Clercq, E.; Ecstein, F.; Eds.; Plenum Press, Newyork, **1979**, 71-164. b) Schreiber, S. L.; Ikemoto, N.; *Tetrahedron. Lett.*, **1988**, 26, 3211-4.
16. Elliott, R.D.; Pruett, P.S.; Brocman, R. W.; Montgomery, J. A.; *J. Med. Chem.;* **1987**, 30, 927-30.
17. Elliott, R.D.; Montgomery, J.A.; Riordan, J.M. *J. Org. Chem.*, **1987**, 52, 2892-6.

18. *The Chemist's Companion, A Handbook of Practical Data, Techniques and References*; Gordon, A.J.; Ford, R.A. Eds; John Wiley & Sons, New York, **1972**, pp 59-60.

19. Secrist III, J. A.; *Carbohydr. Res.*, **1975**, 42, 379-81.

20. Sudhakar, Rao; Reese, C.B.; *J. Chem. Soc. Chem. Commun.*, **1989**, 997-8.

21. Principles of Nucleic acid structure; Saenger, W.; Speringer Verlag, New York, 1983, pp. 108.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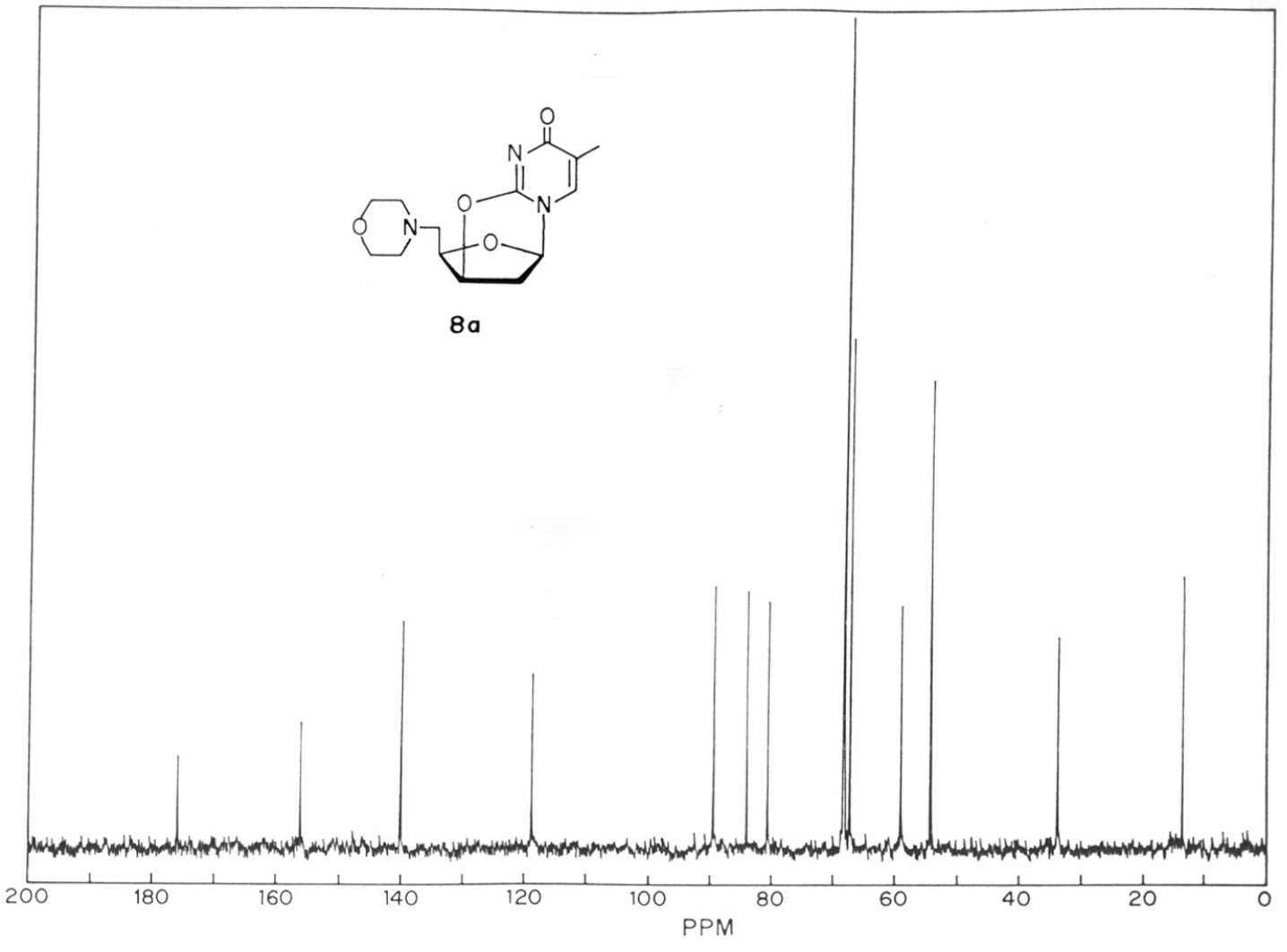

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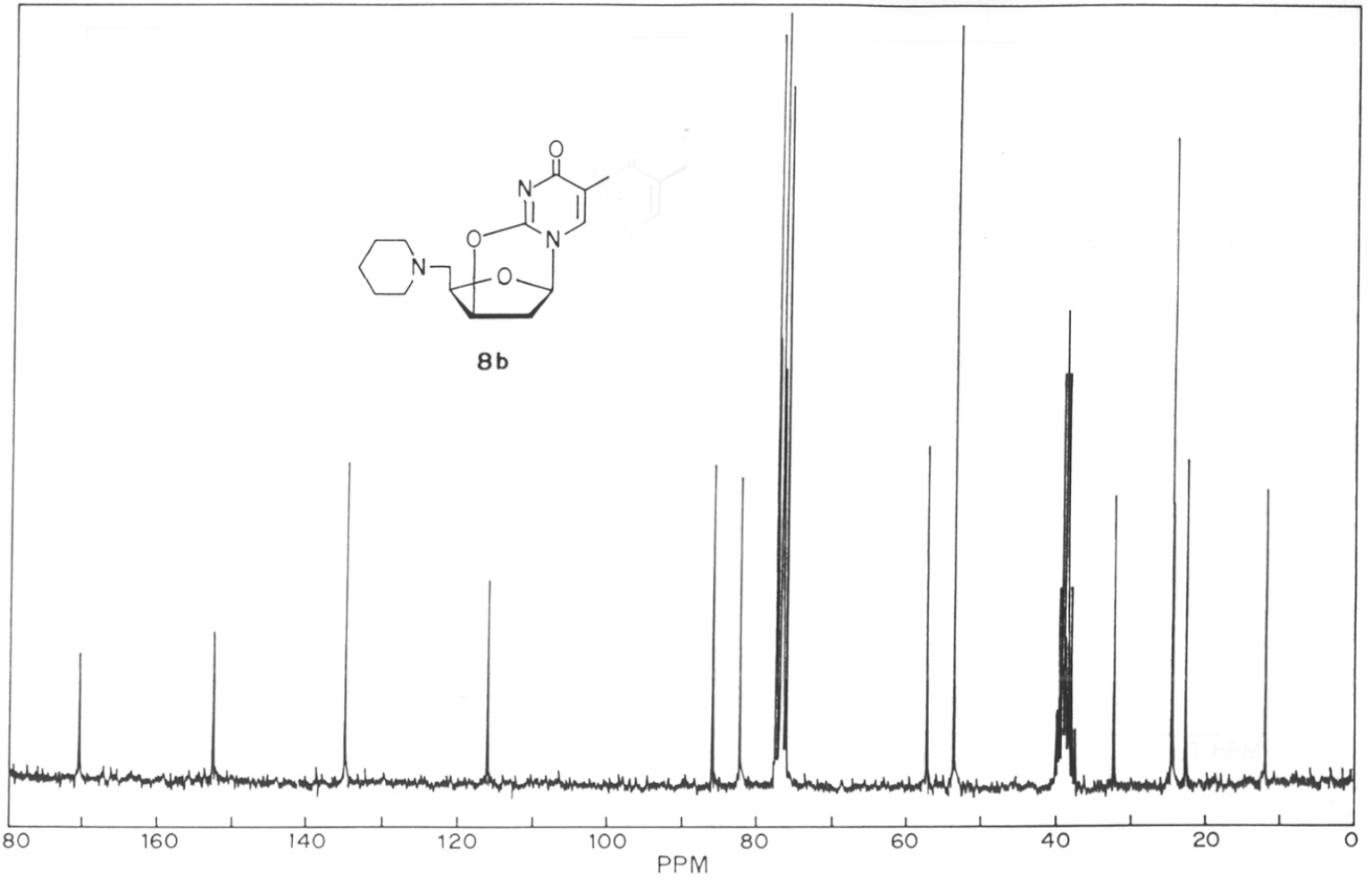

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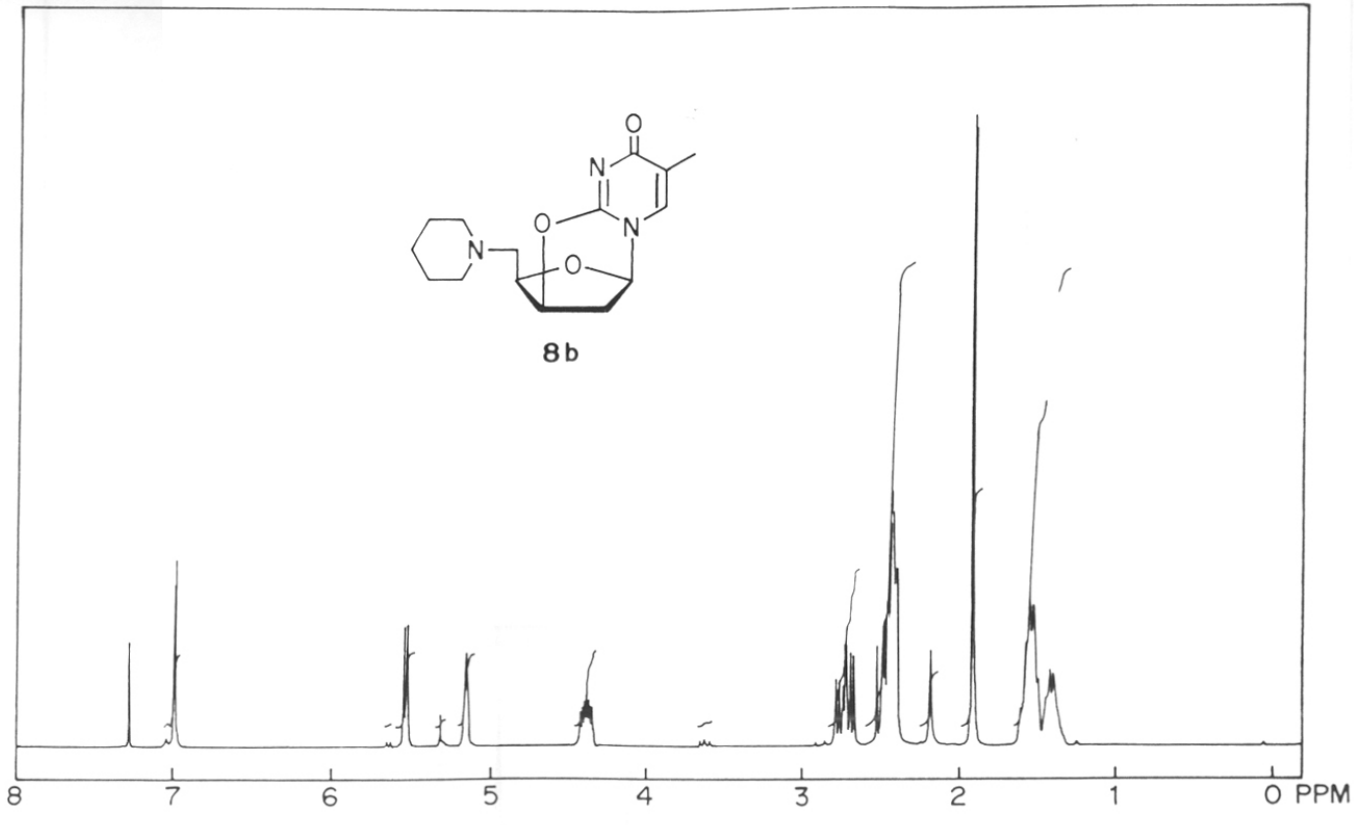

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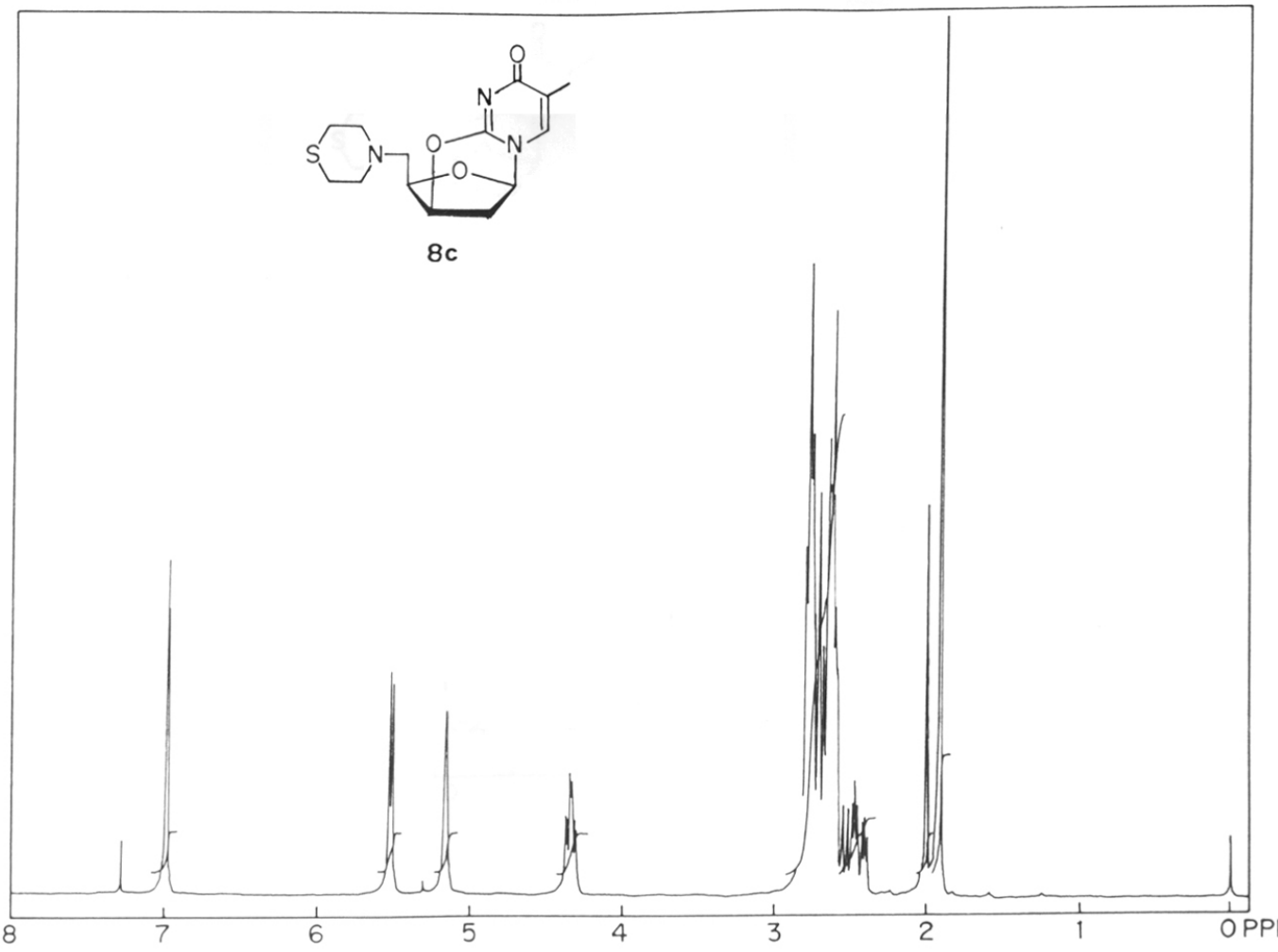

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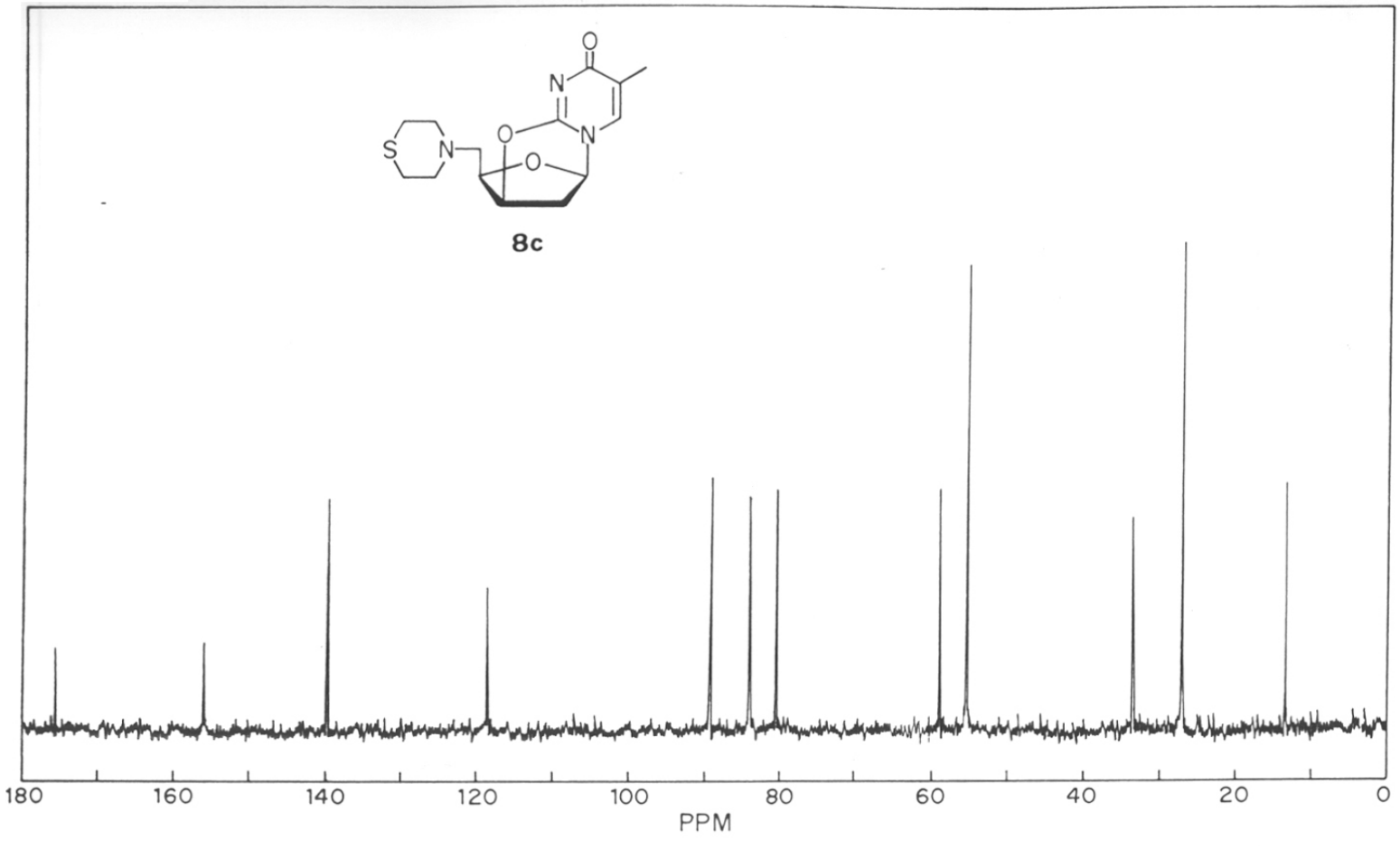

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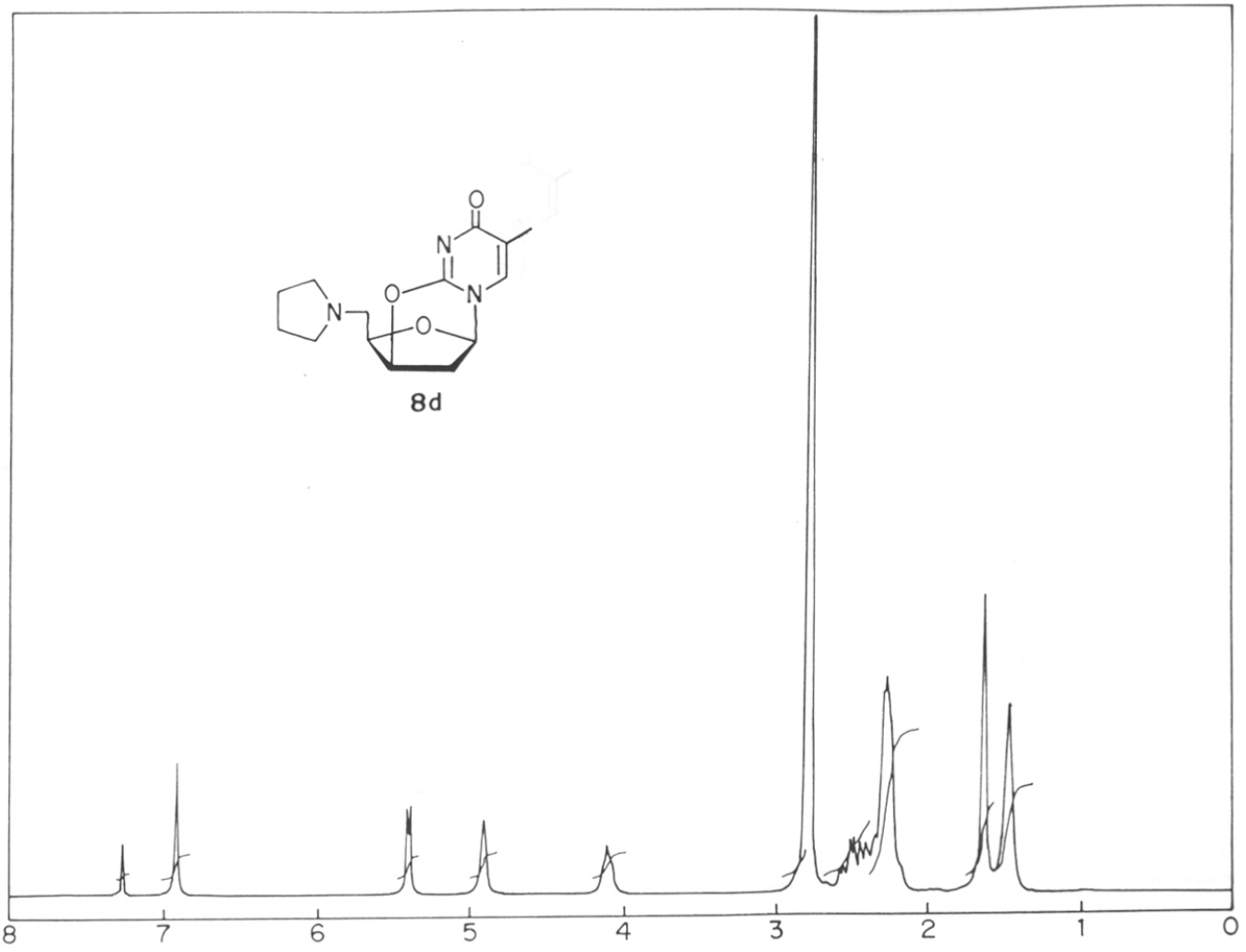

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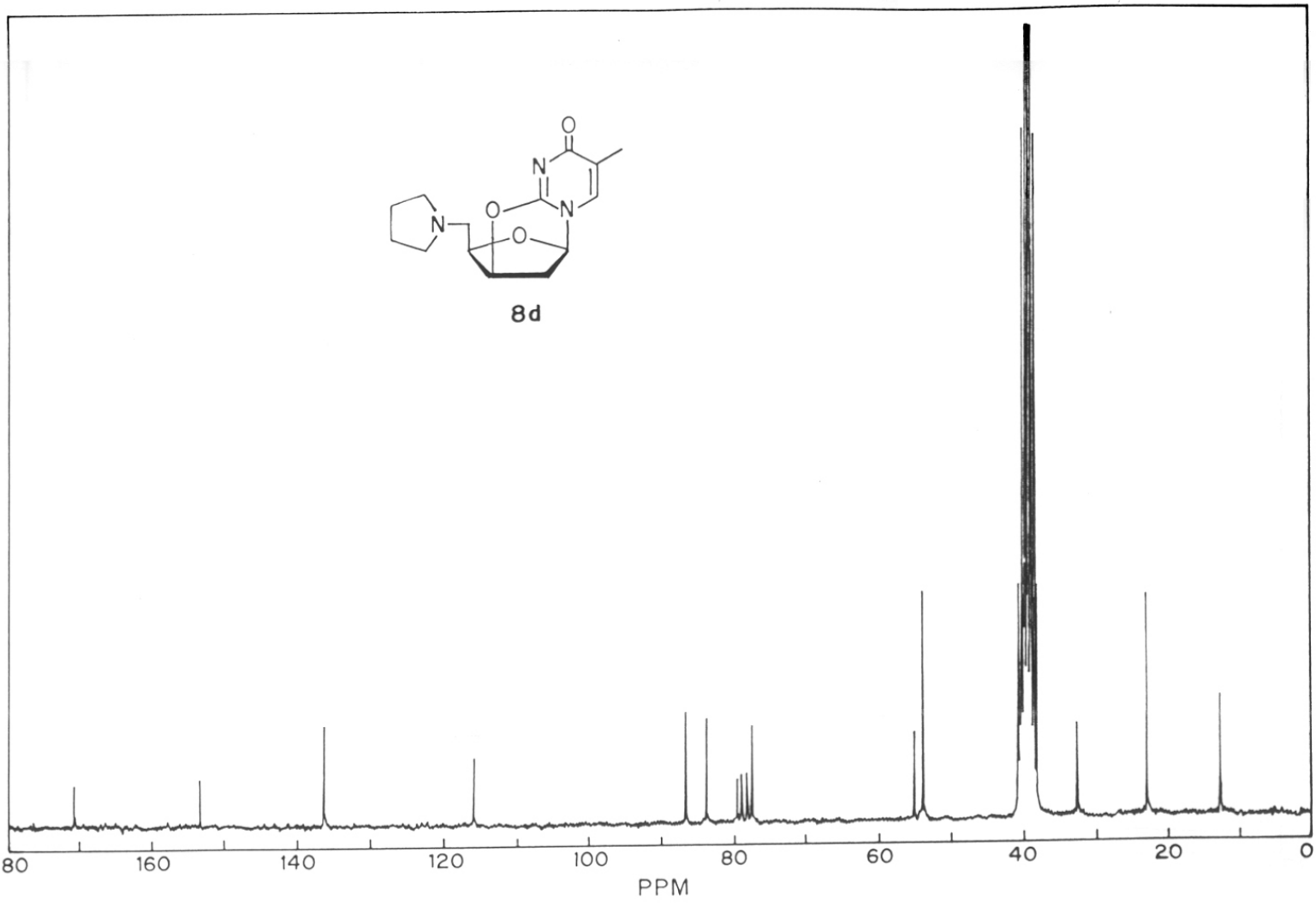

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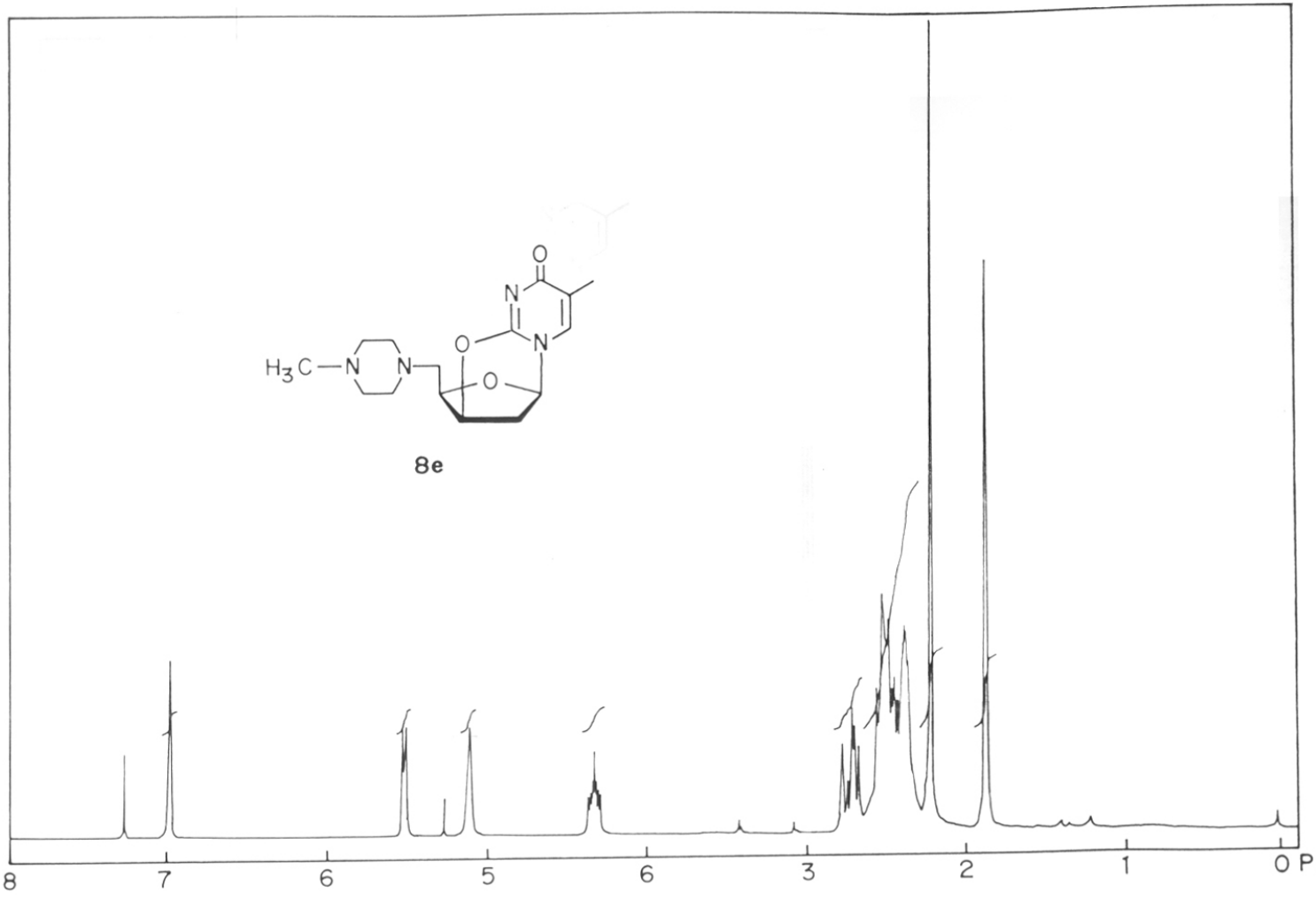

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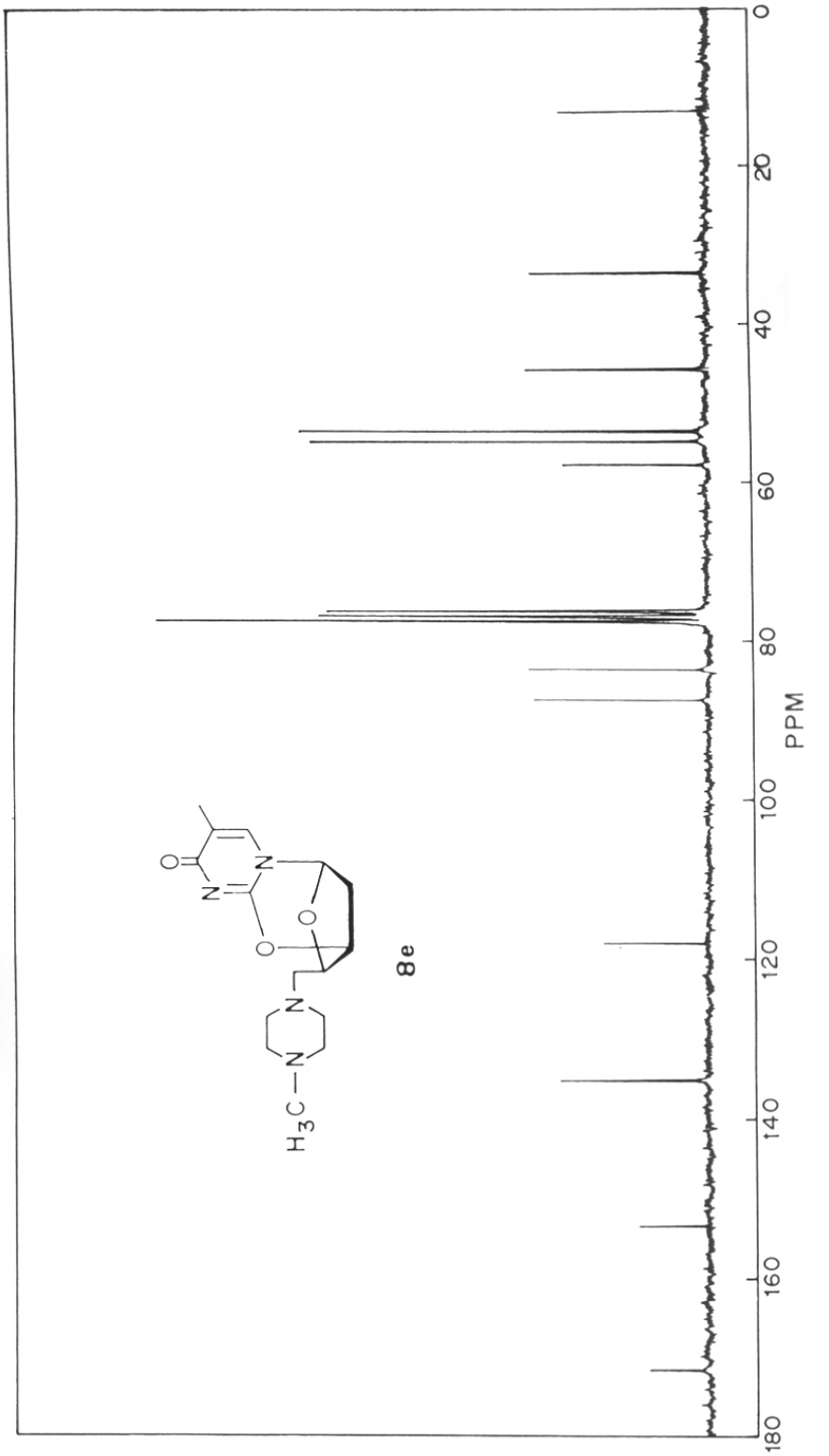

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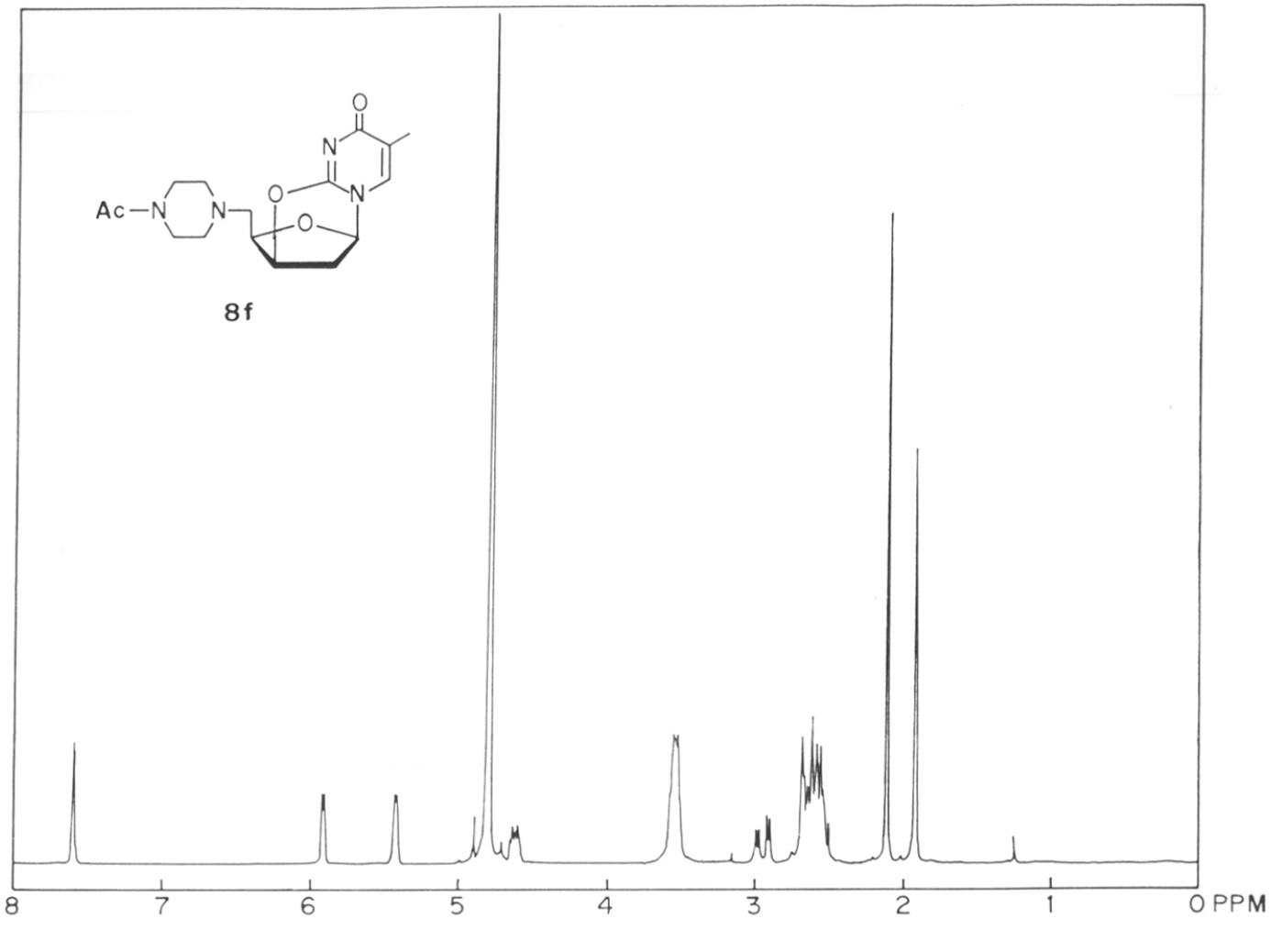

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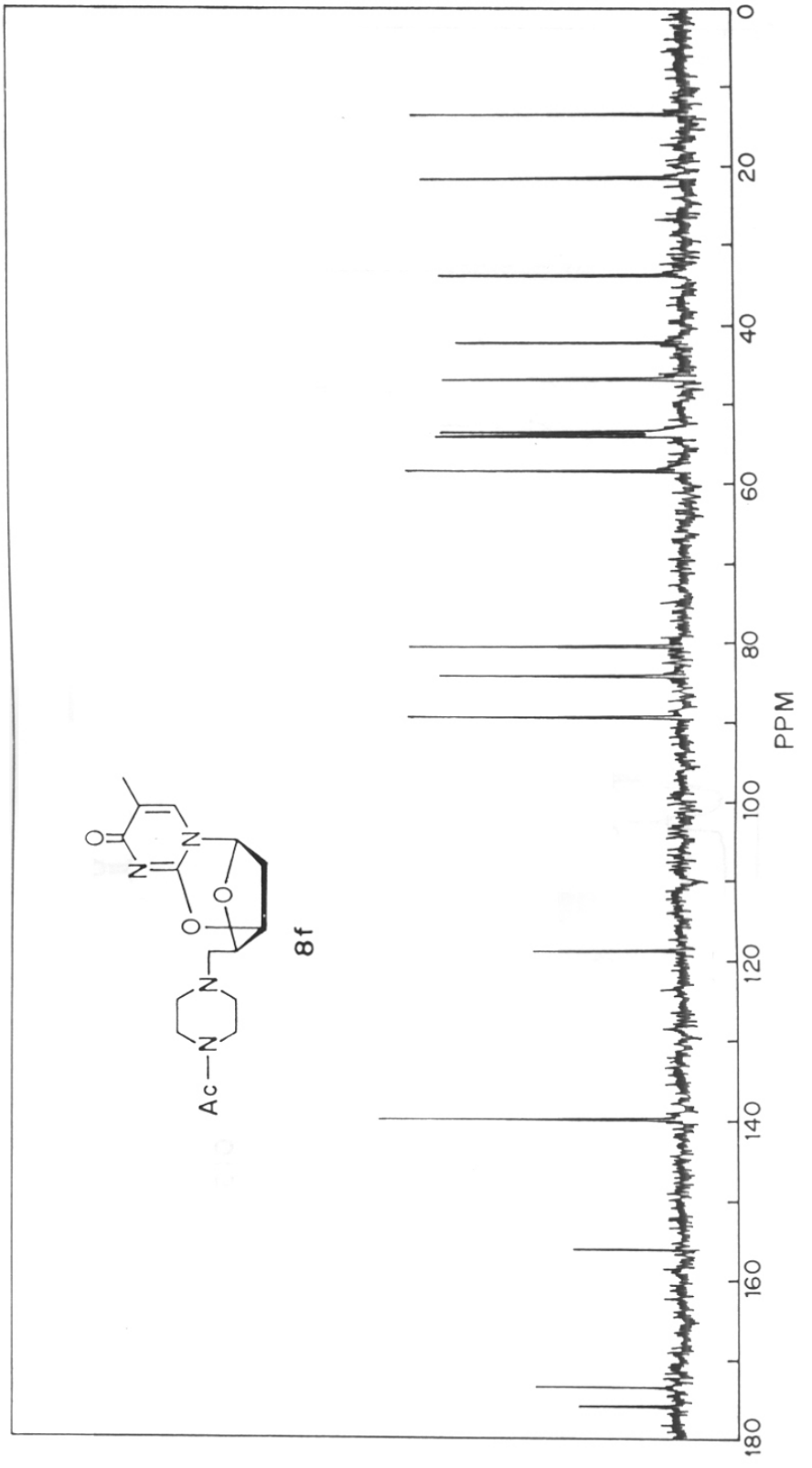

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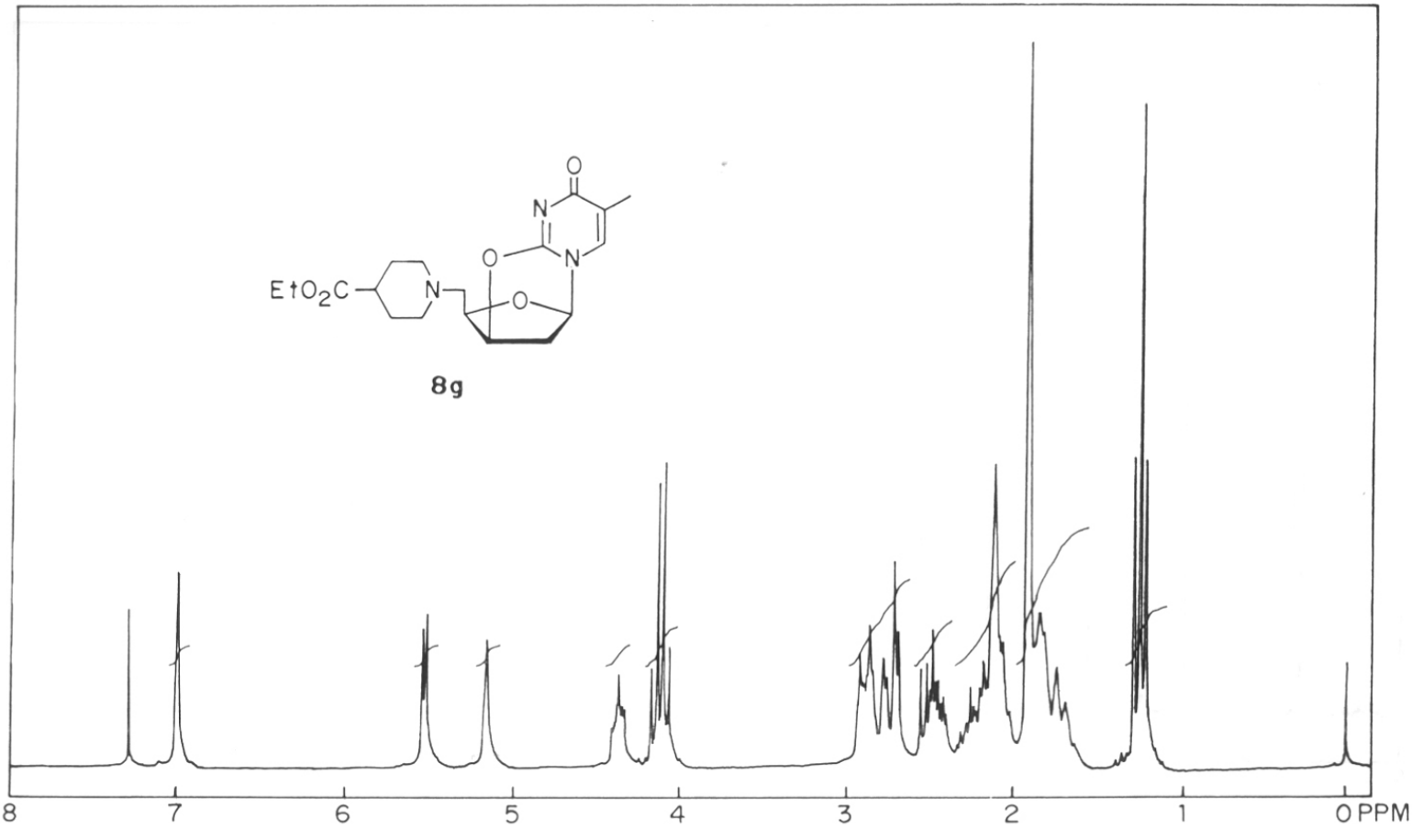

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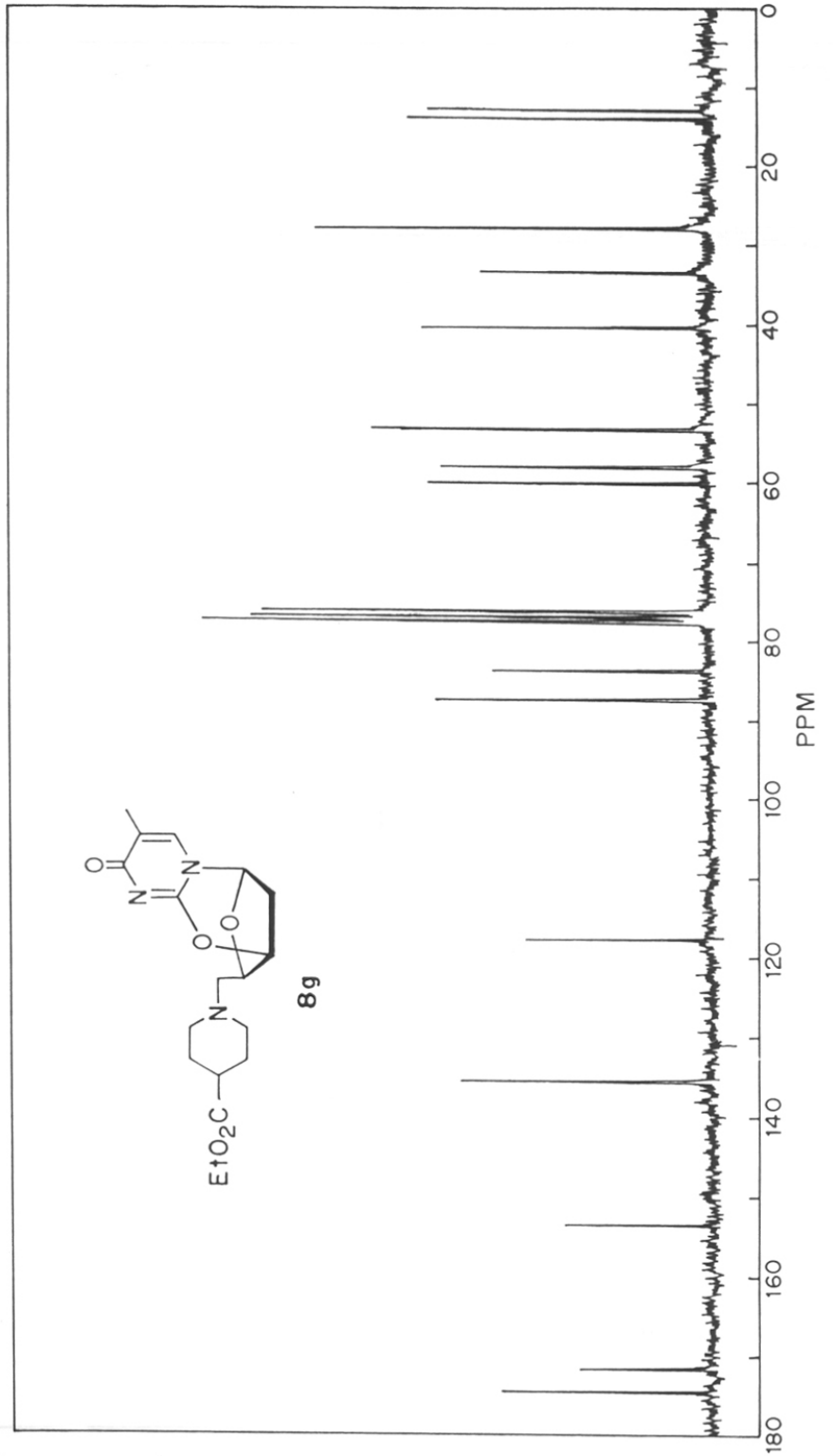

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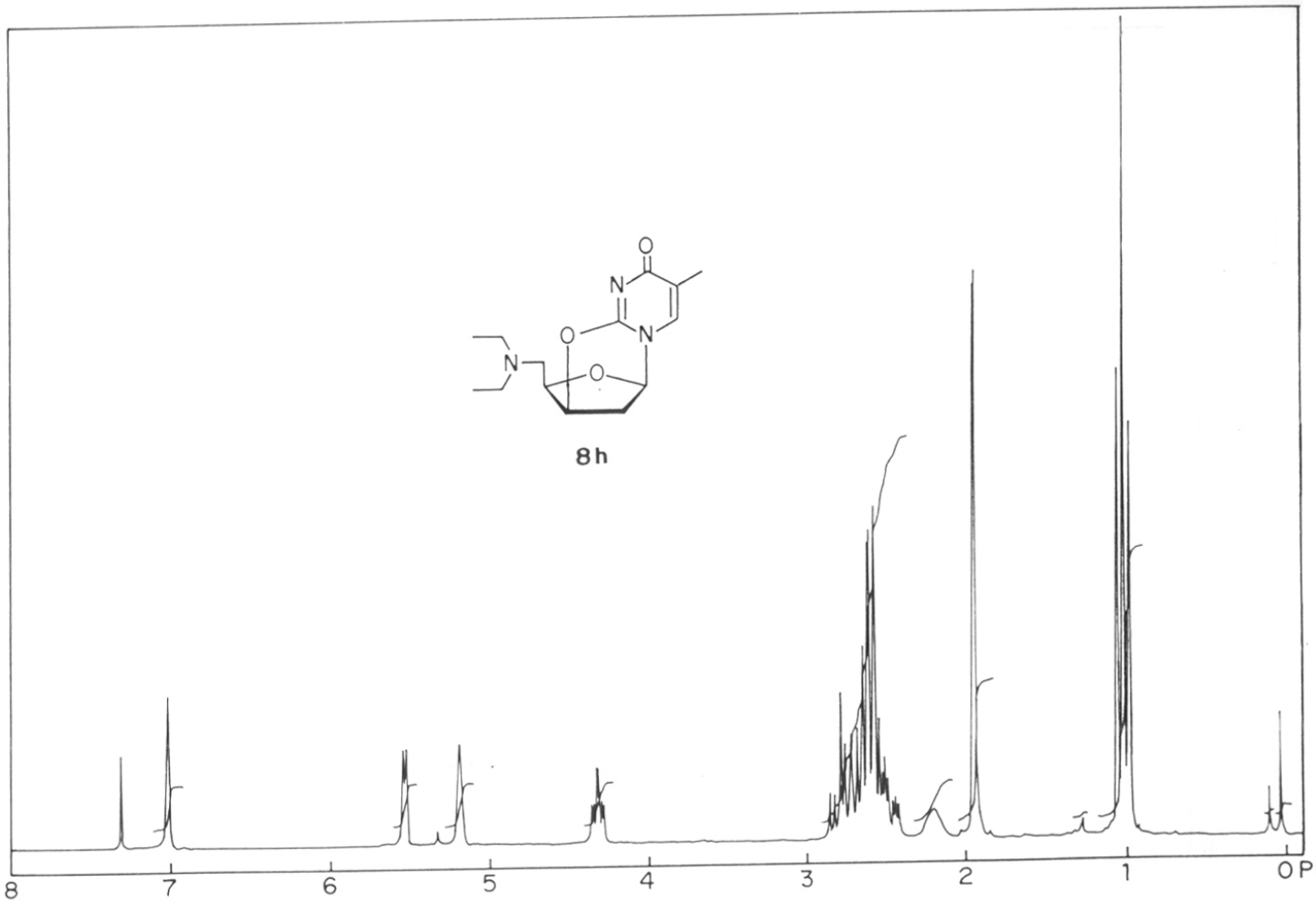

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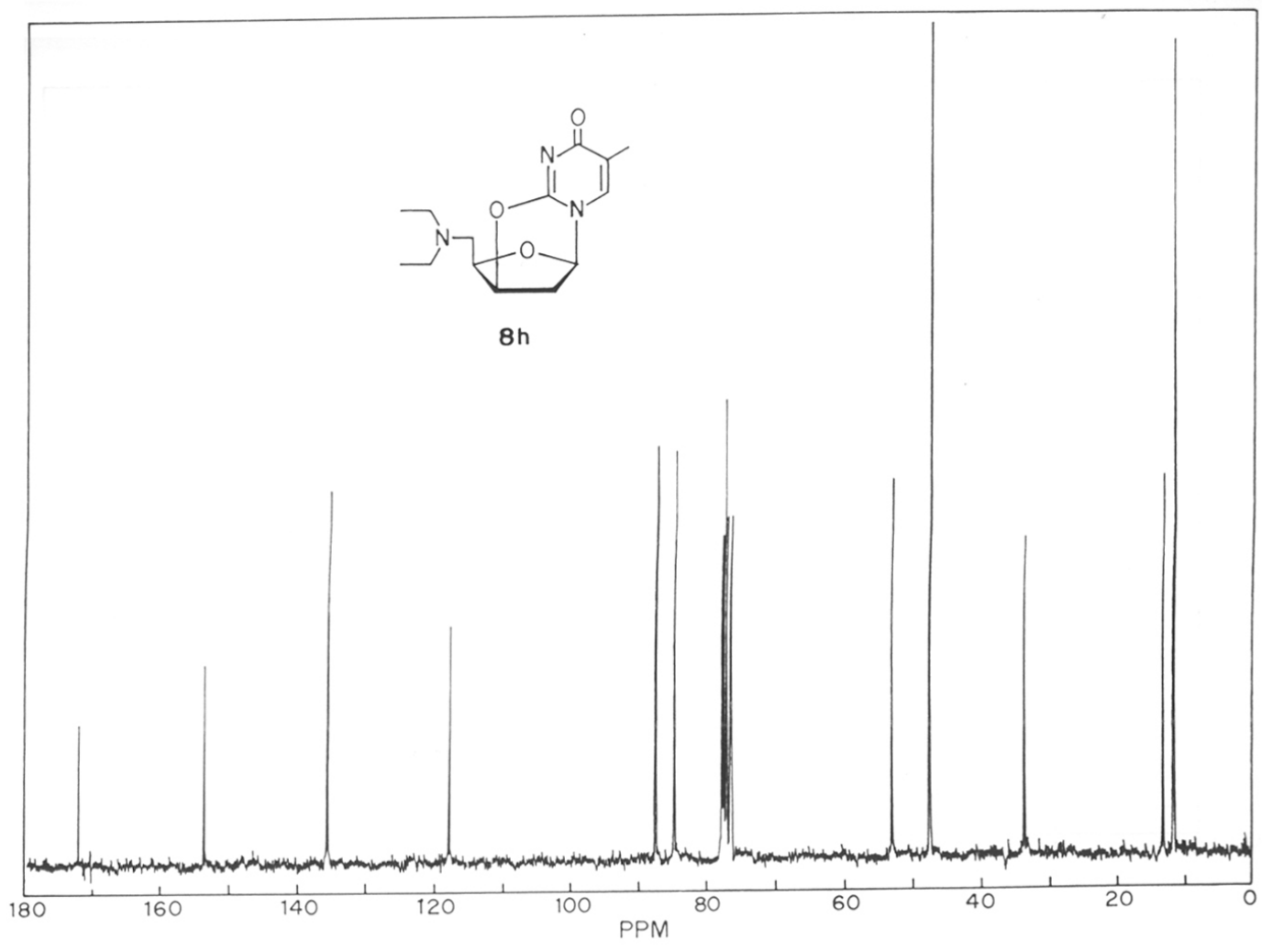

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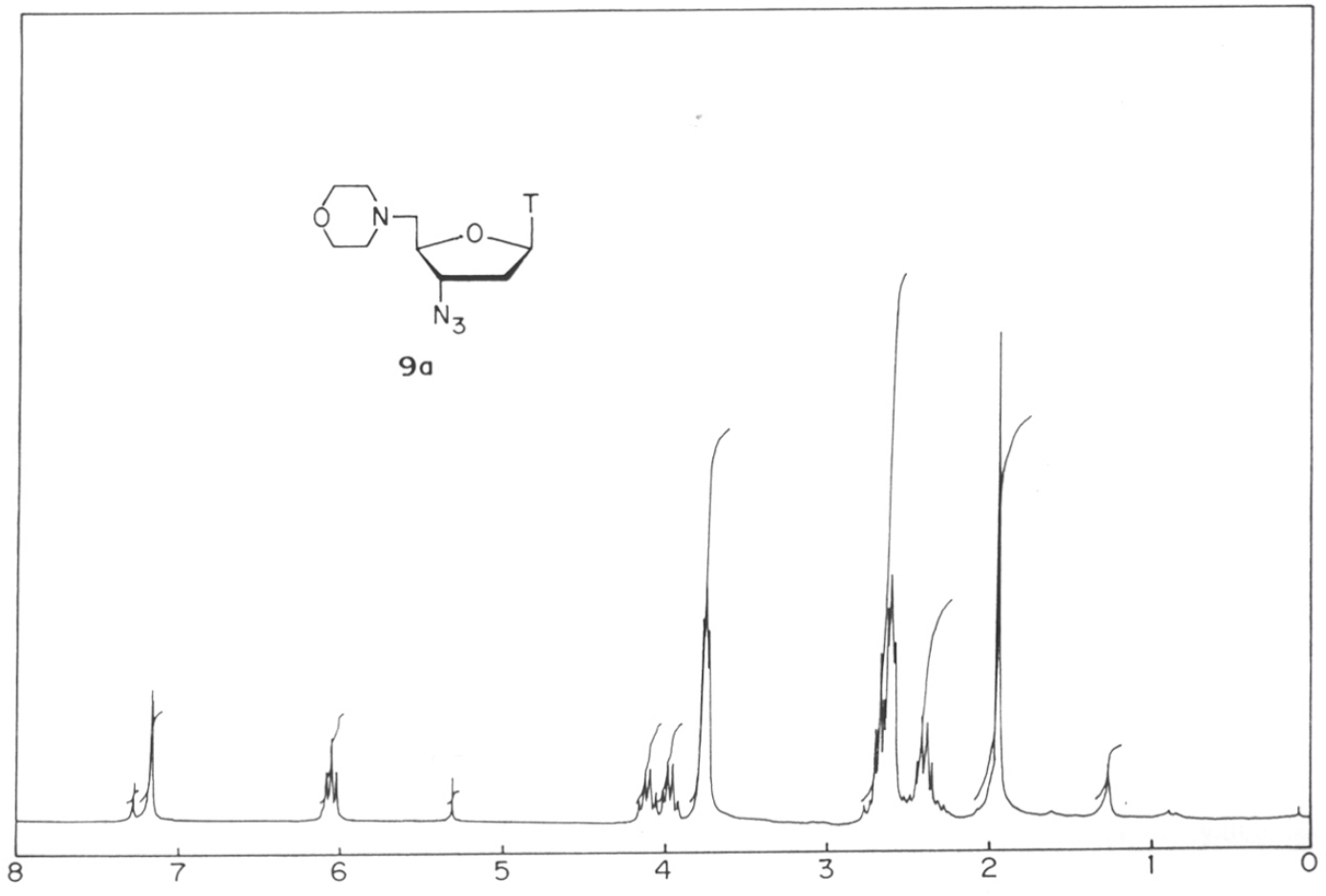

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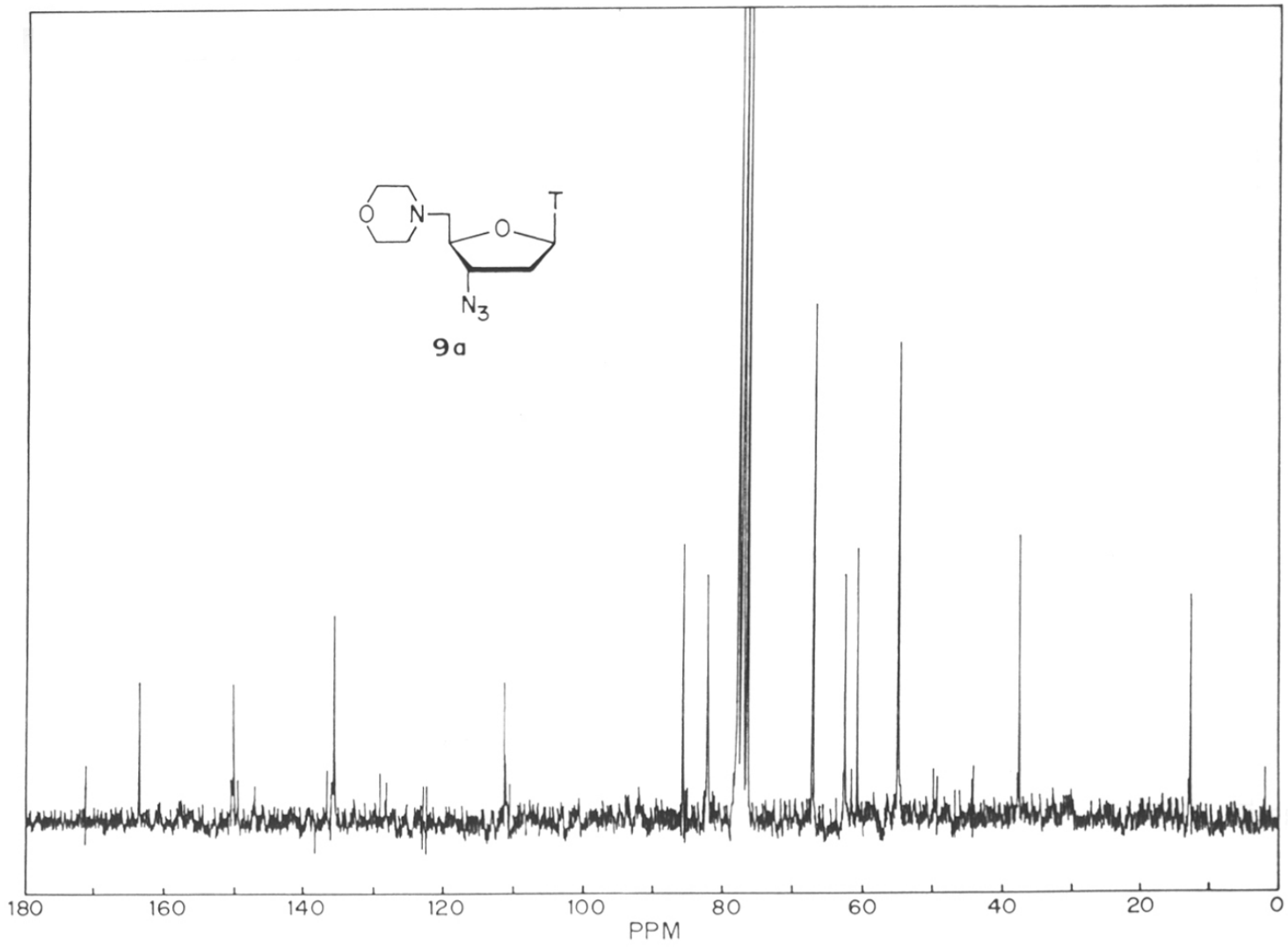
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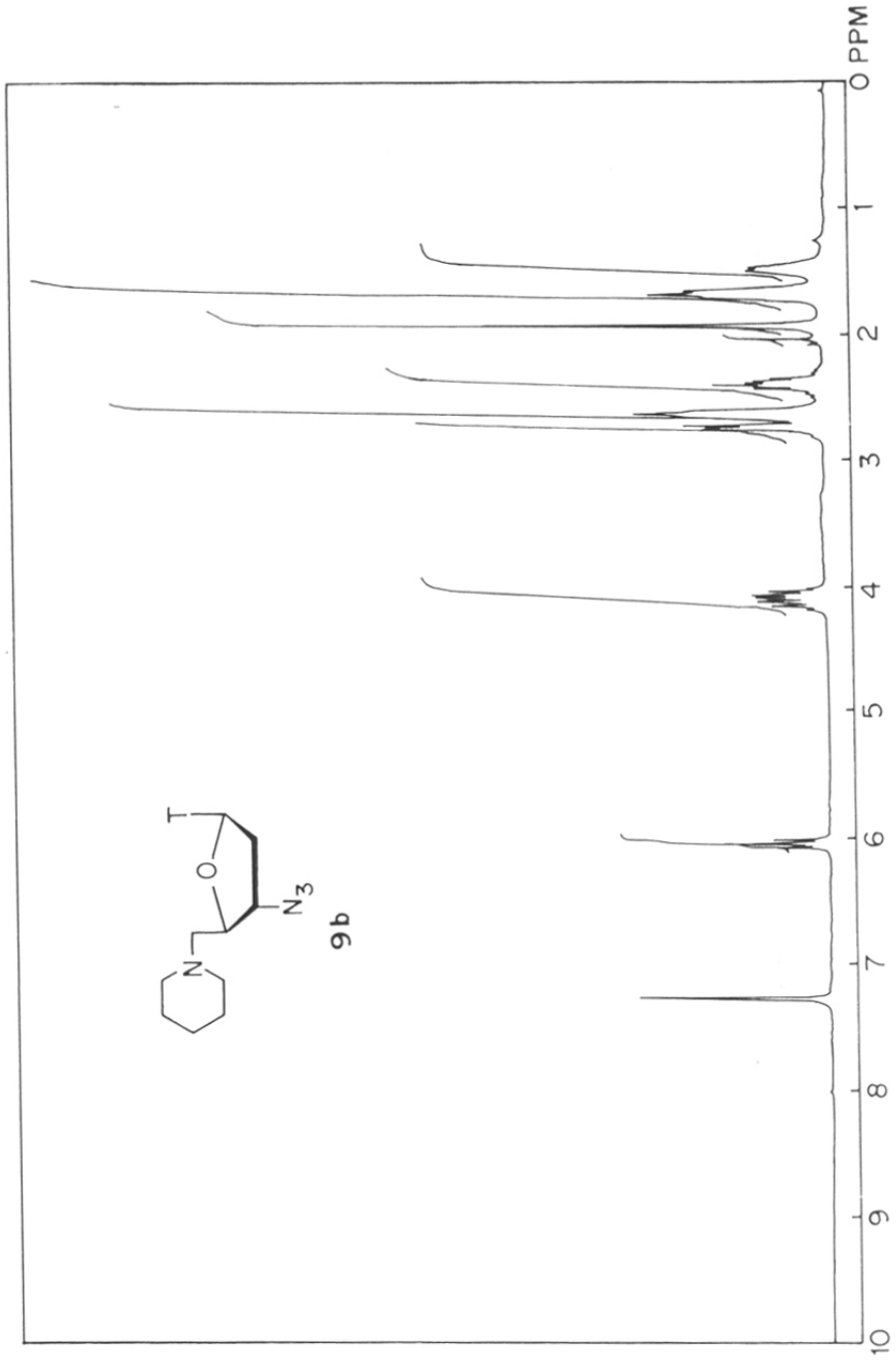
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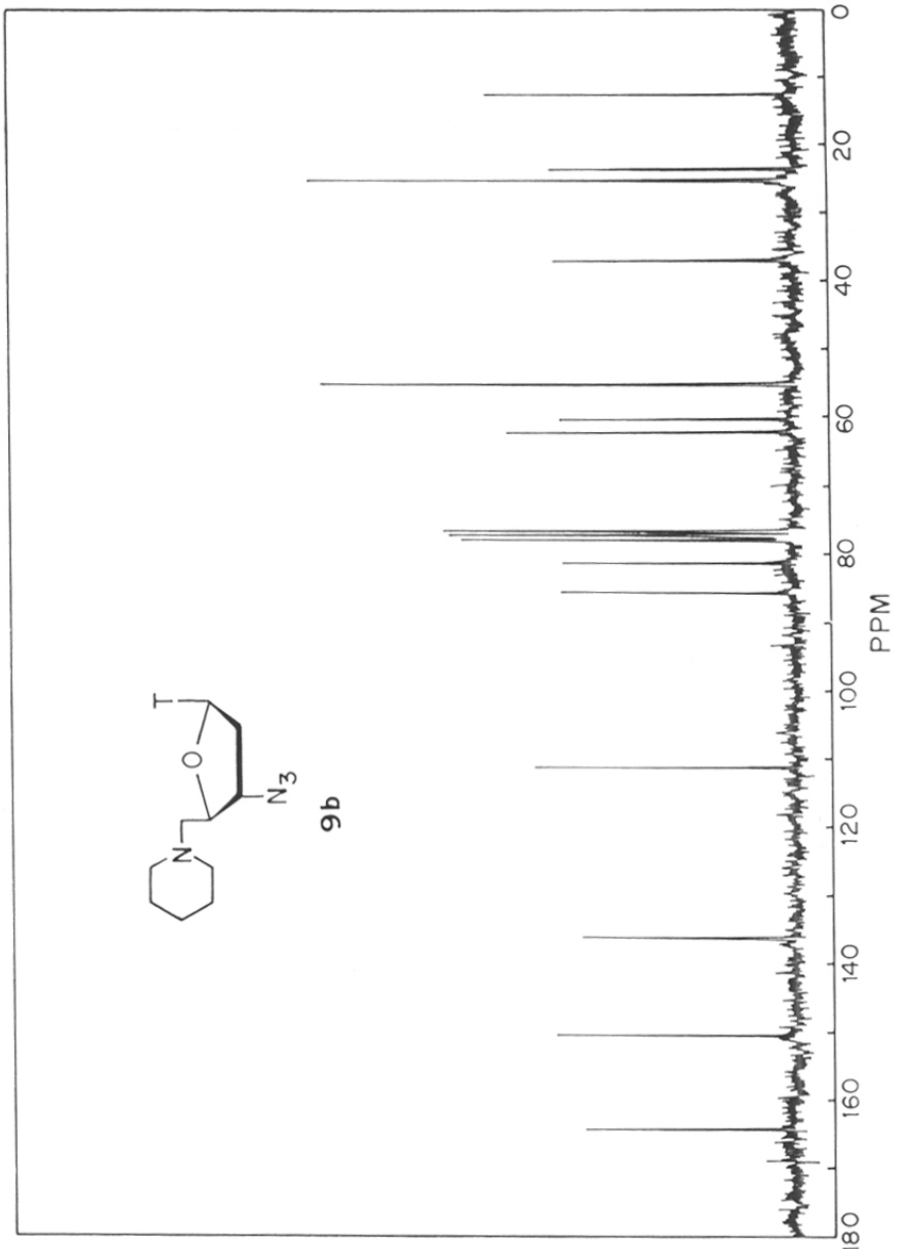
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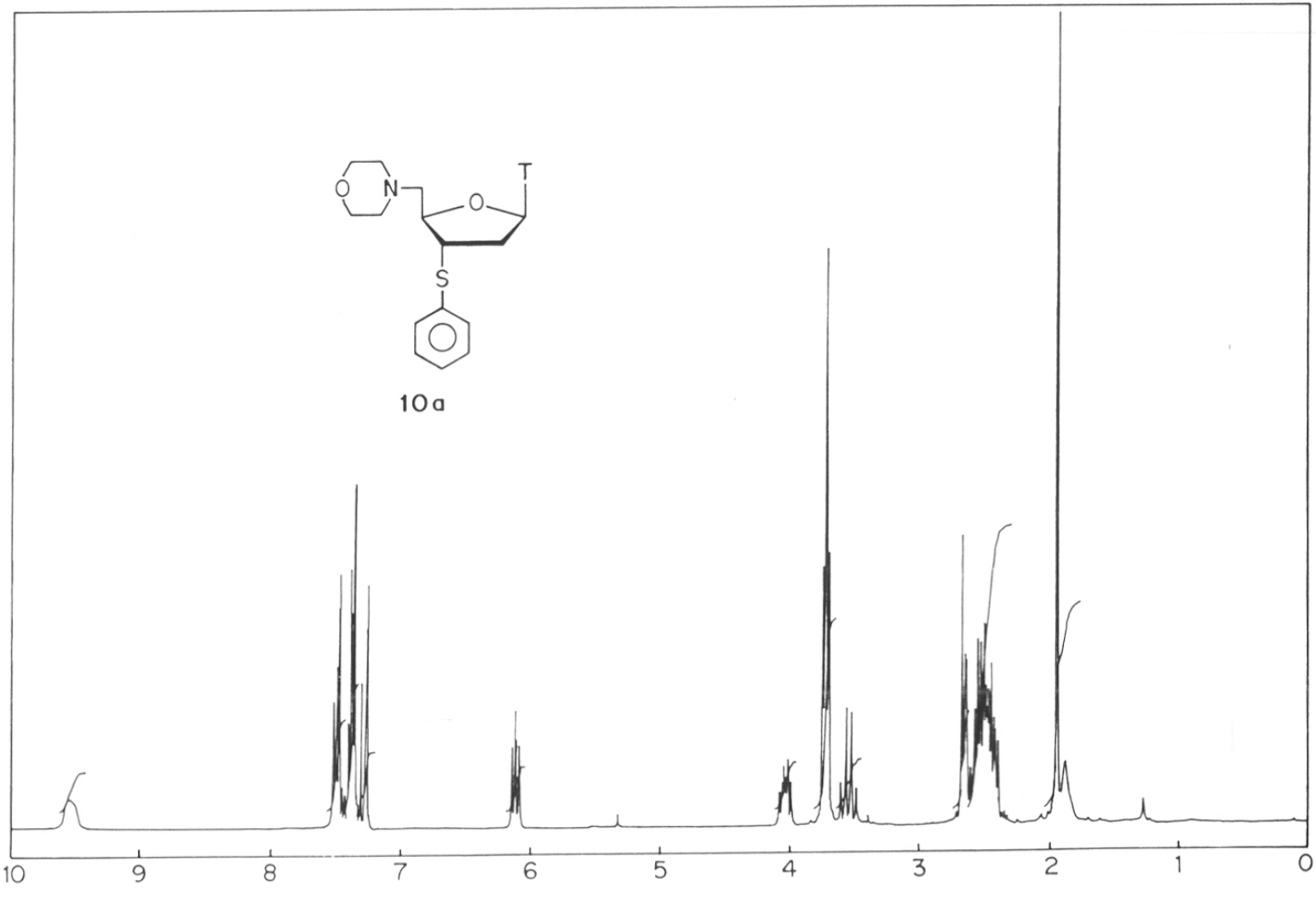
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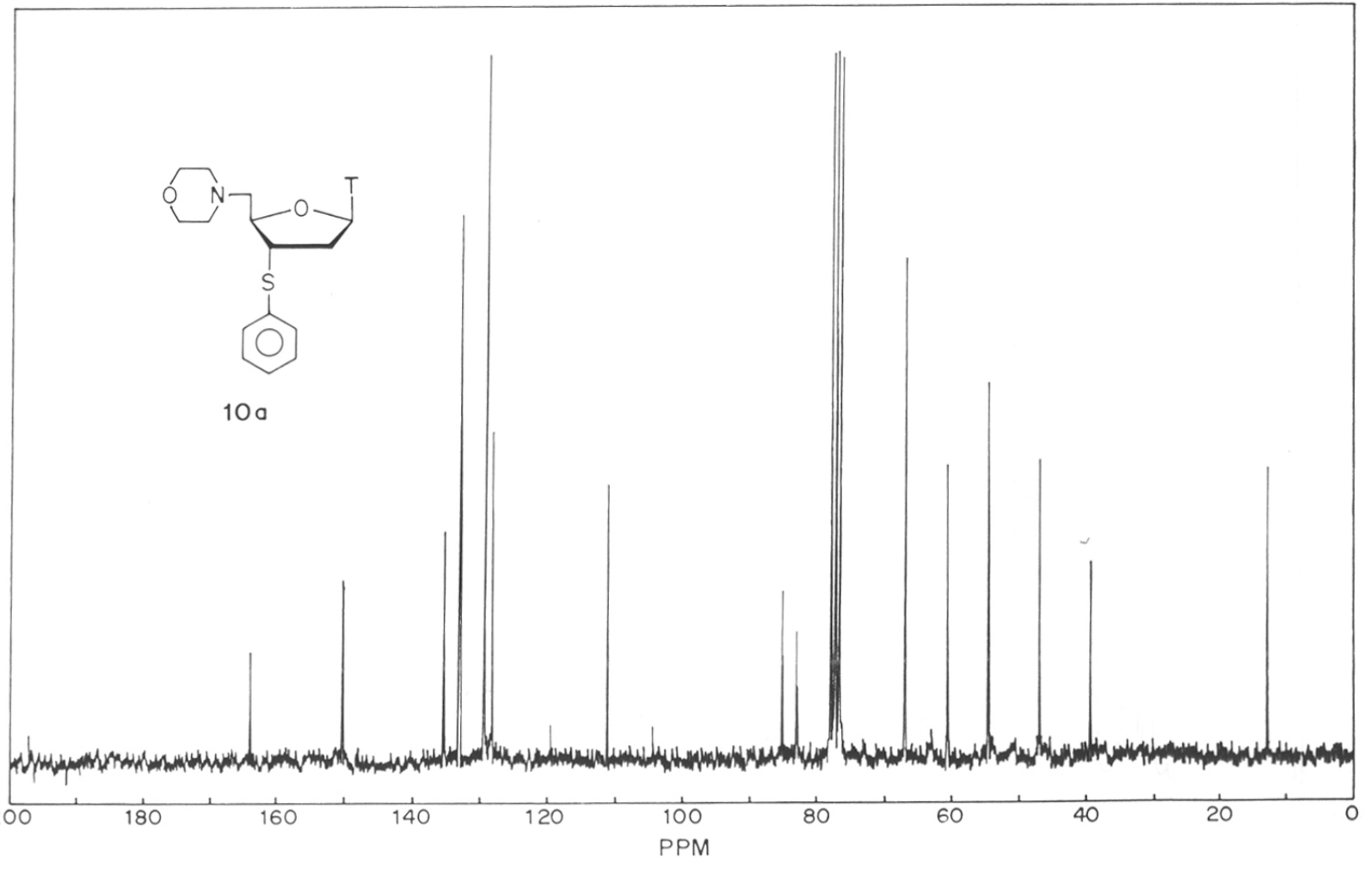

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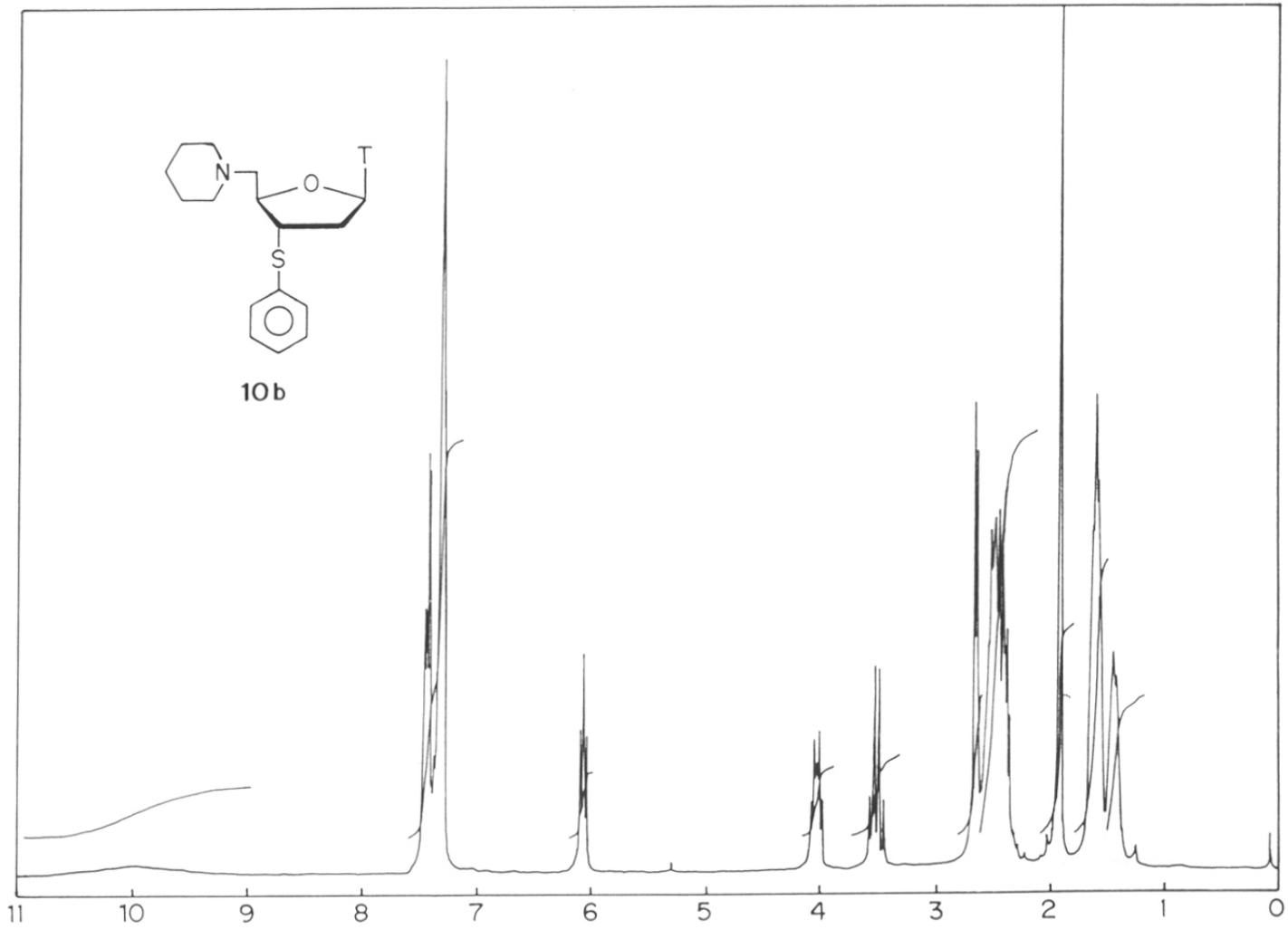
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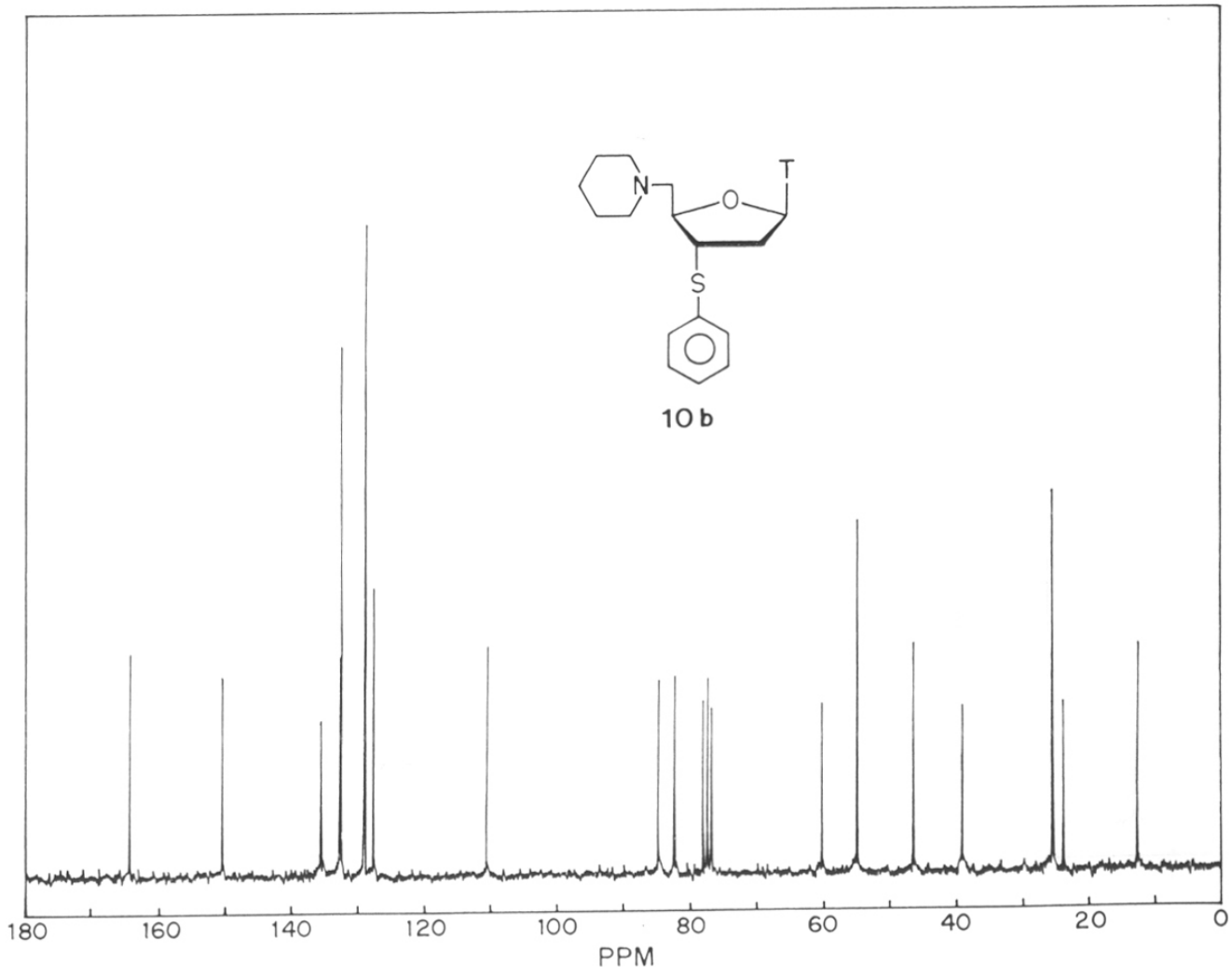

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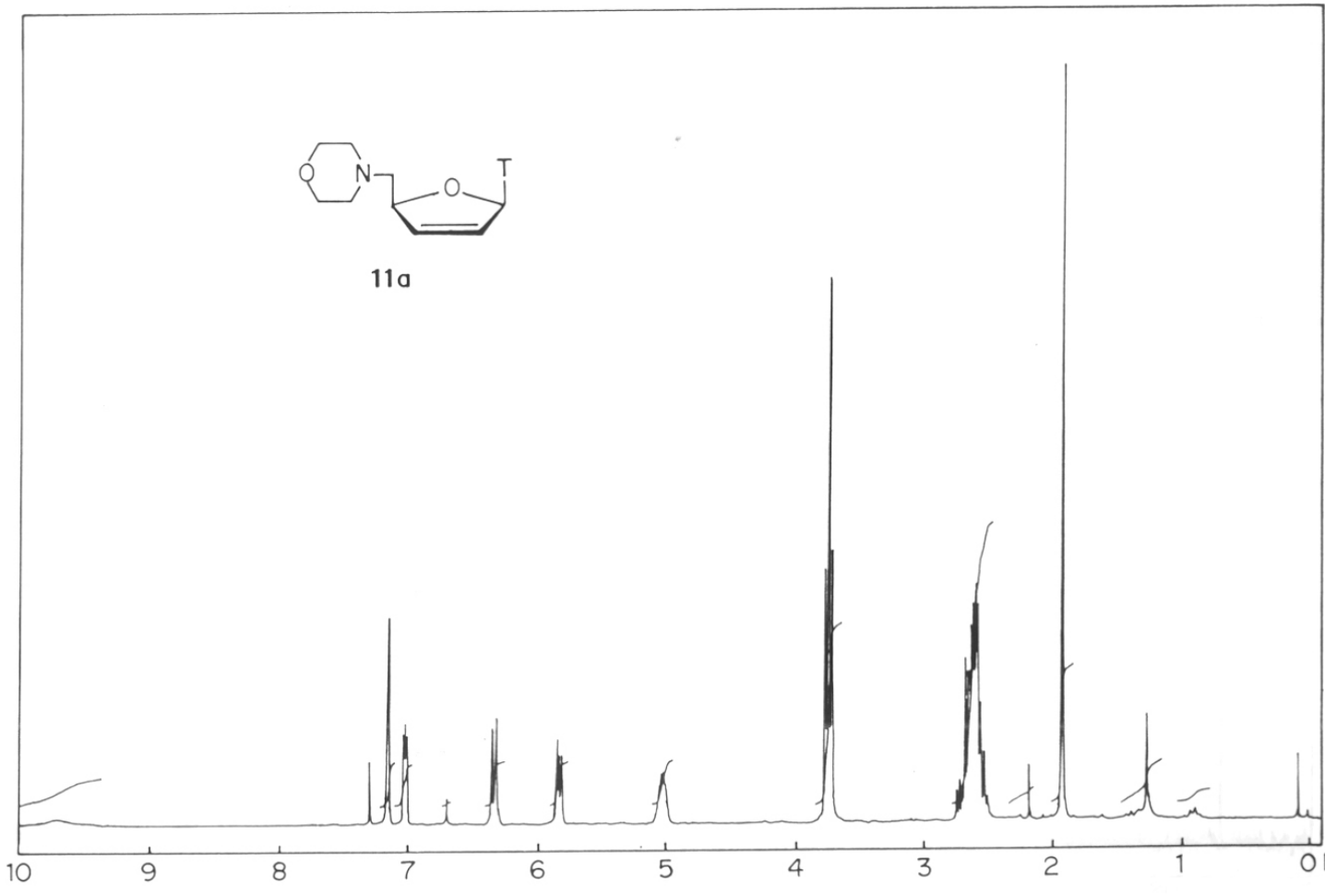
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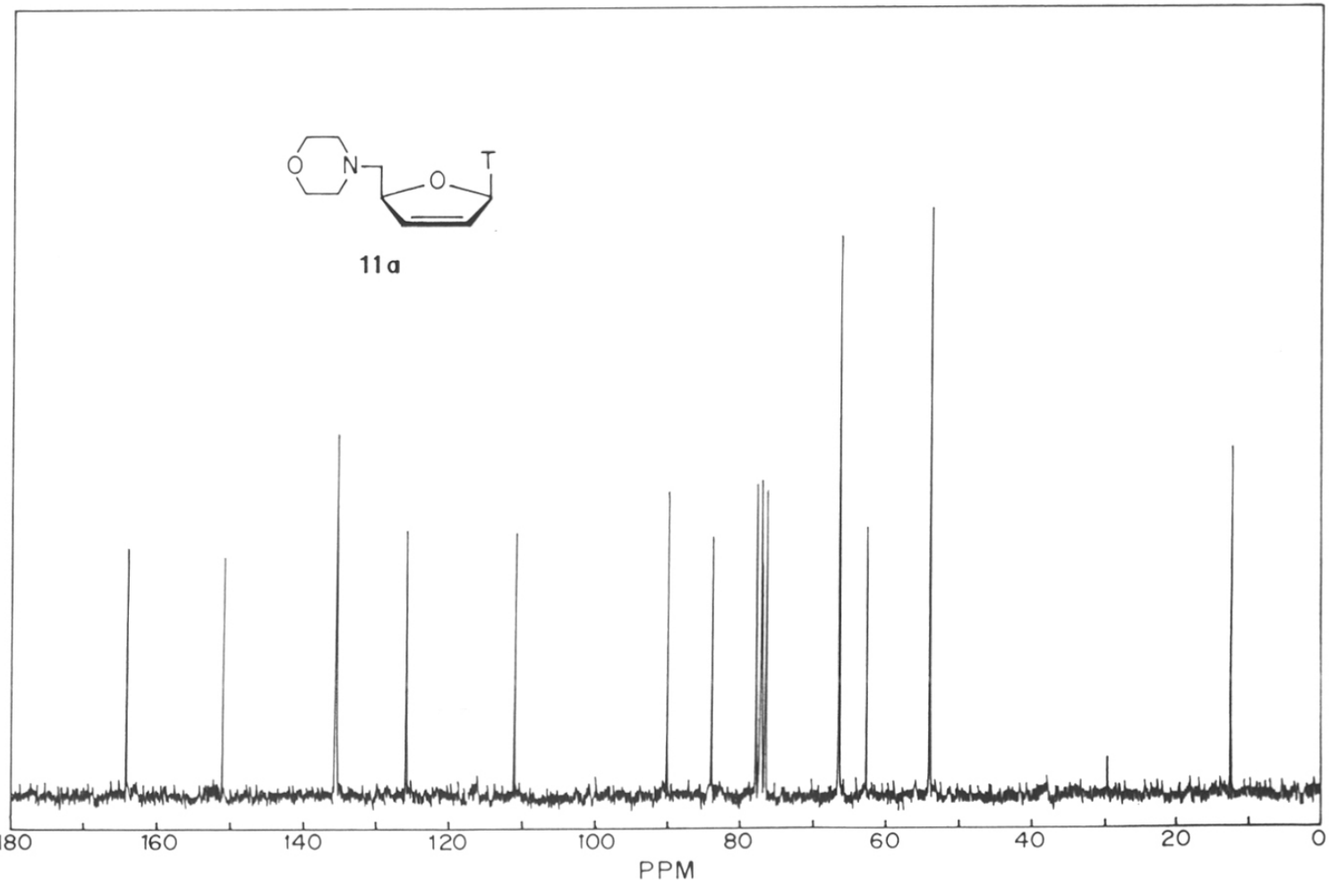

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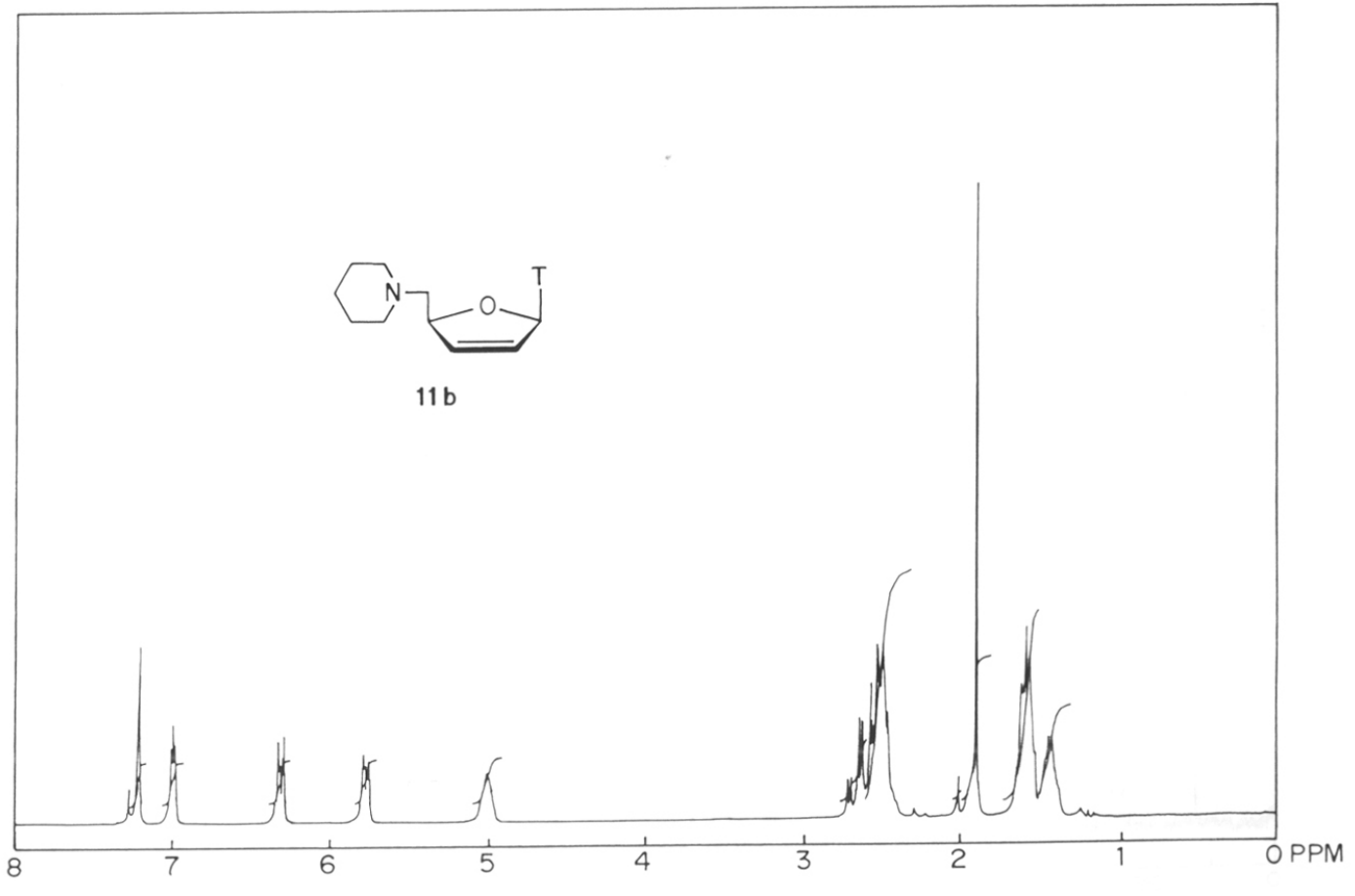

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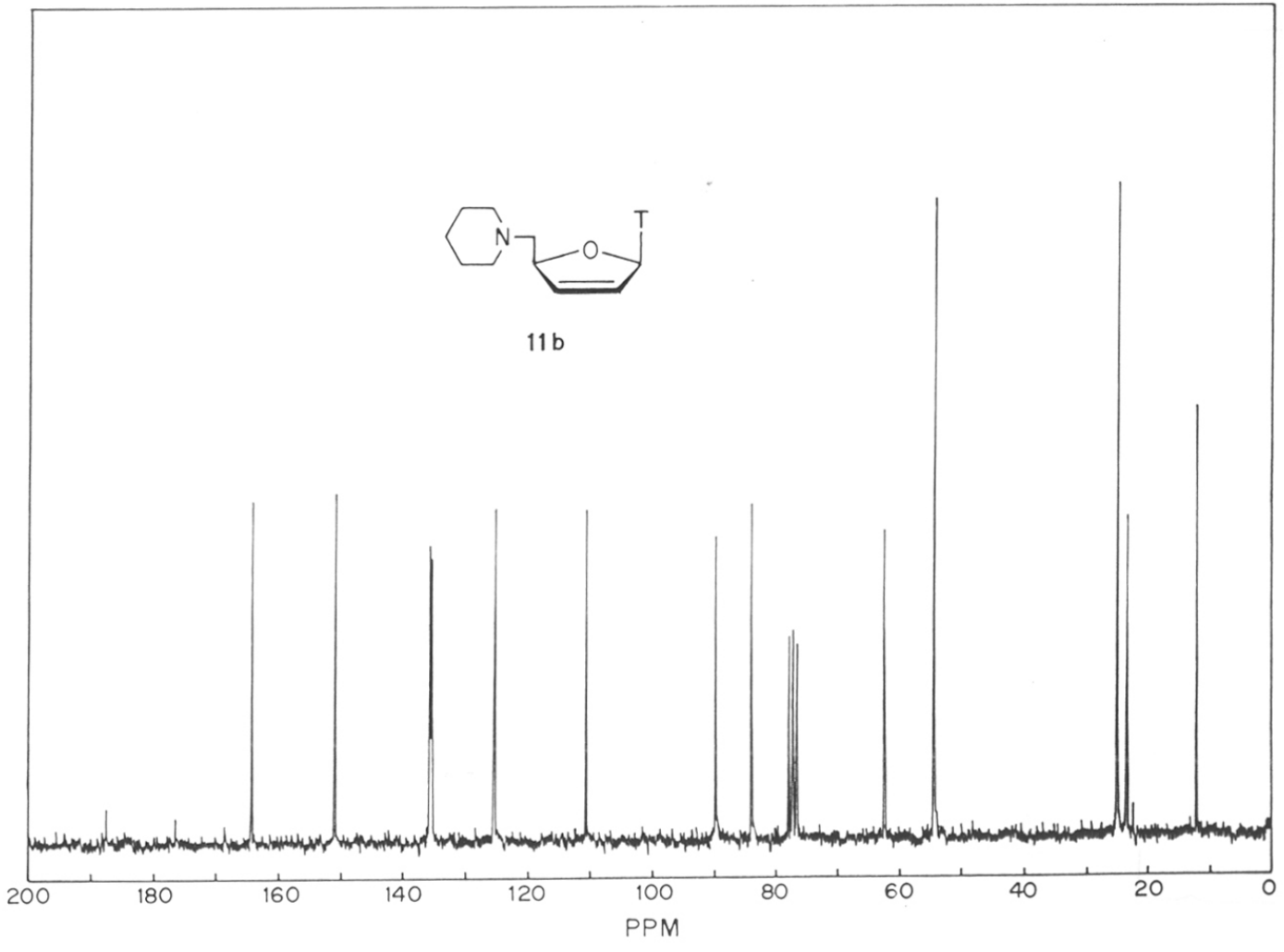

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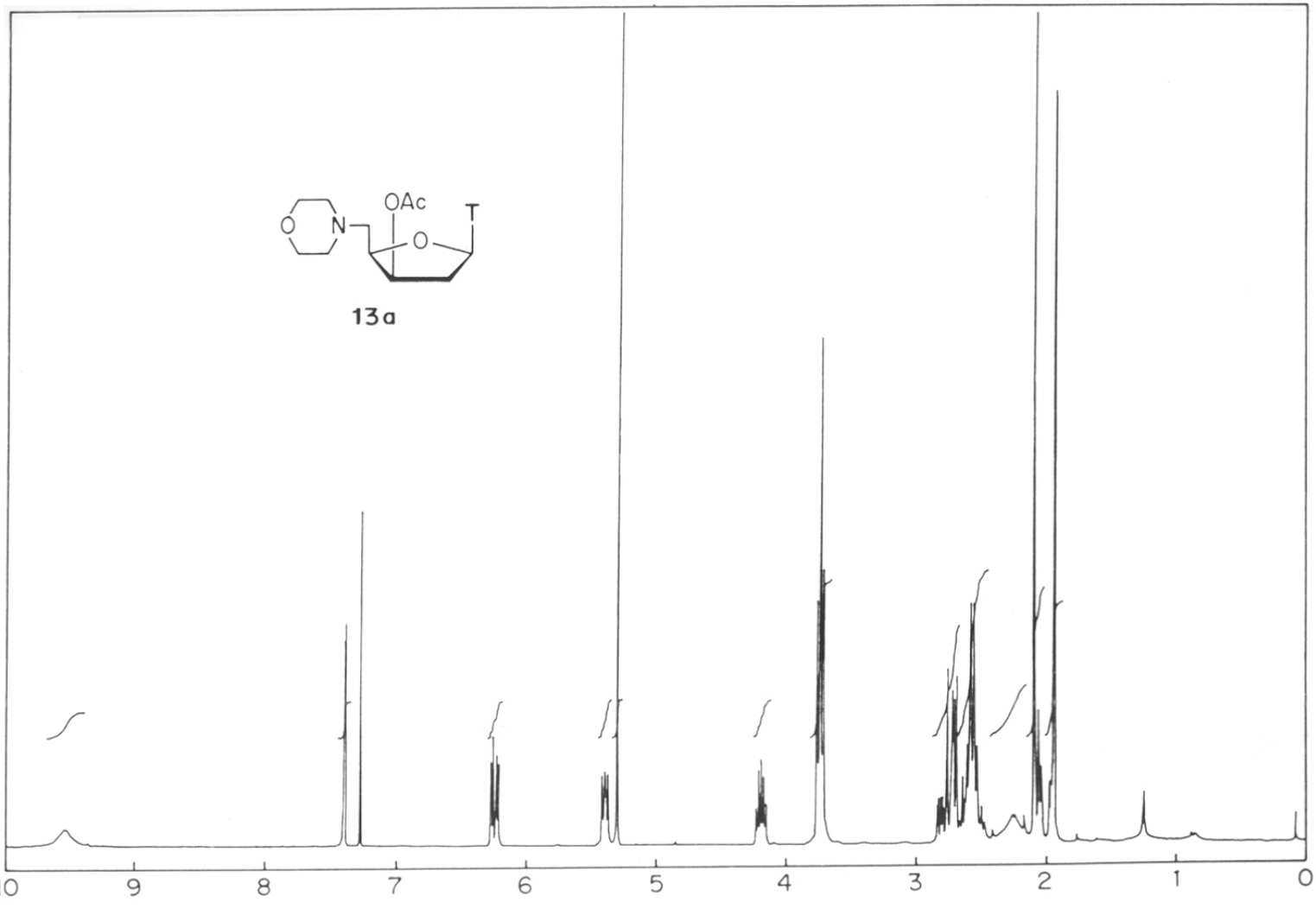
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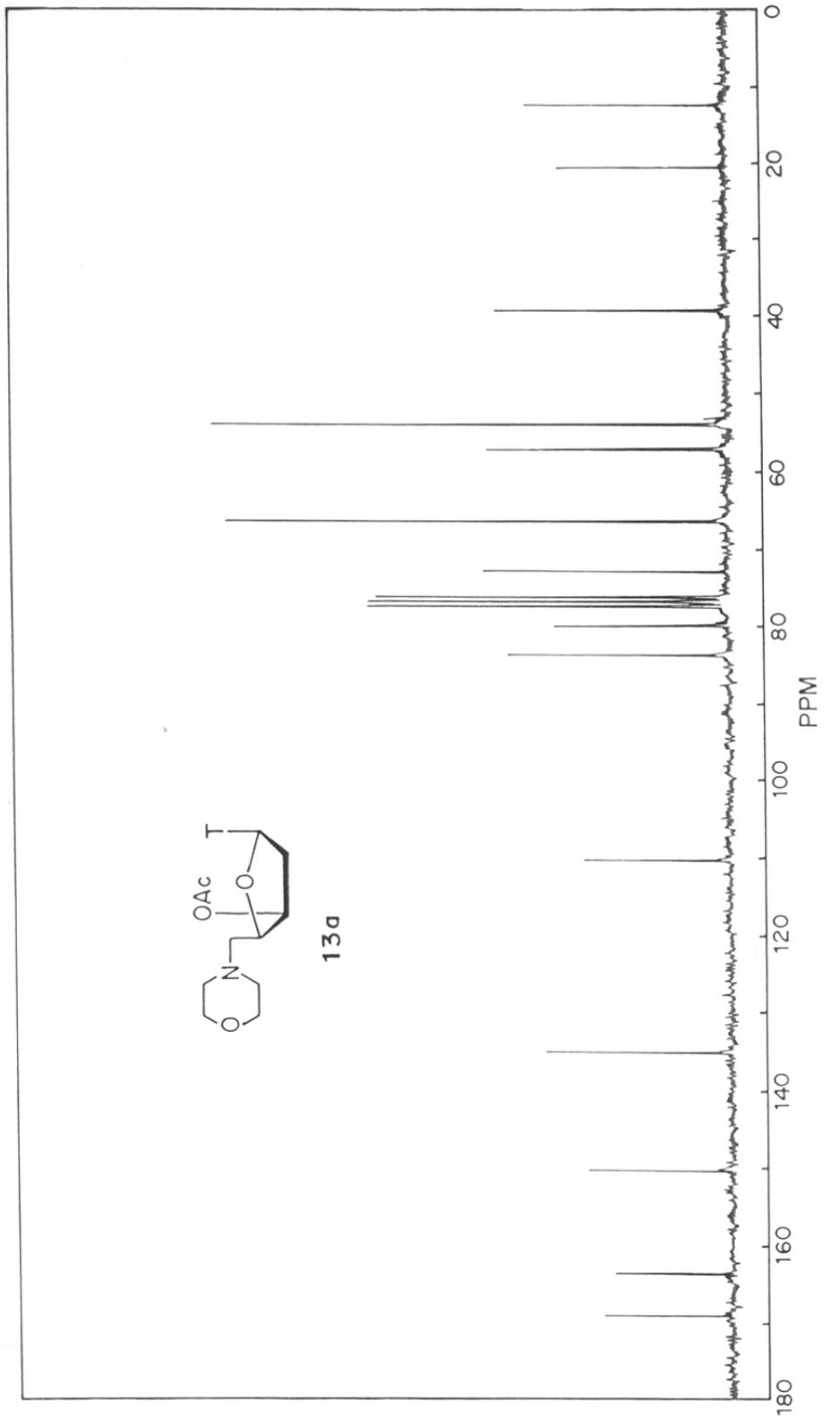
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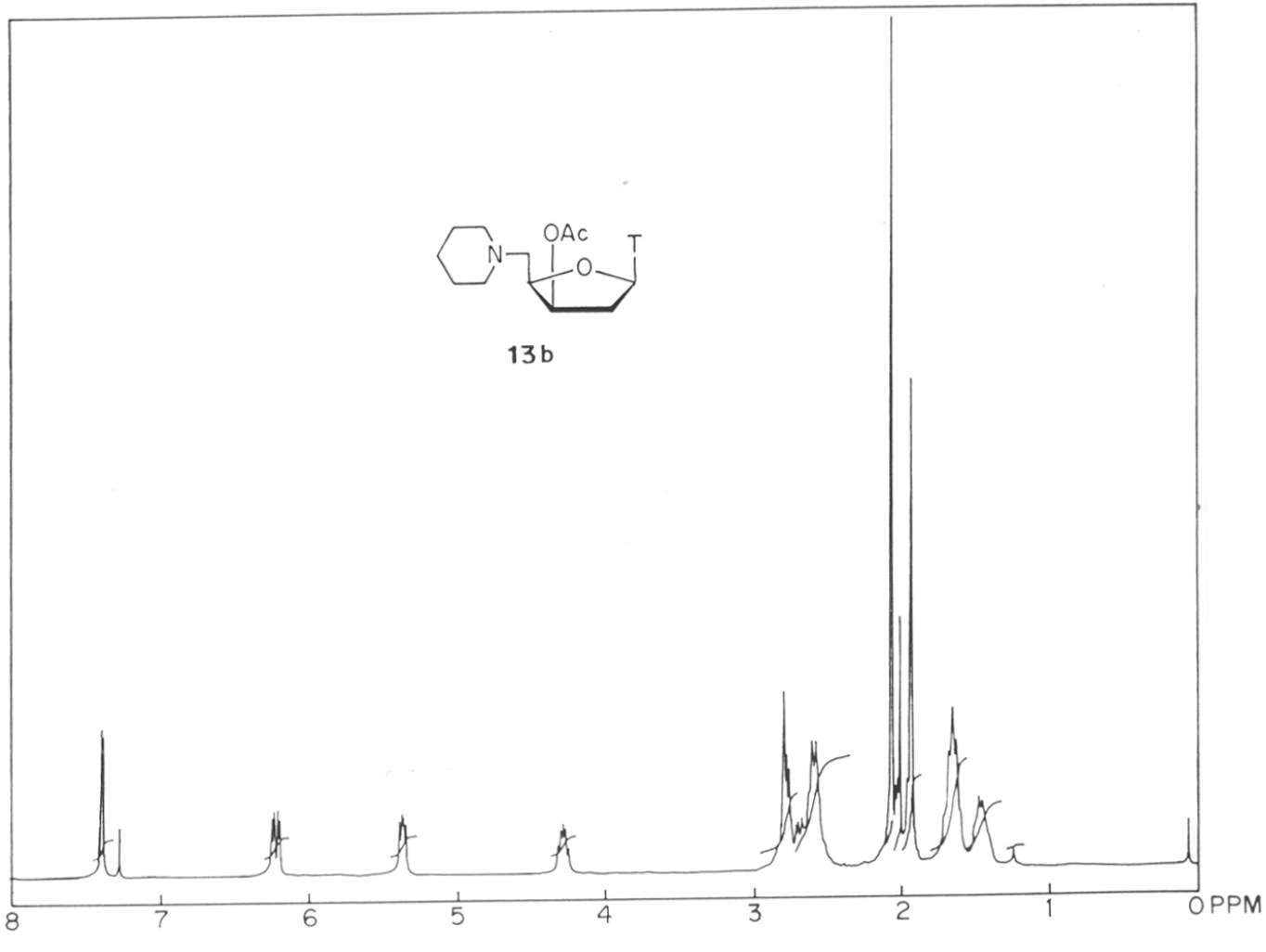
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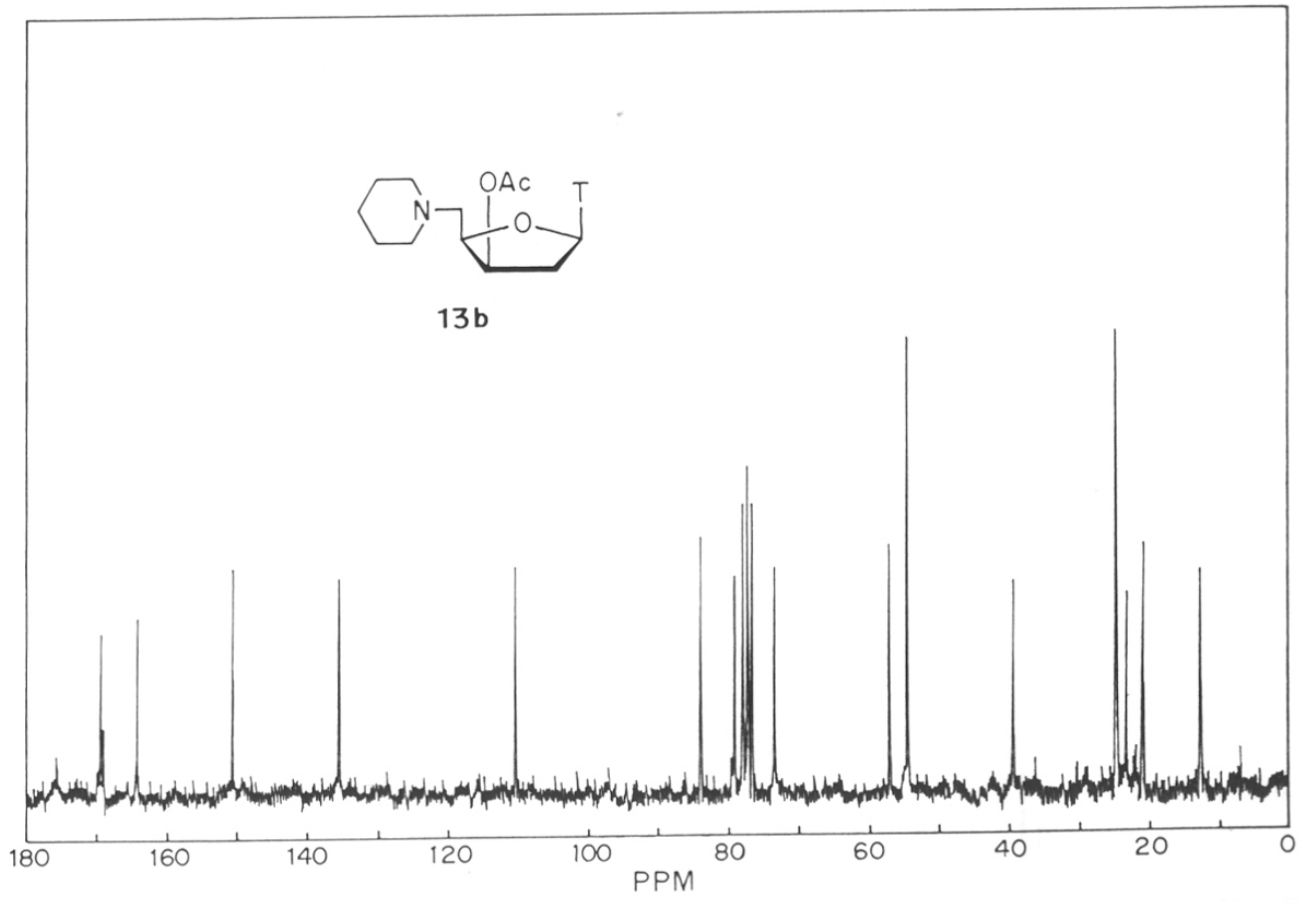
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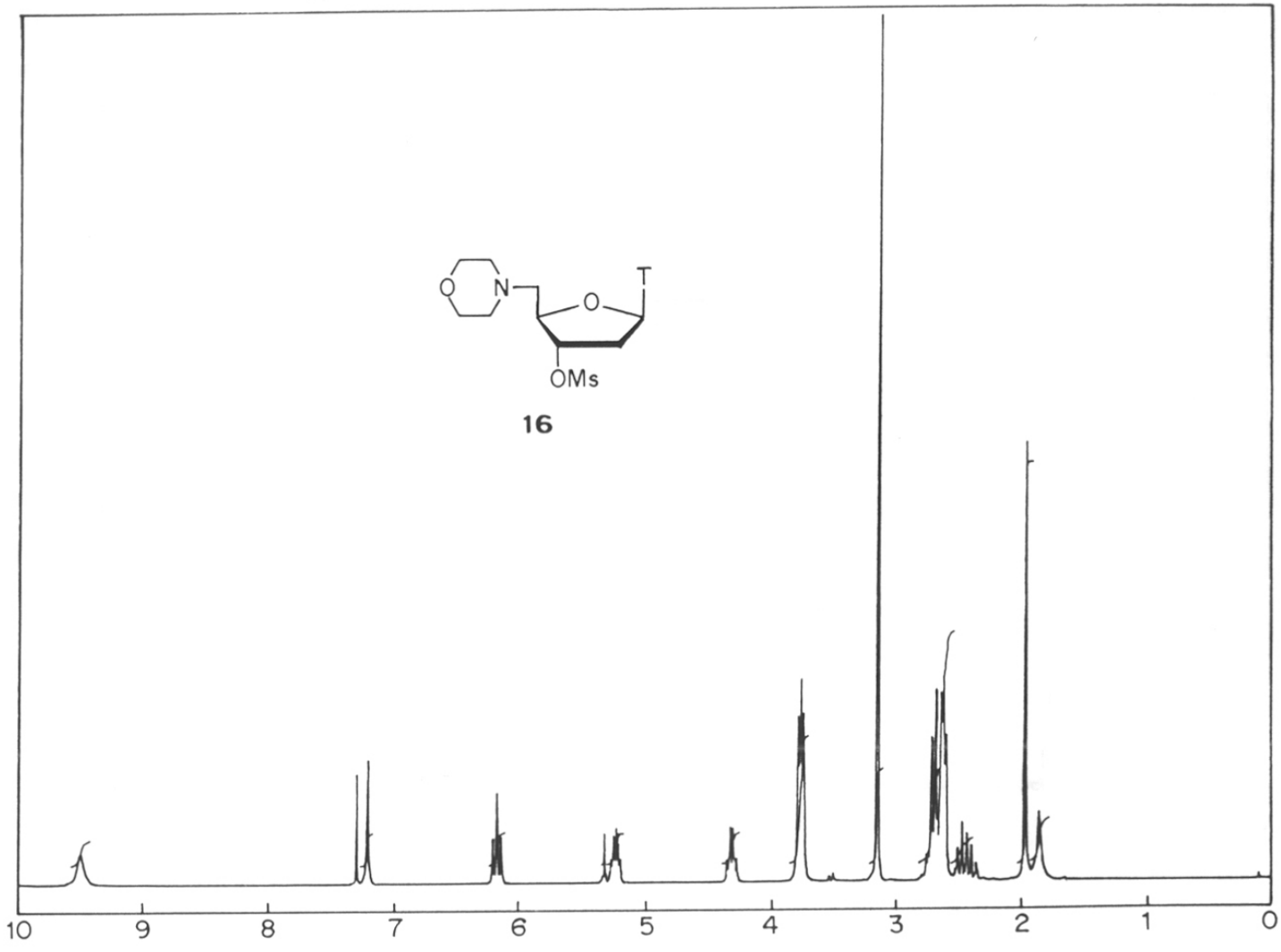

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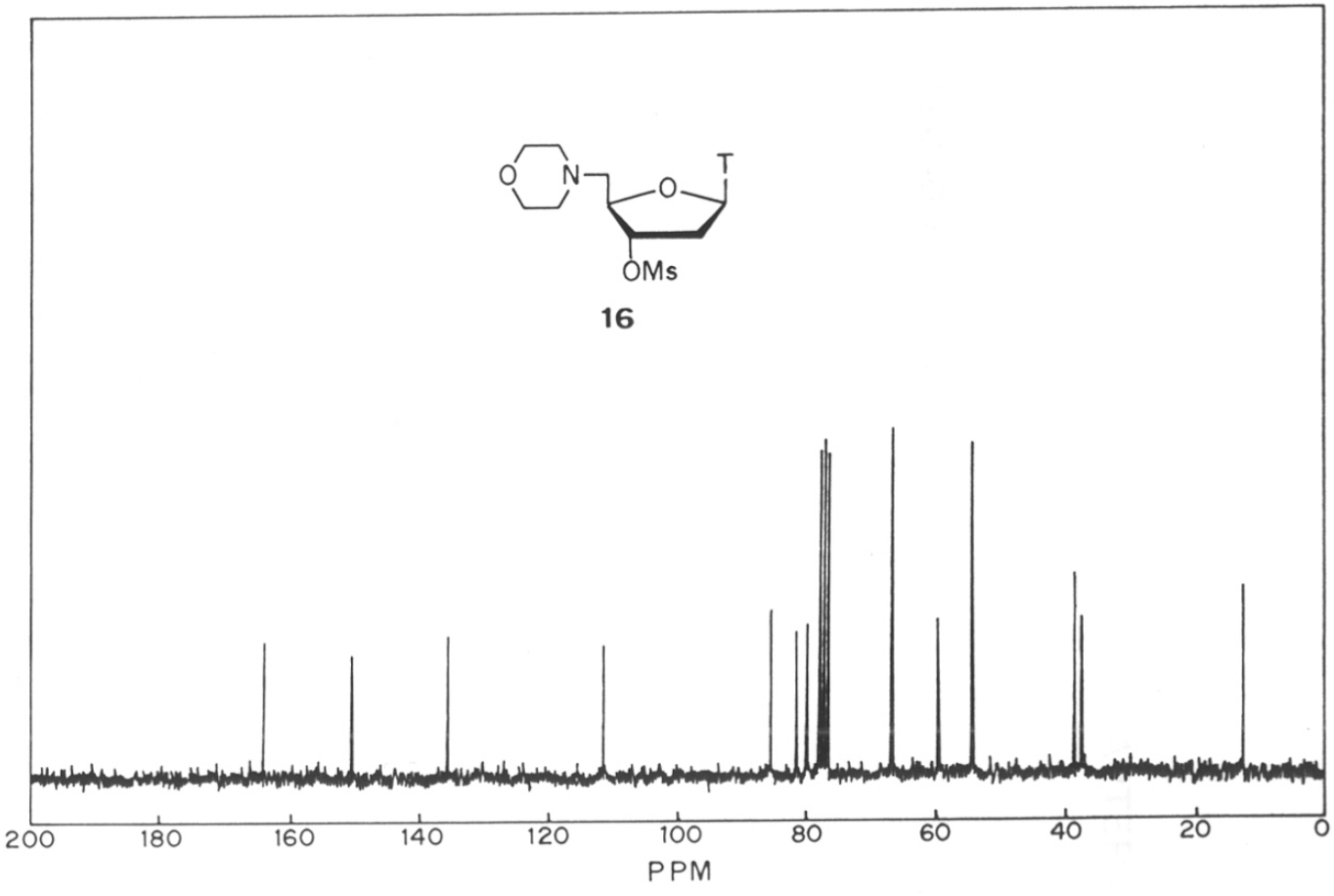

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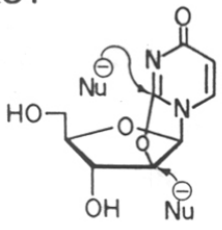
CHAPTER-III

Reactions of 2',3'-Di-O-mesyl-5'-O-trityluridine with Secondary Amines

3.1. Introduction

The cyclic 2,2', 2,3' and 2,5'-O-anhydro- pyrimidine nucleosides **1-3** are extensively used as precursors for synthesising modified (base or sugar) nucleosides[1,2]. These anhydro-derivatives **1-3** were opened either at C-2 or C2'/C-3'/C-5' positions by various nucleophiles such as, halides, sulphides, amines, azides etc[1,2] (**Fig-3.1**). In this connection,

Fig-3.1



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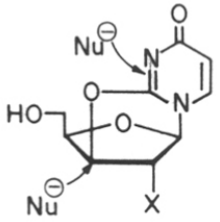
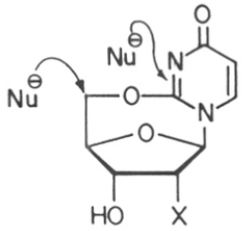


2a : X = H
2b : X = OH

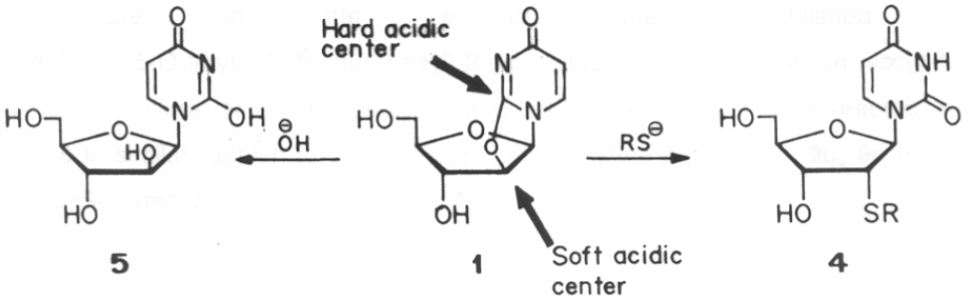


3a : X = H
3b : X = OH

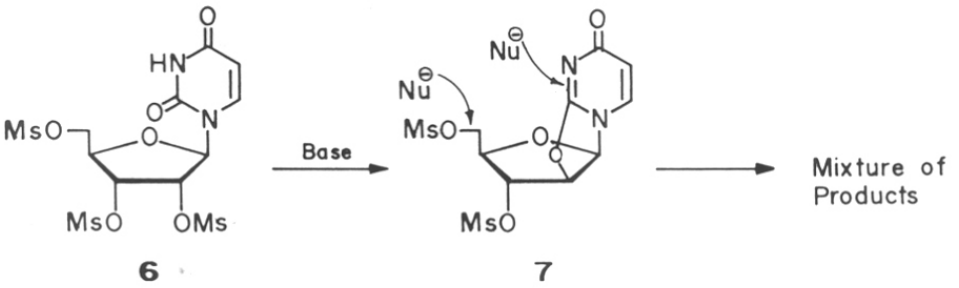
Hirota and coworkers reported[3] that the nucleophilic opening of 2,2'-O-anhydrouridine **1** can be rationalised on the basis of the Hard and Soft Acids and Bases principle (HSAB). The 2-position of the pyrimidine ring and 2'-position of the ribosyl moiety in the 2,2'-O-anhydrouridine are regarded as hard and soft acid sites respectively. Therefore, a soft thiolate anion attacked at the 2'-position to produce **4**, whereas hard hydroxide ion caused substitution at C-2 position to give **5** (**Scheme-3.1**).

In the previous chapter, we described[4] that 3',5'-di-O-mesylthymidine on reaction with secondary amines underwent "one-pot-two-steps" transformation to produce 2,3'-O-anhydro-5'-deoxy-5'-alkylaminothymidines (**Scheme-2.1** in Chapter-II). In an attempt to broaden the scope of such reactions, we decided to react various sulphonylated derivatives of the other pyrimidine nucleoside, uridine with secondary amines. Attempted reactions between 2',3',5'-tri-O-mesyluridine **6** and neat piperidine at ambient temperature produced an inseparable mixture of compounds. As under basic conditions 2,2'-O-anhydro-ring formation was much faster than 2,3'-O-anhydro- and 2,5'-O-anhydro- ring formation[5], it may

Scheme-3.1



Scheme-3.2



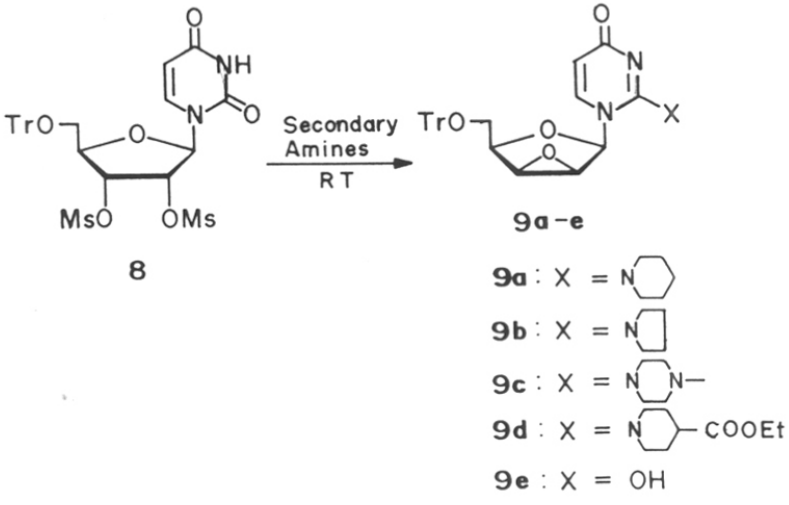
be concluded that at least one pathway of the reactions between 2',3',5'-tri-O-mesyluridine **6** and neat piperidine or morpholine must had been the 2,2'-O-anhydro- ring formation **7** (**Scheme-3.2**). The additional complications may have arisen from the direct displacement of the 5'-O-mesyl- group by piperidine in a fashion similar to that described for 3',5'-di-O-mesylthymidine[4]. In order to reduce the number of pathways involved and simplify the product distribution, we decided to study the reactions of 2',3'-di-O-mesyl-5'-O-trityluridine **8** with secondary amines; the absence of the 5'-O-mesyl- group would remove the pathway generated from the displacement reactions.

3.2. Present work

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D-lyxofuranosyl)- 2-dialkylamino-4-pyrimidone 9a-d: 2',3'-Di-O-mesyl-5'-O-trityluridine **8** was treated with piperidine either

or in DMSO solution at room temperature. In both cases single product was obtained and the structure of the product was established as 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)-2-piperidino-4-pyrimidone **9a**, an *iso*cytidine derivative. Pyrrolidine, N-methylpiperazine and ethyl *iso*nepicotate also reacted with compound **8** in similar fashion to produce various *iso*cytidine derivatives, **9b, 9c** and **9d** respectively (**Scheme-3.3**).

Scheme -3.3



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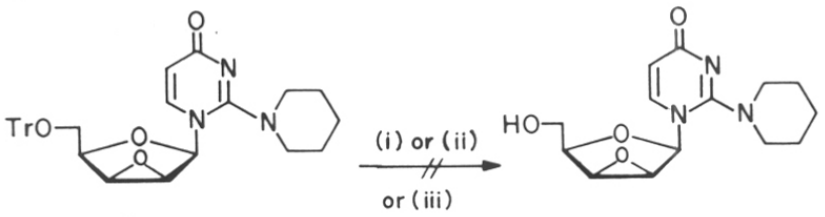
Synthesis of 1-(2,3-O-anhydro-β-D-lyxofuranosyl)-2-dialkylamino- 4-pyrimidone 12a-d: As attempted detritylation of compounds **9a-d** using hydrochloric acid in methanol or trifuloroacetic acid in dichloromethane or BF_3.etherate in dichloromethane produced mixture of products (**Scheme-3.4**), we chose to study the reactions of secondary amines with 2,2'-O-anhydro-3'-O-mesyluridine **11** which could be synthesised[6] very easily from **10**. Thus, compound **11** on reaction with piperidine, pyrrolidine, N-methylpiperazine and ethyl *iso*nepicotate at room temperature produced compounds **12a**, **12b**, **12c** and **12d** respectively (**Scheme-3.5**).

Attempts to synthesise 1-(2,3-O-anhydro-5-O-trityl-β-D-lyxo- furanosyl)-2-morpholino-4-pyrimidone 9f: 2',3'-Di-O-mesyl-5'-O-trityluridine **8** on reaction with

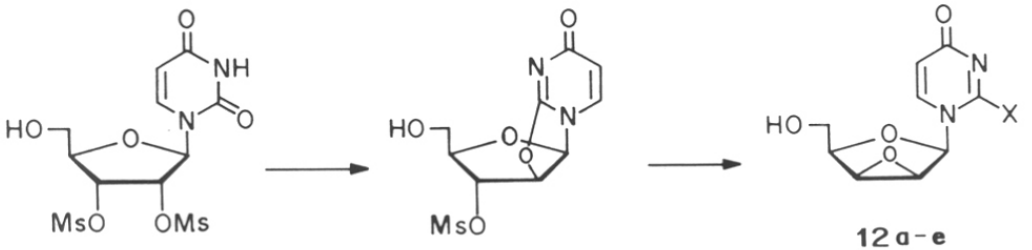
Scheme - 3·4



9a

(i) HCl / MeOH , (ii) CF_3COOH / CH_2Cl_2
(iii) $BF_3 \cdot Et_2O$ / CH_2Cl_2

Scheme - 3·5



10 **11** **12a-e**

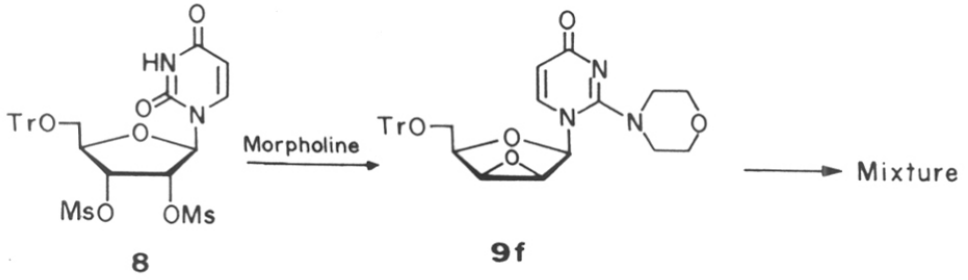
12a : X = N⬡
12b X = N⬡
12c X = N⬡N—
12d X = N⬡—COOEt
12e X = OH

morpholine produced a mixture, but one of those products certainly was the similar kind of *iso*cytidine derivatives **9f** as was evident by the ^{1}H-NMR of the mixture; the structure of the morpholino derivative was also confirmed by mass spectrum (M^+ as well as 2-morpholino-4-pyrimidone - 1 peaks). However prolonged reaction time yielded the mixture of products (**Scheme-3.6**).

Attempted reactions of 2',3'-Di-O-mesyl-5'-O-trityluridine 8 **with diethylamine and some bifunctionalised amines:** Extensive cleavage occurred when **8** was treated with

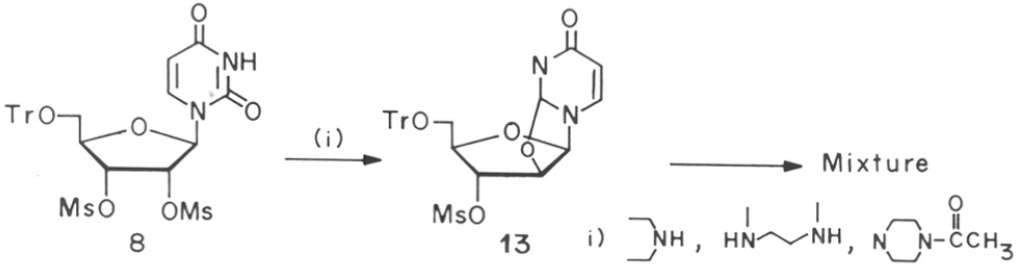
diethylamine, N-methylethanolamine, N,N'-dimethylethylenediamine and N-acetylpiperizine; all these reactions, however, did produce the 2,2'-O-anhydro derivative **13** (tlc) which eventually got cleaved (**Scheme-3.7**).

Scheme - 3·6



8 **9f**

Scheme - 3·7



8 **13**

3.3. Structural Assignment

The structures of all new compounds **9a-d** and **12a-d** were assigned unambiguously by spectroscopy. A comparison of the UV spectra of compounds **12a-d** (**Table-3.1**) with that of the known epoxide **12e** (ref.7) showed a distinct hypsochromic shift (**Fig-3.2**), proving thereby that the base modification must have taken place. In case of the ^{1}H-NMR, H-1' signal of compounds **9a-d** was shielded by 0.5ppm and H-5 was deshielded by 0.3ppm when compared with the same signals of **9e** (ref.8); the same signals of compounds **12a-d** shifted positions in a similar fashion by 0.3ppm when compared with the same signals of **12e**. It is interesting to note that in the case of both the sets of compounds the H_5-H_6 coupling constants changed

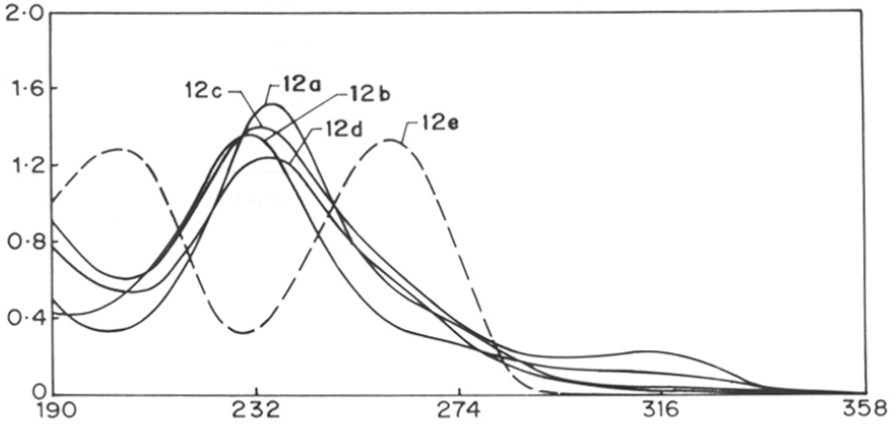
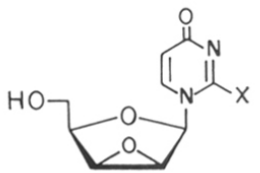


Fig.3·2



12a : X =  ; λ_{max} = 235·2 nm

12b : X =  ; λ_{max} = 230·3 nm

12c : X =  ; λ_{max} = 232·4 nm

12d : X =  ; λ_{max} = 234·4 nm

12e : X = OH ; λ_{max} = 259·7, 204·4 nm

Table - 3.1

Comp. No:	H-1'	H-3' $J_{H-3',H-2'}$	H-2' $J_{H-2',H-3'}$	H-4'	H-5 $J_{H-5,H-6}$	H-6 $J_{H-6,H-5}$	UV-λ_{max} (H_2O)
9e ($CDCl_3$)	6.2 (s)	3.94(d) 2.8 Hz	3.89 (d) 2.8 Hz	4.19 (t)	5.67 (d) 8.2 Hz	7.55 (d) 8.2 Hz	-
9a ($CDCl_3$)	5.74 (s)	3.95 (d) 2.9 Hz	3.89 (d) 2.9 Hz	4.16(t)	6.0 (d) 7.8 Hz	7.61 (d) 7.8 Hz	-
9b ($CDCl_3$)	5.68 (s)	3.95 (d) 2.9 Hz	3.88 (d) 2.9 Hz	4.13 (t)	5.98 (d) 7.7 Hz	7.62 (d) 7.7 Hz	-
9c ($CDCl_3$)	5.73 (s)	3.97 (d) 2.9 Hz	3.88 (d) 2.9 Hz	4.15 (t)	6.02 (d) 7.7 Hz	7.65 (d) 7.7 Hz	-
9d ($CDCl_3$)	5.75 (s)	3.96 (d) 2.7 Hz	3.88 (d) 2.7 (Hz)	4.18 (m)	6.04 (d) 7.7 Hz	7.67 (d) 7.7 Hz	-
12e (D_2O)	6.2 (s)	4.18 (d) 3.6 Hz	4.12 (d) 3.6 Hz	4.29 (t)	5.87 (d) 8.2 Hz	7.88 (d) 8.2 Hz	259.7 nm
12a (D_2O)	5.89 (s)	4.19 (d) 3.2 Hz	4.12 (d) 3.2 Hz	4.28 (t)	6.13 (d) 7.7 Hz	8.0 (d) 7.7 Hz	235.2 nm
12b (D_2O)	5.95 (s)	4.16 (d) 3.3 Hz	4.07 (d) 3.3 Hz	4.22 (t)	6.01 (d) 7.7 Hz	7.89 (d) 7.7 Hz	230.3 nm
12c (D_2O)	5.96 (s)	4.19 (d) 3.0 Hz	4.13 (d) 3.5 Hz	4.29 (t)	6.19 (d) 7.7 Hz	8.05 (d) 7.7 Hz	232.4 nm
12d (D_2O)	5.93 (s)	Merged with H-4'	Merged with H-4'	4.24 (m)	6.18 (d) 7.7 Hz	8.05 (d) 7.7 Hz	234.4 nm

by almost 0.4 Hz (**Table-3.1**). In the case of the ^{13}C-NMR, C-1', C-2/C-4 and C-5, signals of compounds **9a-d** were deshielded by 3.5, 6-8 and 7ppm respectively when compared with

the same signals of **9e**; the same signals of compounds **12a-d** shifted positions in a similar fashion (except for compounds **12b** and **12d** where the C-4'signal shifted by 2ppm; it should be noted, however that ^{13}C-NMR of **12b** was recorded in DMSO-d_6) when compared with the same signals of **12e**. Both the proton and the carbon signals were assigned on the basis of ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra of compound **9a** (**Fig-3.3** and **3.4**). It was assumed that the proton and carbon signals of both the tritylated and non-tritylated compounds followed the same order as there was no significant change in the positions of peaks in a particular group of compounds. All tritylated derivatives **9a-d** gave molecular ion peak in the mass spectra but in case of the nontritylated compounds only **12b-d** gave the same. On the other hand, only **9a-b** and **12a-b** produced fragments corresponding to (2-piperidino-4-pyrimidone - 1) and (2-pyrrolidino-4-pyrimidone - 1) as base peaks (**Fig-3.5**).

3.4. Discussion

A perusal of the litrature[9-11,14] on the opening of the 2,2'-O-anhydro- bridge of pyrimidines by amines revealed that all the amino groups which were attacking the C-2 position were primary in nature; for example, the nucleophilic opening of 2,2'-O-anhydro-*aza*-uridine **14** with various amino acid derivatives produced 2-N-alkyaminoacid-*iso*-cytidine derivatives **15a-d** (ref.9) (**Scheme-3.8**). Beranek and coworkers reported[10] that 4-aminobenzeneslphonamide on reaction with 2,2'-O-anhydro-uridine **16a** and 5'-deoxy-5' -chloro-2,2'-O-anhydro- uridine **16b** produced C-2 aminobenzenesulphonamido- *ara*-uridine derivative **17a-b** and 2,5'-(aminobenzenesluphonyl)imino- *ara*- uridine **18** respectively (**Scheme-3.9**). As already mentioned in Chapter-I, Minamoto and coworkers reported[11] the reactions of 5'-O-benzoyl-3'-O-mesyl-2,2'-O-anhydro-uridine **16c** with various primary amines. The initial nucleophilic attack at C-2 position produced the expected 2-amino(alkylamino)-*ara*-uridine **19** which further cyclised intramolecularly to give 2,3'-alkylimino-*ara*-uridine **20** (**Scheme-3.10**).

Interestingly, however, Reese and coworkers described[12,13] the nucleophilic opening reactions of 8,2'-O-anhydro-purine nucleosides by both primary and secondary amines. Thus 8-bromo-2'-O-tosyladenosine **21** on treatment with primary amines and secondary amines produced 8-alkylamino(dialkylamino)-*ara*- adenosine **23a-e** *via*, the formation of

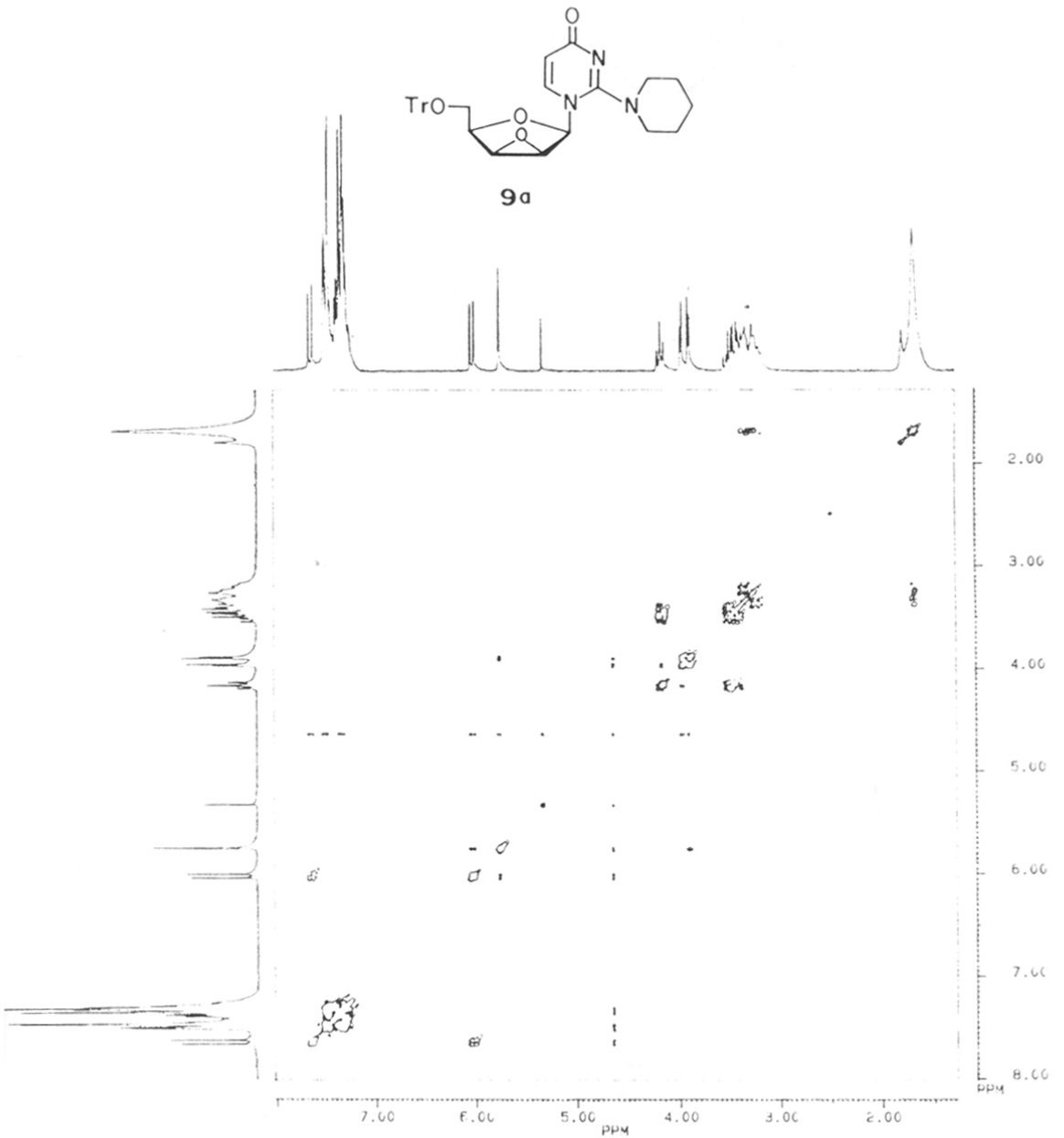
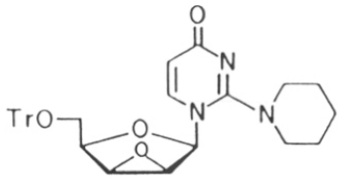

TrO
O
N
N
N
O
O
9a
2.00
3.00
4.00
5.00
6.00
7.00
8.00
ppm
7.00
6.00
5.00
4.00
3.00
2.00
ppm

Fig-3.3


O
N
TrO
O
O
N
N

9a

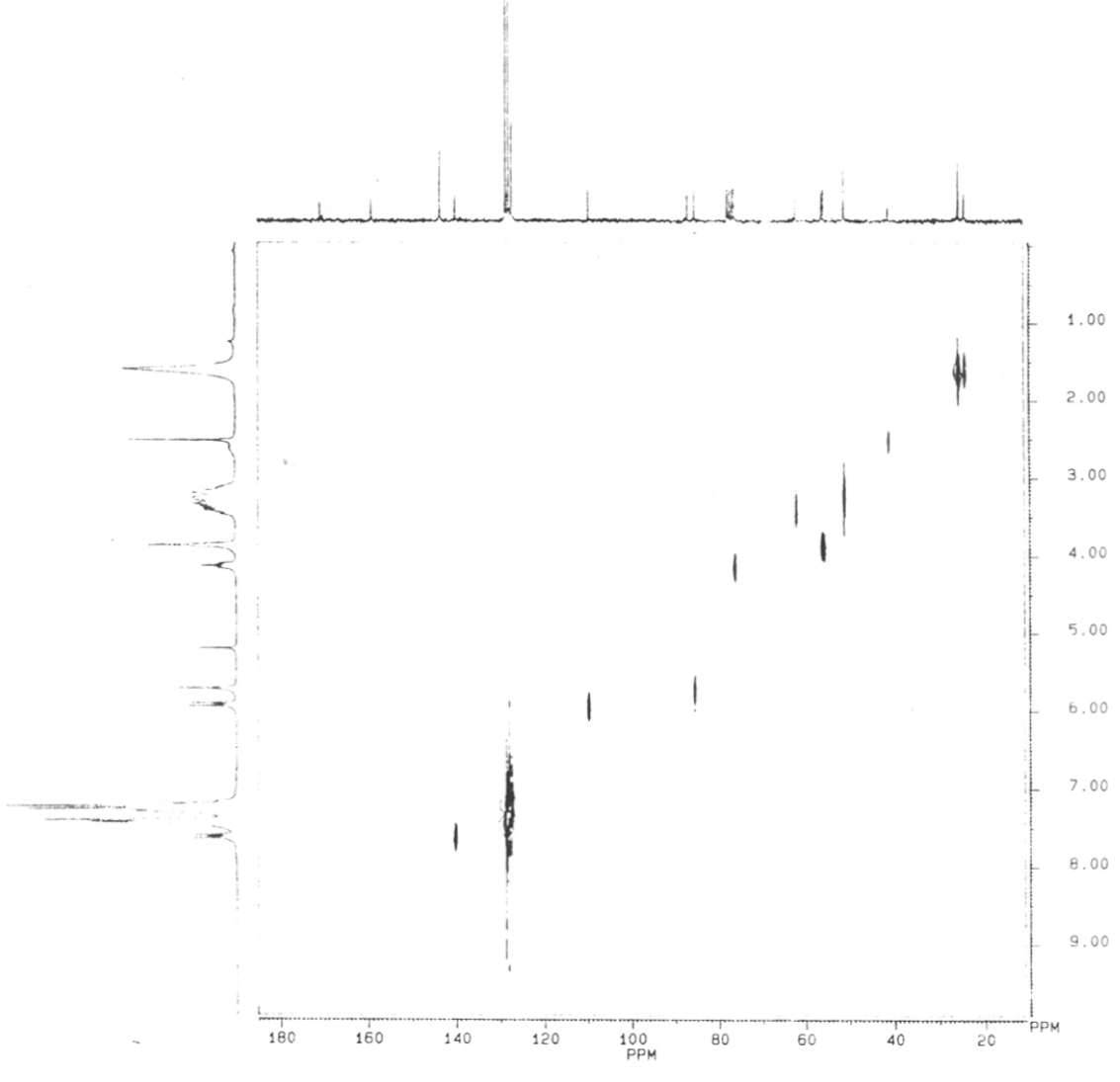

1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
180
160
140
120
100
80
60
40
20
PPM
PPM

Fig-3.4

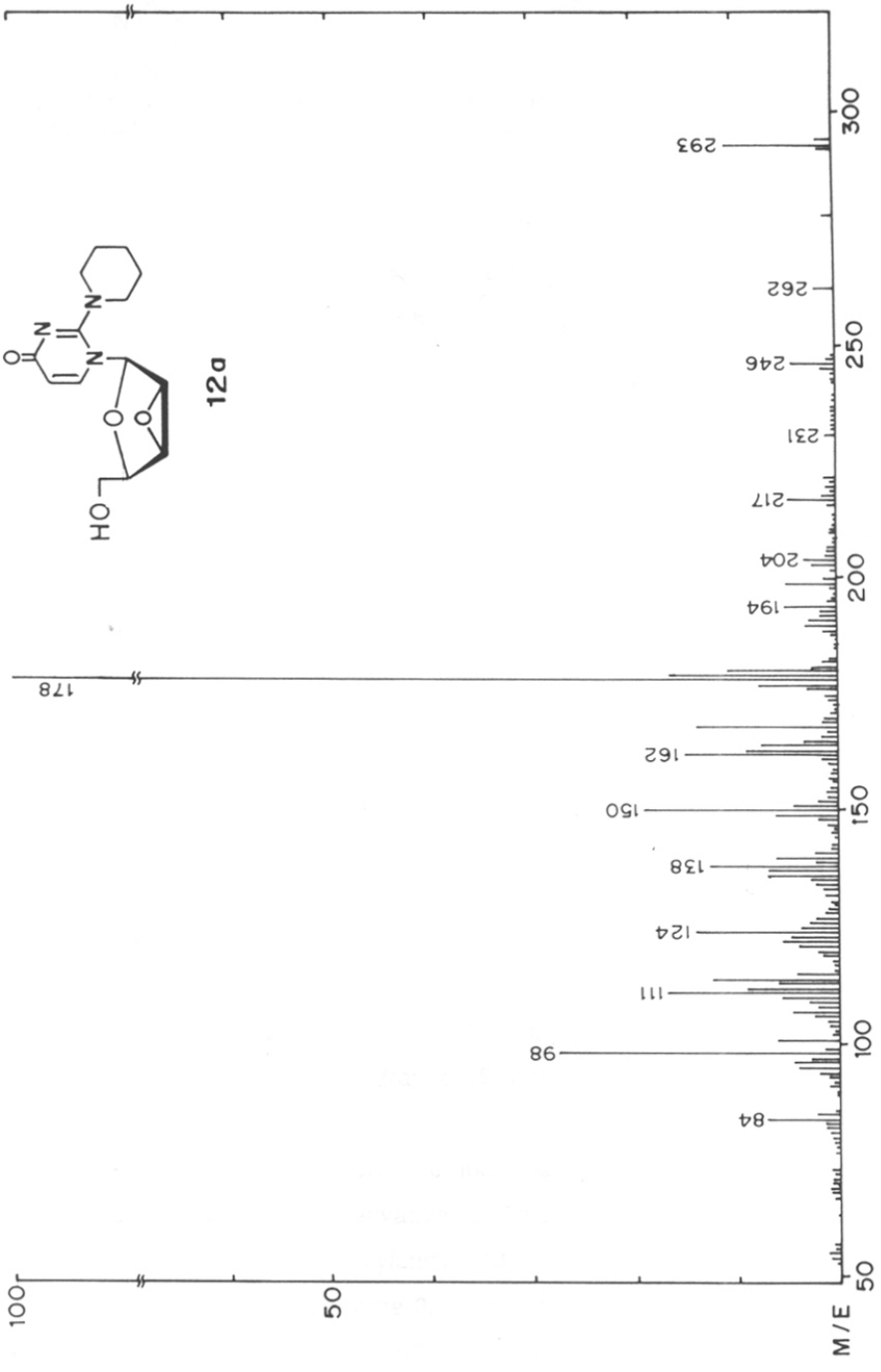
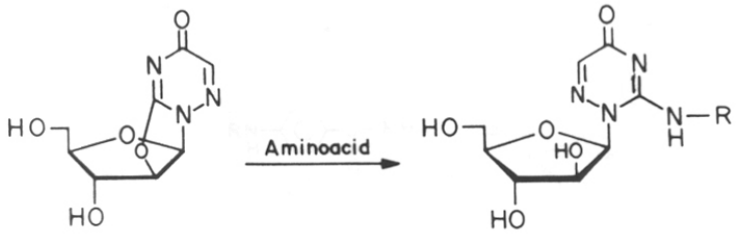

100
50
M/E
50
84
98
111
124
138
150
162
178
194
204
217
231
246
262
293
300
250
200
150
100
HO
12a

Fig-3·5

Scheme-3.8



14 **15a-d**

15a : R = CH_2COOH

15b : R = $(CH_2)_4 - CH(NH_2) - COOH$

15c : R = $(CH_2)_4 - CH(COOH) - NHCHO$

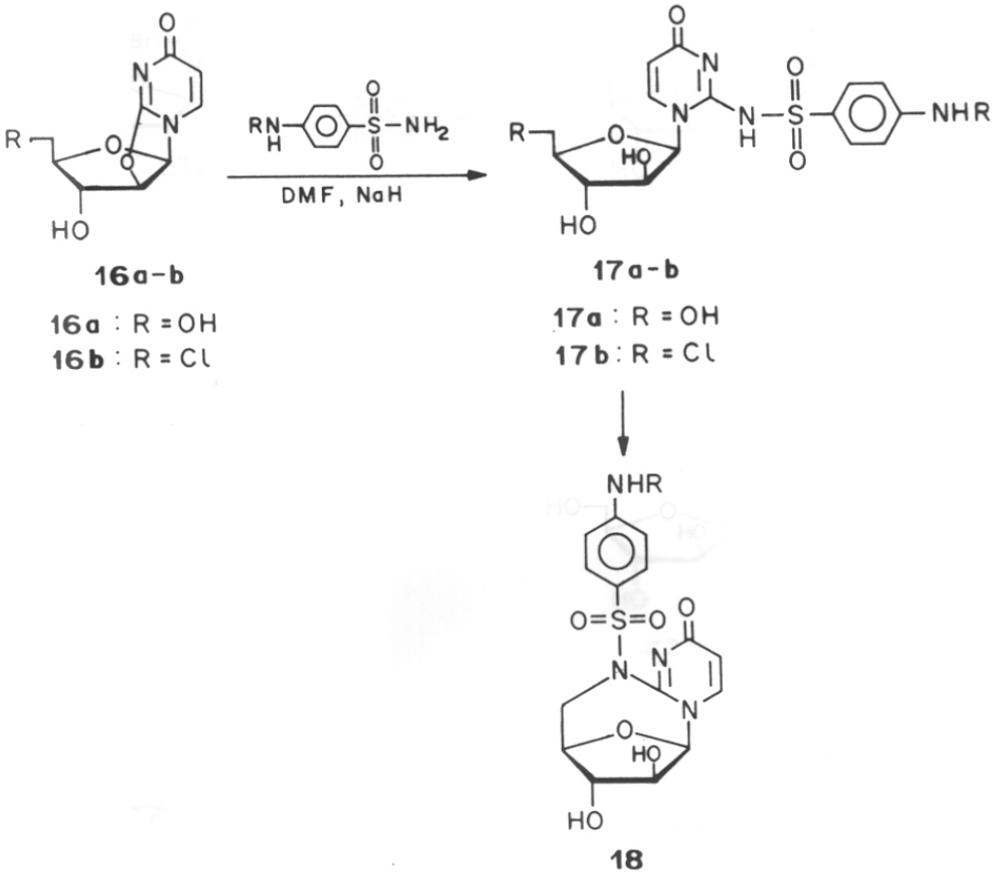
15d : R = $-CH(COOH)-(CH_2)_3-NH-C(=NH)-NH_2$

8,2'-O-anhydroadenosine **22** (ref.12). It was also reported[13] that compounds **24a** and **24b** on reaction with both primary and secondary amines afforded 8-aminosubstituted products **25a-c** and **26a-c** respectively (**Scheme-3.11**).

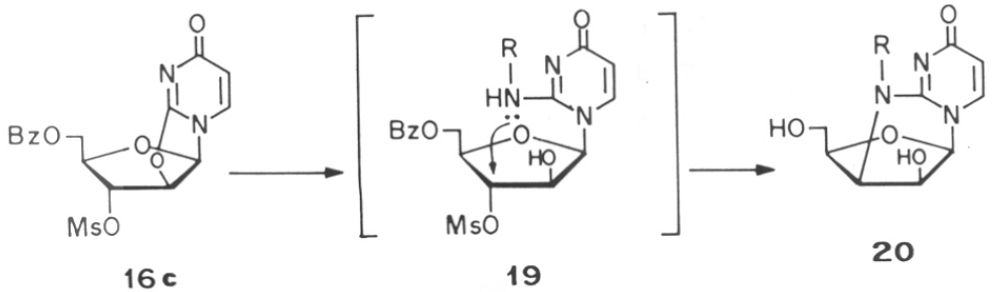
As far as our knowledge goes in the litrature[9-11], there was no report on the opening of 2,2'-O-anhydro-ring by secondary amines. However it was reported[14] that 2,2'-O-anhydrouridine **16a**, on reaction with primary amines produced C-2 amino substituted *ara*uridine derivatives **27** (*iso*cytidines, R= alkyl, benzyl etc.) but *remained unaffected by secondary amines* due to the "steric hindrance" (**Scheme-3.12**).

In our case, the mechanism of formation of compounds **9a-d** from **8** was believed to involve the formation of the 2,2'-O-anhydro-derivative **13**. This conclusion corroborated by the fact that 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine **13** (ref.15) on reaction with neat piperidine produced compound **9a** within 1h (**Scheme-3.13, path-a**). The opening of the 2,2'-O-anhydro-bridge by secondary amines in presence of 3'-O-mesyl- group could also be explained by

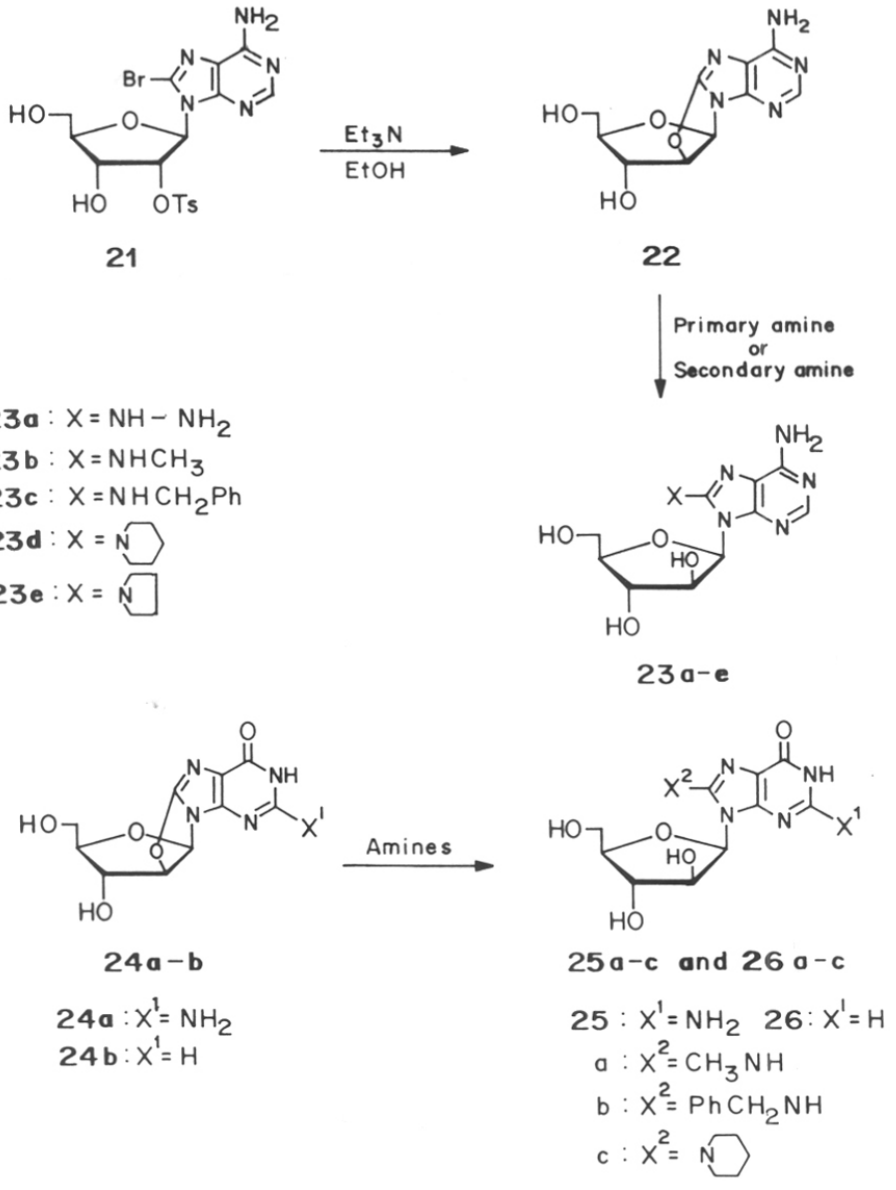
Scheme - 3·9



Scheme - 3·10

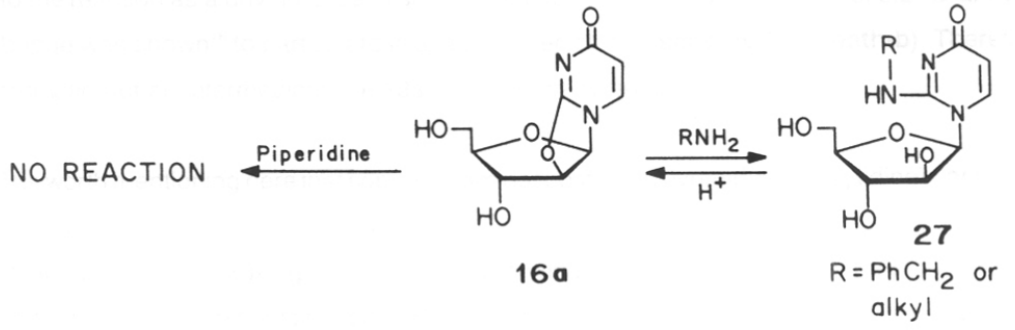


Scheme - 3·11

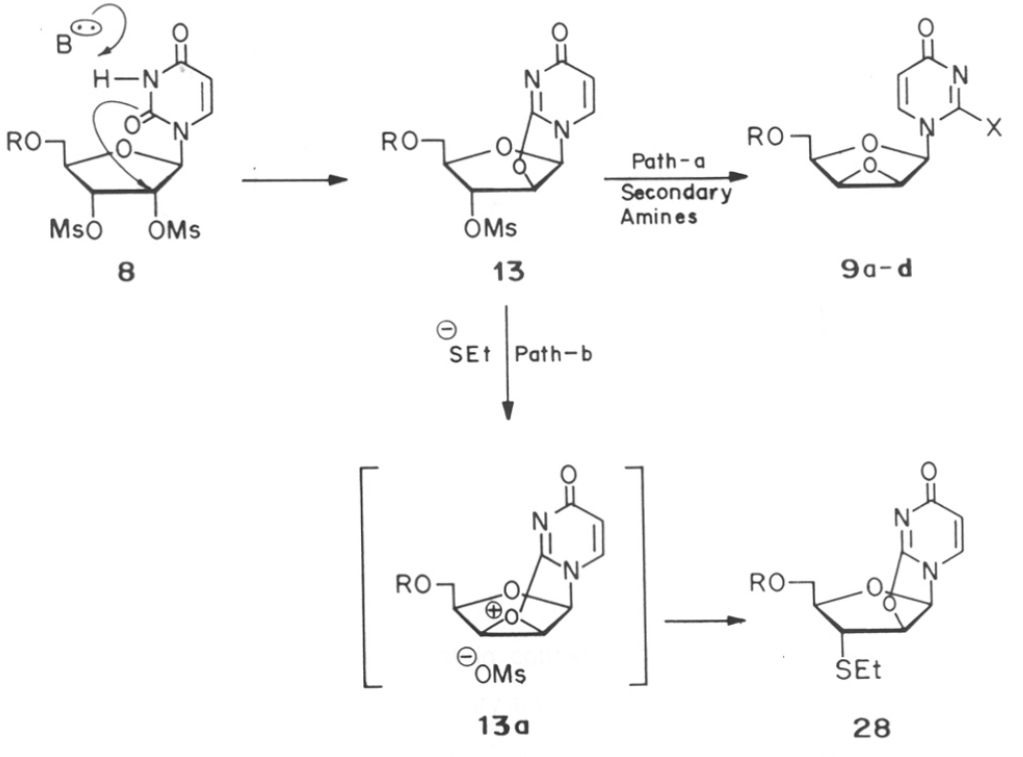


HSAB principle laid down by Hirota and coworkers[3] for nucleosides. The hard nucleophiles, secondary amines attacked the hard acidic C-2 position as expected followed by intramolecular epoxidation reaction to produce compounds **9a-d** and **12a-d**. It was obvious

Scheme - 3·12



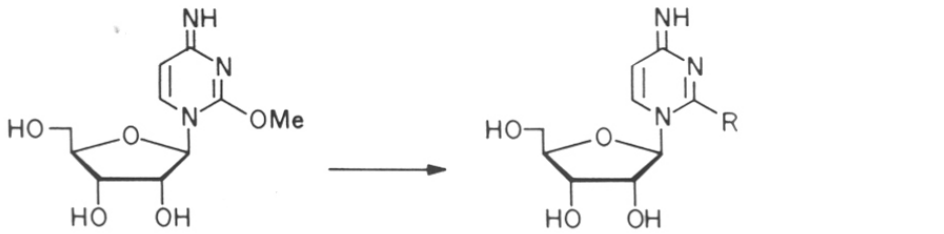
Scheme - 3·13



that the presence of an electron-withdrawing and a leaving group adjacent to the C-2' position of 2,2'-O-anhydrouridine enhanced the electrophilicity of the C-2 carbon, thereby nullifying the "steric" effect. However, it was not clear whether or not the epoxide formation contributed to the reaction as a driving force. It should be noted, that, the oxygen atom of 2,2'-O-anhydro bridge was shown[16] to participate in a fashion depicted in **scheme 3.13 (path-b)**. Therefore, formation of an intermediate like **13a** could not be ruled out.

It is worth mentioning here that some C-2 aminosubstituted pyrimidine (isocytidine) derivatives displayed interesting biological properties[10,17]. 4-Amino-2-(N^6-lysino)-1-(β-D-ribofuranosyl)prymidinium(lysine) **30** in the the first position of the anti-codon of minor isoleucine tRNA has been isolated and the structure was confirmed by chemical synthesis of **30** from **29** (ref.17) (**Scheme-3.14**).

Scheme - 3.14



29 **30**

$R = NH-(CH_2)_3-CH_2-\underset{\underset{COOH}{|}}{CH}-NH_2$

3.5. Conclusion

We have shown for the first time that in cotrast to the reported inert behaviour of 2,2'-O-anhydrouridine **16a** towards secondary amines, some secondary amines successfully opened the 2,2'-O-anhydro-bridge of 2,2'-O-anhydrouridines **13** and **11** containing 3'-O-mesyl group to produce compounds **9a-d** and **12a-d**, a new class of *iso*cytidine derivatives.

3.6. Experimental

Melting points were uncorrected. All amines were purchased from Aldrich, U.S.A. and were used without further purification. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS, solvent chloroform-d or dioxane (in case of D_2O) as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

Synthesis of 2',3'-di-O-mesyl-5'-O-trityluridine 8:

Compound **8** was synthesised using reported procedure[8].

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D- *lyxo*furanosyl)-uracil 9e: Compound **9e** was synthesised using a reported procedure[8].

Yield : 84%

^{1}H-NMR : ($CDCl_3$): δ 9.18 (bs,1H) NH; 7.55 (d, 8.2 Hz, 1H) H-6; 7.49-7.22 (m, 15H) trityl; 6.2 (s, 1H) H-1'; 5.67 (d, 8.2 Hz, 1H) H-5; 4.19 (t, 5.66 and 5.77 Hz, 1H) H-4'; 3.94 (d, 2.8 Hz, 1H) H-3'; 3.89 (d, 2.8 Hz, 1H) H-2'; 3.52-3.32 (m, 2H) H-5', H-5'

^{13}C-NMR : ($CDCl_3$): δ 163.60, C-4; 150.9, C-2; 143.6, trityl; 141.5, C-6; 128.8, 128.2, 127.4, trityl; 102.6, C-5; 87.3, trityl; 81.9, C-1'; 76.9, C-4'; 62.4, C-5'; 56.4/56.2, C-2'/C-3'.

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl) -2-piperidino-4-pyrimidone 9a:

Method A: Compound **8** (1mmol) was treated with neat piperidine (3ml) at ambient temperature. After 5h, the reaction mixture was poured into petroleum ether (50ml) and the liquid was decanted off. The oily residue was purified by column chromatography on basic alumina. Yield: 50%.

Method B: A solution of compound **8** (1mmol) in DMSO (2ml) was treated with piperidine (15mmol) at ambient temperature. After 48h the reaction mixture was poured into water. The white precipitate was collected by filteration and dissolved in dichloromethane (25ml). The solution was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified as above.

Yield : 55%

M.P : 102°C

^{1}H-NMR : ($CDCl_3$): δ 7.61 (d, 7.8 Hz, 1H) H-6; 7.5-7.24 (m, 15H) trityl; 6.0 (d, 7.8 Hz, 1H) H-5; 5.74 (s, 1H) H-1'; 4.16 (t, 6.1 and 6.0 Hz, 1H) H-4'; 3.95 (d, 2.9 Hz, 1H) H-3'; 3.89 (d, 2.9 Hz, 1H) H-2'; 3.53-3.18 (m, 6H) H-5', H-5'', H_2C-N-CH_2; 1.66 (bs, 6H) H_2C-CH_2-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 171.0, C-4; 159.3, C-2; 143.8, trityl; 140.1, C-6; 128.8, 128.2, 127.5, trityl; 110.2, C-5; 87.5, trityl; 85.8, C-1'; 76.5, C-4'; 62.3, C-5'; 56.3/55.8, C-2'/C-3'; 51.2, H_2C-N-CH_2; 25.7 and 24.4, H_2C-CH_2-CH_2

Mass (EI) : : 535 (M^+, 6%); 178 ($C_9H_{12}N_3O^+$, 100%).

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)- 2-pyrrolidino-4-pyrimidone 9b:

Compound **8** (1mmol) was treated with neat pyrrolidine (3ml) at ambient temperature. After 3h, the reaction mixture was evaporated to dryness under reduced pressure. The oily residue was purified by column chromatography on basic alumina.

Yield : 50%

M.P : 95°C

^{1}H-NMR : ($CDCl_3$): δ 7.62 (d, 7.7 Hz, 1H) H-6; 7.51-7.23 (m, 15H) trityl; 5.98 (d, 7.7 Hz, 1H) H-5; 5.68 (s, 1H) H-1'; 4.13 (t, 6.2 and 6.0 Hz, 1H) H-4'; 3.95 (d, 2.9 Hz, 1H) H-3'; 3.88 (d, 2.9 Hz, 1H) H-2'; 3.58-3.27 (m, 6H) H-5', H-5'', H_2C-N-CH_2; 2.0-1.92 (m, 4H) CH_2-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 170.6, C-4; 156.9, C-2; 143.8, trityl; 139.6, C-6; 128.9, 128.2, 127.6, trityl; 109.8, C-5; 87.5, trityl; 85.4, C-1'; 76.5, C-4'; 62.3, C-5'; 56.4/55.7, C-2'/C-3'; 50.9, H_2C-N-CH_2; 25.9, CH_2-CH_2

Mass (EI) : : 521 (M^+, 2%); 164 ($C_8H_{10}N_3O^+$, 100%)

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)- 2-(N-methylpiperazino)-4-pyrimidone 9c:

Compound **8** (1mmol) was treated with neat N-methylpiperazine (2ml) at ambient temperature for 48h. The product was isolated and purified as described in Method B for the preparation of compound **9a**.

Yield : 42%

M.P : 96°C

^{1}H-NMR : ($CDCl_3$): δ 7.65 (d, 7.7 Hz, 1H) H-6; 7.54-7.24 (m, 15H) trityl; 6.02 (d, 7.7 Hz, 1H) H-5; 5.73 (s, 1H) H-1'; 4.15 (t, 6.2 and 6.0 Hz, 1H) H-4'; 3.97 (d, 2.9 Hz, 1H) H-3'; 3.88 (d, 2.9 Hz, 1H) H-2'; 3.59-3.28 (m, 6H) H-5', H-5'', H_2C-N-CH_2; 2.64-2.43 (m, 4H) H_2C-N-CH_2; 2.35 (s, 3H) N-CH_3

^{13}C-NMR : ($CDCl_3$): δ 170.7, C-4; 158.3, C-2; 143.6, trityl; 139.9, C-6; 128.7, 128.0, 127.4, trityl; 110.2, C-5; 87.4, trityl; 85.6, C-1'; 76.4, C-4'; 62.1, C-5'; 56.1/55.6, C-2'/C-3'; 54.4 and 49.6 (H_2C-N-CH_2)$_2$; 46.0, N-CH_3

Mass (EI) : : m/z 550 (M^+, 2%)

Synthesis of 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)-2-(ethyl *iso*nipecotyl)-4-pyrimidone 9d:

Compound **8** (1mmol) was treated with neat ethyl *iso*nipecotate (2ml) at ambient temperature for 21h. The product was isolated and purified as described in Method A for the preparation of compound **9a**.

Yield : 40%

M.P : 93°C

^{1}H-NMR : ($CDCl_3$): δ 7.67 (d, 7.7 Hz, 1H) H-6; 7.57-7.27 (m, 15H) trityl; 6.04 (d, 7.7 Hz, 1H) H-5; 5.75 (s, 1H) H-1'; 4.24-4.12 (m, 3H) H-4', ethyl CH_2; 3.96 (d, 2.7 Hz, 1H) H-3'; 3.88 (d, 2.7 Hz, 1H) H-2'; 3.87-3.37/3.14-2.79/2.58-2.48/2.12-1.7 (m, 11H) H-5', H-5'', H_2C-N-CH_2, H_2C-CH-CH_2; 1.3 (t, 3H) ethyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 174.5, ethyl CO; 170.9, C-4; 158.9, C-2; 143.7, trityl; 140.1, C-6; 128.9, 128.2, 127.5, trityl; 110.4, C-5; 87.5, trityl; 85.7, C-1'; 76.5, C-4'; 62.2, C-5'; 60.9 ethyl CH_2; 56.2/55.8, C-2'/C-3'; 50.0 and 49.3, H_2C-N-CH_2; 40.9 nipecotyl CH; 28.0 and 27.9, nipecotyl CH_2; 14.4, ethyl CH_3

Mass (EI) : : m/z 607 (M^+, 2%)

Synthesis of 2,2'-O-anhydro-3'-O-mesyluridine 11:

Compound **11** was synthesised using reported procedure[6].

Synthesis of 1-(2,3-O-anhydro-β-D-*lyxo*-furanosyl)-uracil 12e:

Compound **12e** was synthesised using a reported procedure[7].

Yield : 90%

M.P : 138°C (139-140°C)[7]

UV-λ_{Max} : 259.7nm (H_2O)

^{1}H-NMR : (D_2O): δ 7.88 (d, 8.2 Hz, 1H) H-6;6.2 (s, 1H) H-1'; 5.87 (d, 8.2 Hz, 1H) H-5; 4.29 (t, 6.01 and 5.23 Hz, 1H) H-4'; 4.18 (d, 3.6 Hz, 1H) H-3'; 4.12 (d, 3.6 Hz, 1H) H-2'; 3.98-3.81 (m, 2H) H-5', H-5''

^{13}C-NMR : (D_2O): δ 167.2, C-4; 152.7, C-2; 143.9, C-6; 103.1, C-5; 83.2, C-1'; 78.9, C-4'; 61.1, C-5'; 57.2/57.1, C-2'/C-3'.

Synthesis of 1-(2,3-O-anhydro-β-D-*lyxo*- furanosyl)-2-piperidino-4- pyrimidone 12a:

A solution of compound **11** (1mmol) in DMSO (2ml) was treated with piperidine (2ml) at ambient temperature. After 8h the reaction mixture was poured into ether (50ml) and the liquid was decanted off. The residue was purified by column chromatography on basic alumina.

Yield : 80%

M.P : 75°C

UV-λ_{Max} : 235.2nm (H_2O)

^{1}H-NMR : (D_2O): δ 8.0 (d, 7.7 Hz, 1H) H-6; 6.13 (d, 7.7 Hz, 1H) H-5; 5.89 (s, 1H) H-1'; 4.28 (t, 5.7 and 5.6 Hz, 1H) H-4'; 4.19 (d, 3.2 Hz, 1H) H-3'; 4.12 (d, 3.2 Hz, 1H) H-2'; 4.0-3.8 (m, 2H) H-5', H-5''; 3.41-3.38 (m, 4H) H_2C-N-CH_2; 1.69 (bs, 6H) H_2C-CH_2-CH_2

^{13}C-NMR : (DMSO-d_6): δ 168.9, C-4; 158.3, C-2; 139.9, C-6; 108.9, C-5; 85.2, C-1'; 77.4, C-4'; 59.4, C-5'; 55.7/55.1, C-2'/C-3'; 50.1, H_2C-N-CH_2; 24.7 and 23.5, H_2C-CH_2-CH_2.

Mass (EI) : : m/z 293 (M^+, 11%); 178 ($C_9H_{12}N_3O^+$, 100%).

Synthesis of 1-(2,3-O-anhydro-β-D-*lyxo*- furanosyl)-2-pyrrolidino-4 -pyrimidone 12b:

A solution of compound **11** (1mmol) in DMSO (2ml) was treated with pyrrolidine (2ml) for 10h at ambient temperature. The product was isolated and purified as described in case of compound **12a**.

Yield : 75%

M.P : 70°C

UV-λ_{Max} : 230.3nm (H_2O)

^{1}H-NMR : (D_2O): δ 7.89 (d, 7.7 Hz, 1H) H-6; 6.01 (d, 7.7 Hz, 1H) H-5; 5.95 (s, 1H) H-1'; 4.22 (t, 5.7 and 5.6 Hz, 1H) H-4'; 4.16 (d, 3.3 Hz, 1H) H-3'; 4.07 (d, 3.3 Hz, 1H) H-2'; 3.97-3.8 (m, 2H) H-5', H-5''; 3.7-3.55 (m, 4H) H_2C-N-CH_2; 2.0-1.88 (m, 4H) H_2C-CH_2

^{13}C-NMR : (D_2O): δ 174.2, C-4; 157.9, C-2; 143.3, C-6; 108.0, C-5; 86.7, C-1'; 78.7, C-4'; 61.2, C-5'; 57.3/56.7, C-2'/C-3'; 51.9, H_2C-N-CH_2; 26.3, CH_2-CH_2

Mass (EI) : : m/z 279 (M^+, 4%); 164 ($C_8H_{10}N_3O^+$, 100%)

Synthesis of 1-(2,3-O-anhydro-β-D-*lyxo*-furanosyl)-2- (N-methylpiperazino)-4-pyrimidone 12c:

A solution of compound **11** (1mmol) in DMSO (2ml) was treated with N-methylpiperazine (2ml) at ambient temperature. After 16h the reaction mixture was loaded directly on a basic alumina column packed in petroleum ether. The column was eluted with the same solvent until all the DMSO and excess amine were removed. The polarity of the eluent was increased gradually and the product was eluted with a mixture of methanol-ethyl acetate (1:9).

Yield : 65%

M.P : 65°C

UV-λ_{Max} 232.4nm (H_2O)

^{1}H-NMR : (D_2O): δ 8.05 (d, 7.7 Hz, 1H) H-6; 6.19 (d, 7.7 Hz, 1H) H-5; 5.96 (s, 1H) H-1'; 4.29 (t, 6.1 and 5.2 Hz, 1H) H-4'; 4.19 (d, 3.0 Hz, 1H) H-3'; 4.13 (d, 3.5 Hz, 1H) H-2'; 4.0-3.85 (m, 2H) H-5', H-5''; 3.6-3.4 (m, 4H) H_2C-N-CH_2; 2.64 (bs, 4H) H_2C-N-CH_2; 2.34 (s, 3H) N-CH_3

^{13}C-NMR : (D_2O): δ 174.6, C-4; 160.2, C-2; 143.9, C-6; 109.4, C-5; 87.4, C-1'; 78.7, C-4'; 61.1, C-5'; 57.1/56.6, C-2'/C-3'; 54.3, H_2C-N-CH_2; 49.8, H_2C-N-CH_2; 45.6, N-CH_3

Mass (EI) : : m/z 308 (M^+, 1%)

Synthesis of 1-(2,3-O-anhydro-β-D-*lyxo*- furanosyl)-2-(ethyl *iso*nipecotyl)-4-pyrimidone 12d:

A solution of compound **11** (1mmol) in DMSO (2ml) was treated with ethyl *iso*nipecotate (2ml) for 24h at ambient temperature. The product was isolated and purified as described in case of compound **12a**.

Yield : 40%

M.P : 62°C

UV-λ_{Max} 234.4nm (H_2O)

^{1}H-NMR : (D_2O): δ 8.05 (d, 7.7 Hz, 1H) H-6; 6.18 (d, 7.7 Hz, 1H) H-5; 5.93 (s, 1H) H-1'; 4.34-4.14 (m, 5H) H-2', H-3', H-4', ethyl CH_2 ; 4.03-3.72 (m, 4H)/3.2-3.05 (m, 2H)/2.8-2.65 (m, 1H)/2.1-1.79 (m, 4H) H-5', H-5'', H_2C-N-CH_2, H_2C-CH-CH_2; 1.32 (t, 3H) ethyl CH_3

^{13}C-NMR : (D_2O): δ 173.9, ethyl CO; 168.9, C-4; 158.2, C-2; 140.1, C-6; 109.1, C-5; 85.2, C-1'; 77.5, C-4'; 59.8/59.4, ethyl CH_2/ C-5'; 55.8/55.2, C-2'/C-3'; 48.7 and 48.5, H_2C-N-CH_2; 39.7, nipecotyl CH; 27.2 and 27.0, nipecotyl CH_2; 14.0, ethyl CH_3

Mass (EI) : : m/z 210 ((M^+-$C_8H_{14}NO_2$)+1, 6%)

Synthesis of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine 13:

Compound **13** was synthesised using reported procedure[15].

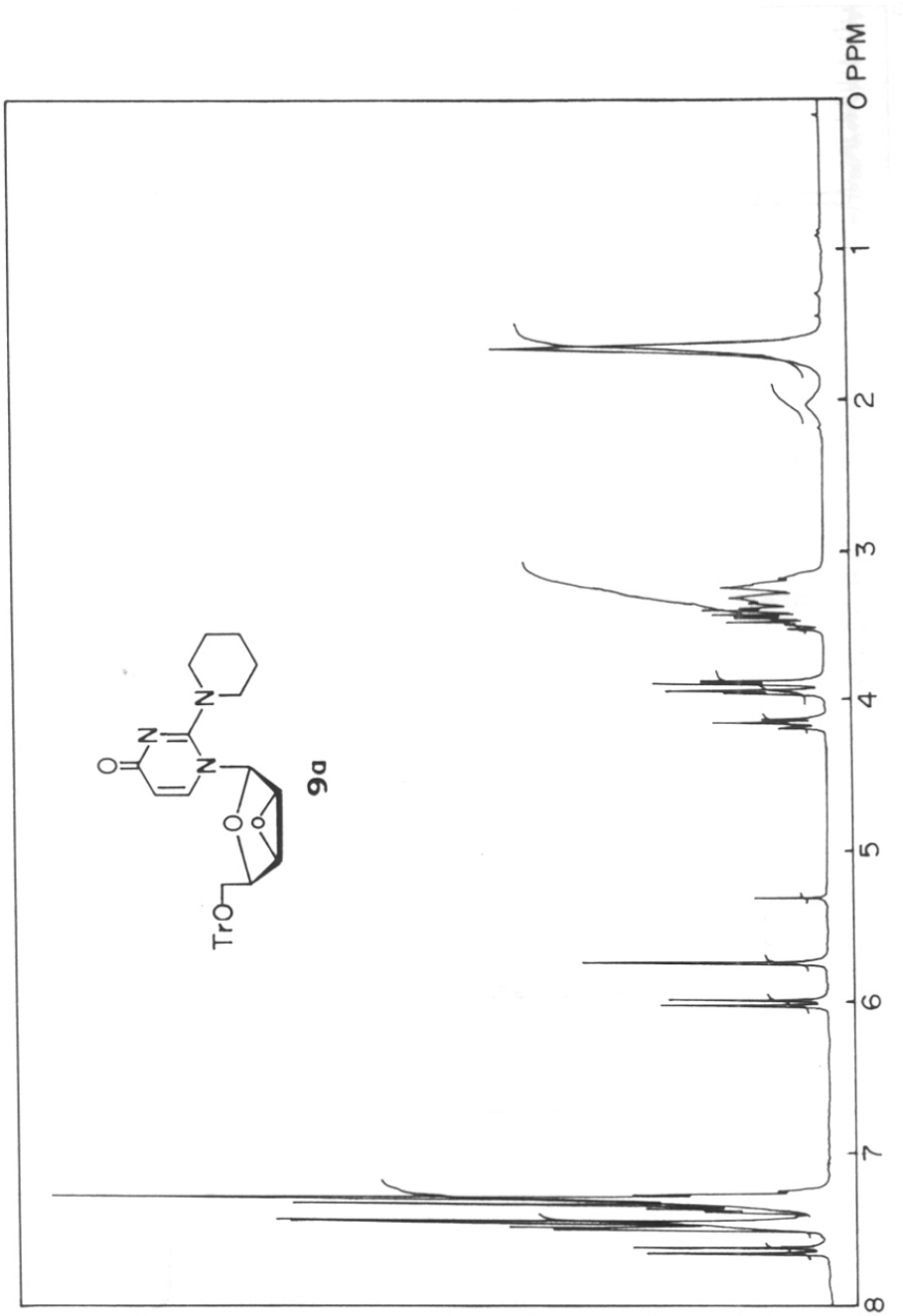
Reaction of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine 13 with piperidine:

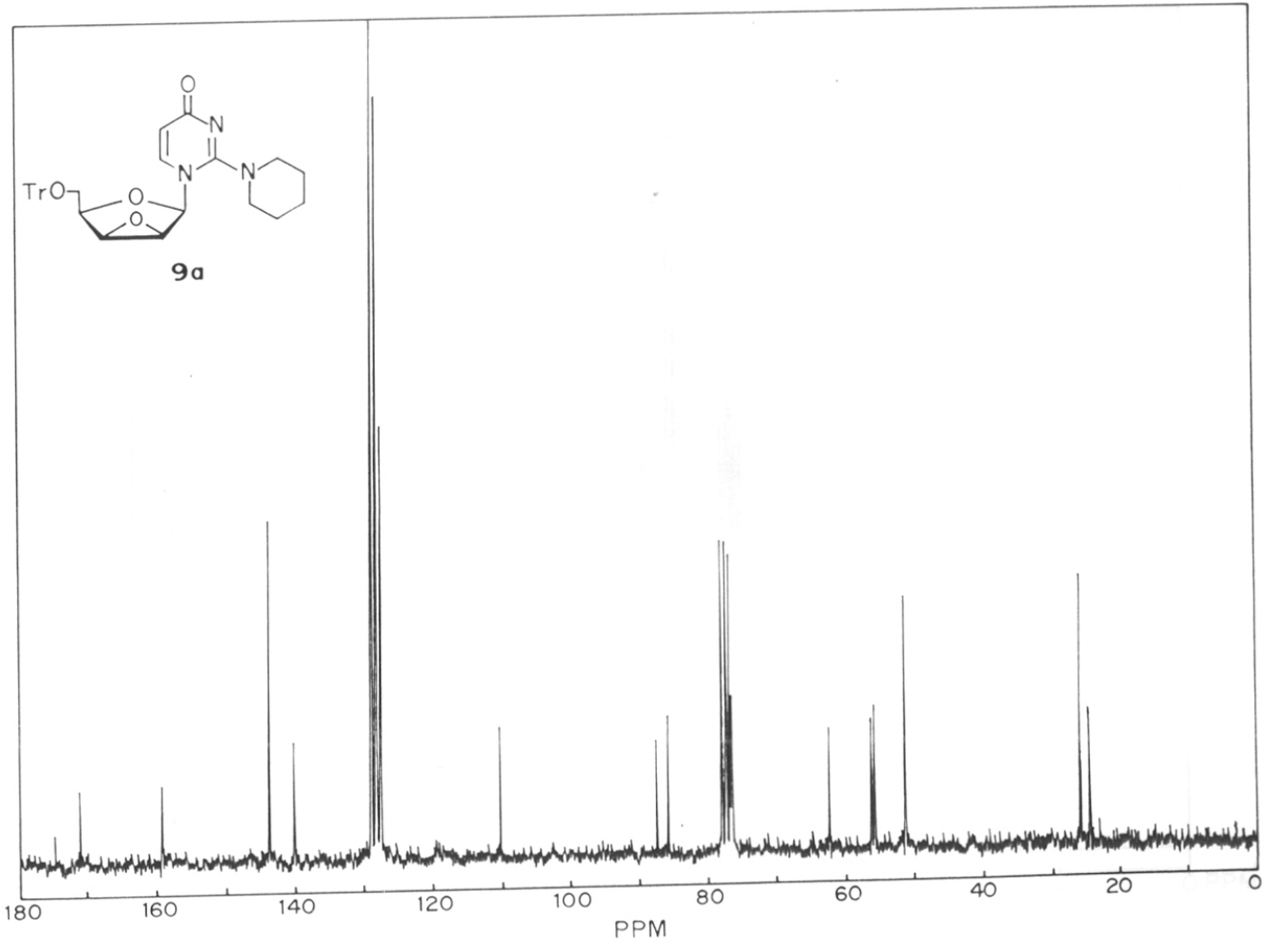
Compound **13** (1mmol) was treated with neat piperidine (3ml) at ambient temperature. After 1h, the reaction mixture was poured into petroleum ether (50ml) and the liquid was decanted off. The oily residue was purified by column chromatography on basic alumina. Yield: 60%.

3.7. References

1. Fox, J. J.; *Pure Appl. Chem;* **1969**, 18, 223-55.
2. Moffatt, J. G.; *In nucleoside Anologues: Chemistry, Biology And Medical Applications.;* Walker, R.T.; De Clercq, E.; Ecstein, F.; Eds.; Plenum Press, Newyork, **1979**, 71-164.
3. Hirota, K.; Kitade, Y.; Tomishi, T.; Maki, Y.; Clarcq, E. De.; *J. Chem. Soc.Perkin Trans I*, **1988**, 2233-41.
4. Sakthivel, K.; Krishna Kumar, R.; Pathak, T. *Tetrahedron*, **1993**, 49, 4365-72.
5. Secrist, J.A. *Carbohydr. Res.*, **1975**, 42, 379-81.
6. Fecher, R.; Codington, J.F.; Fox, J.J. *J. Am. Chem. Soc.*, **1961**, 83, 1889-95.
7. Codington, J.F.; Fecher, R.; Fox, J.J. *J. Org. Chem.*, **1962**, 27, 163-7.
8. Ashwell, M.; Jones, A.S.; Walker, R.T. *Nucleic Acids Res.*, **1987**, 15, 2157-66.
9. Hrebabecky, H.; Beranek, J.; *Collec. Czec. Chem. Commun.*, **1984**, 49, 2689-97
10. Novotny, L;, Hrebabecky, H; Beranek, J. *Collec. Czec. Chem. Commun.*, **1985**, 50, 383-92.
11. Minamoto, K.; Tanaka, T.; Azuma, K.; Suzuki, N.; Eguchi, S. *J. Org. Chem.*, **1986**, 51, 4417-24.
12. Chattopadhyaya, J.B.; Reese, C.B. *J. Chem. Soc. Chem. Comm.*, **1977**, 414-5.
13. Chattopadhyaya, J.B.; Reese, C.B. *Synthesis*, **1978**, 908-10.
14. Delia, T.J.; Beranek, J. *J. Carb. Nucleosides Nucleotides*, **1977**, 4, 349-62.
15. Sasaki, T.; Minamoto, K.; Sugiura, T. *J. Org. Chem.*, **1975**, 40, 3498-502.
16. Hirota, M.; *Chem. Pharm. Bull.*, **1968**, 16, 291-5.
17. Muramatsu, T.; Yokoyama, S.; Horie, N.; Matsuda, A.; Ueda, T.; Yamaizumi, Z.; Kuchino, Y.; Nishimura, S.; Miyazawa, T. *J. Biol. Chem.*, **1988**, 263, 9261-7.

3.8. Spectra

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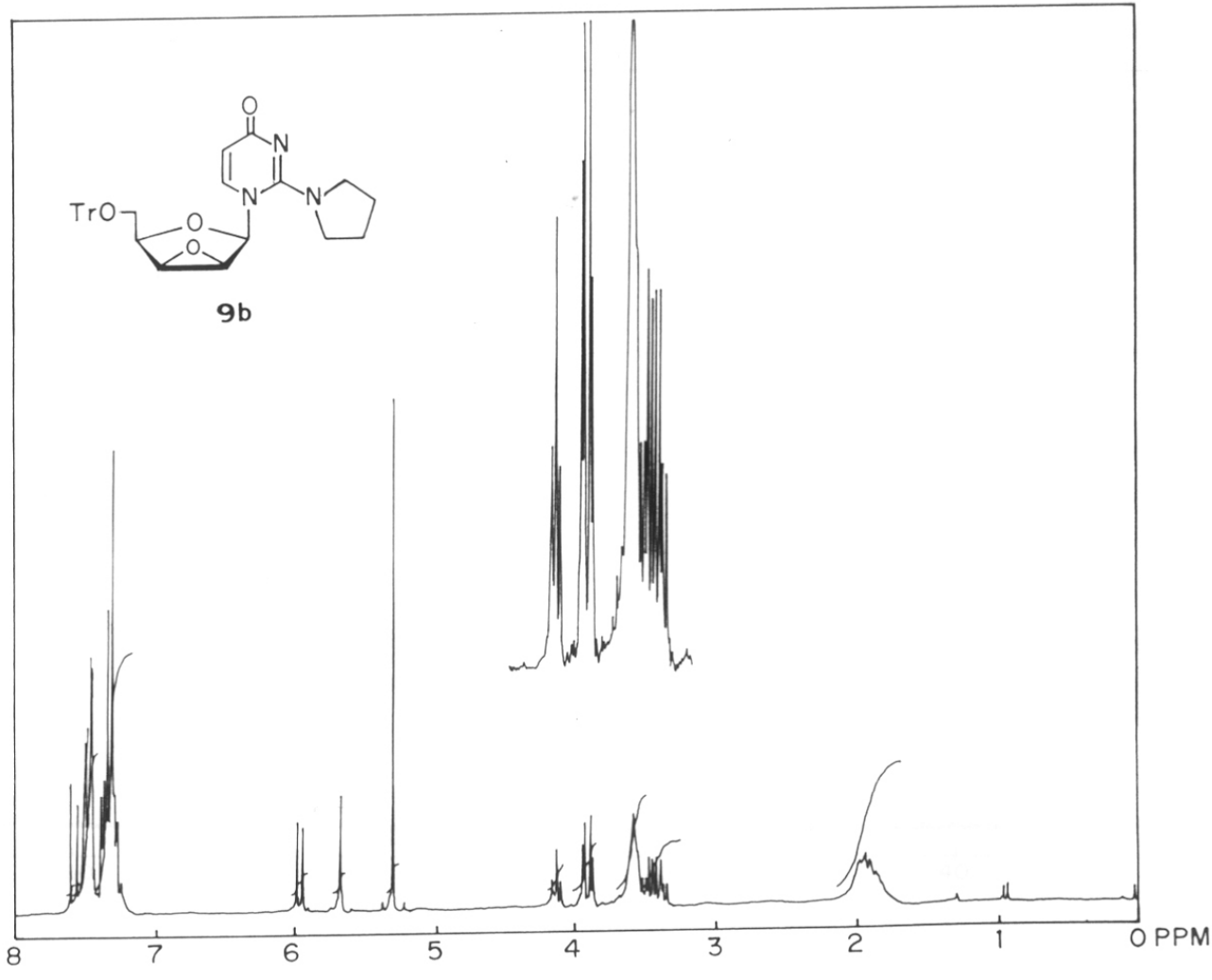
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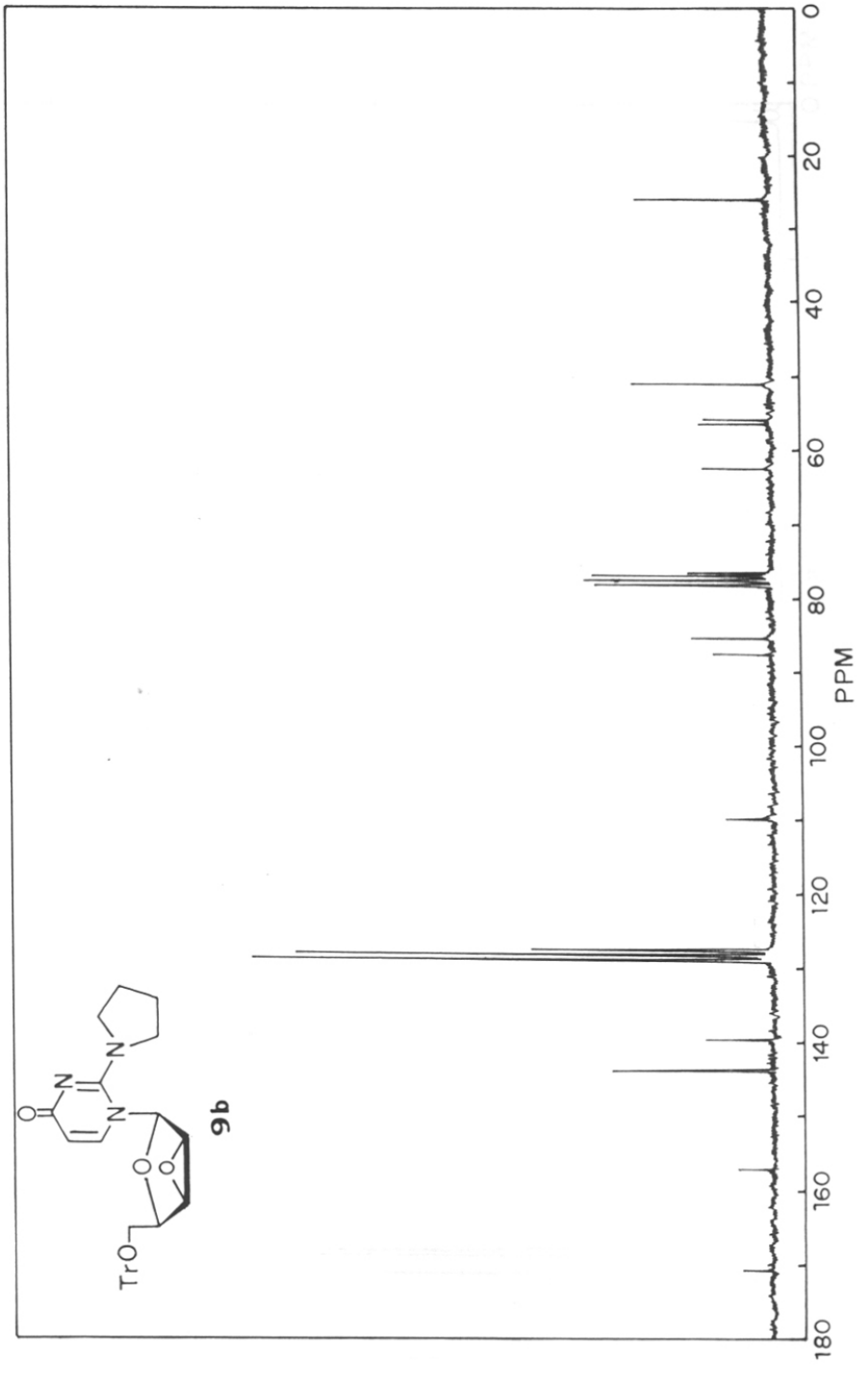
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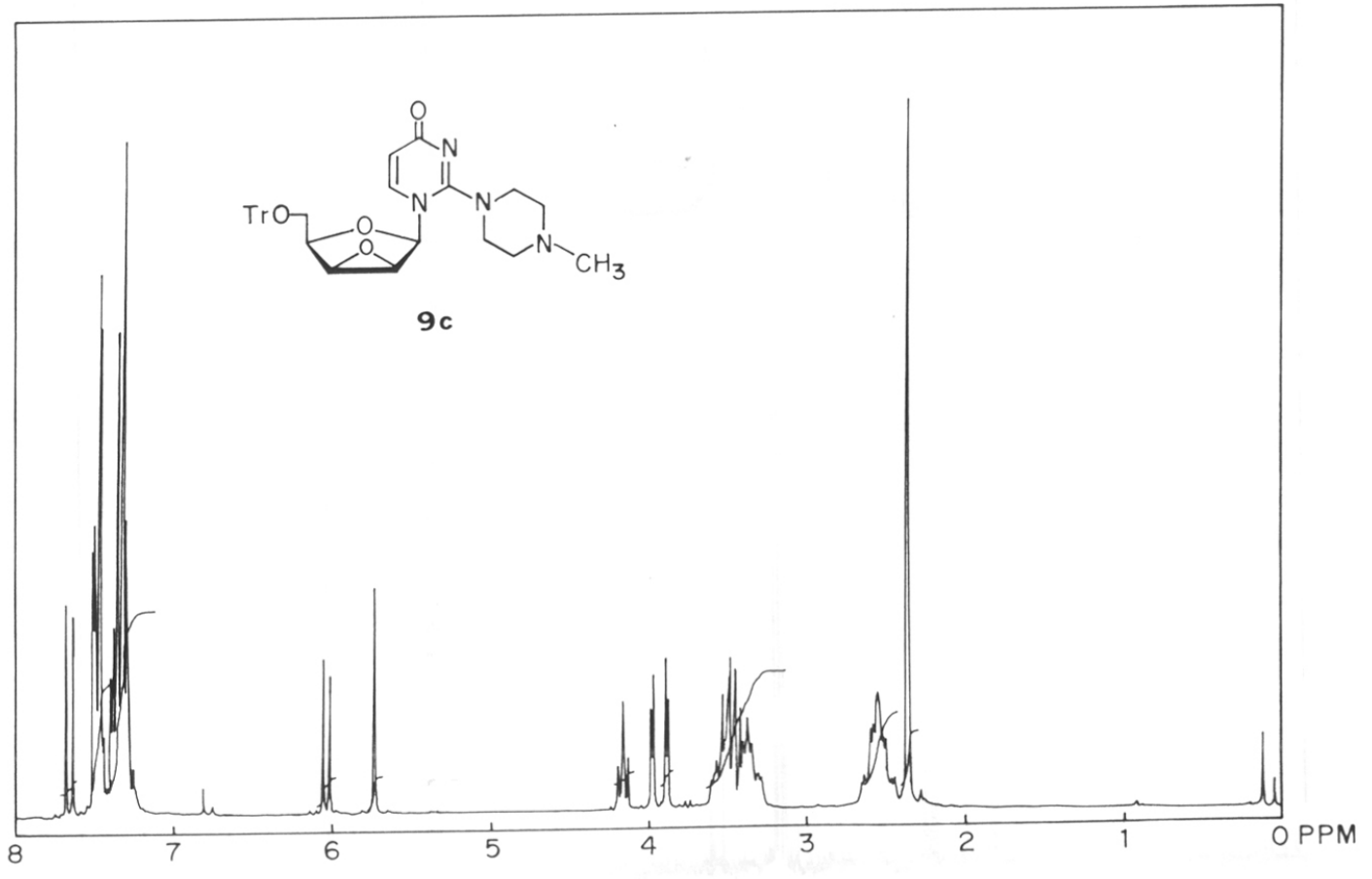
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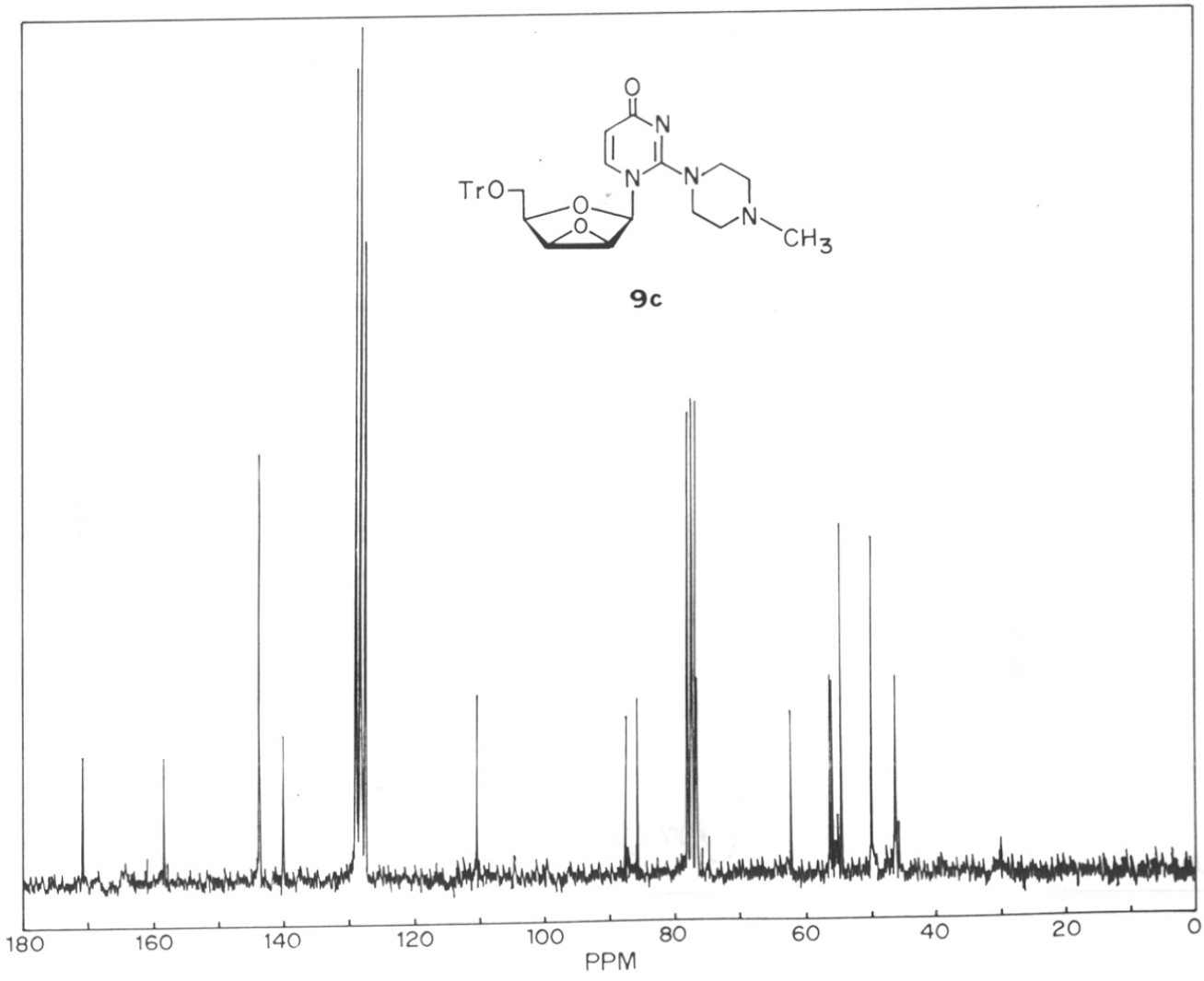

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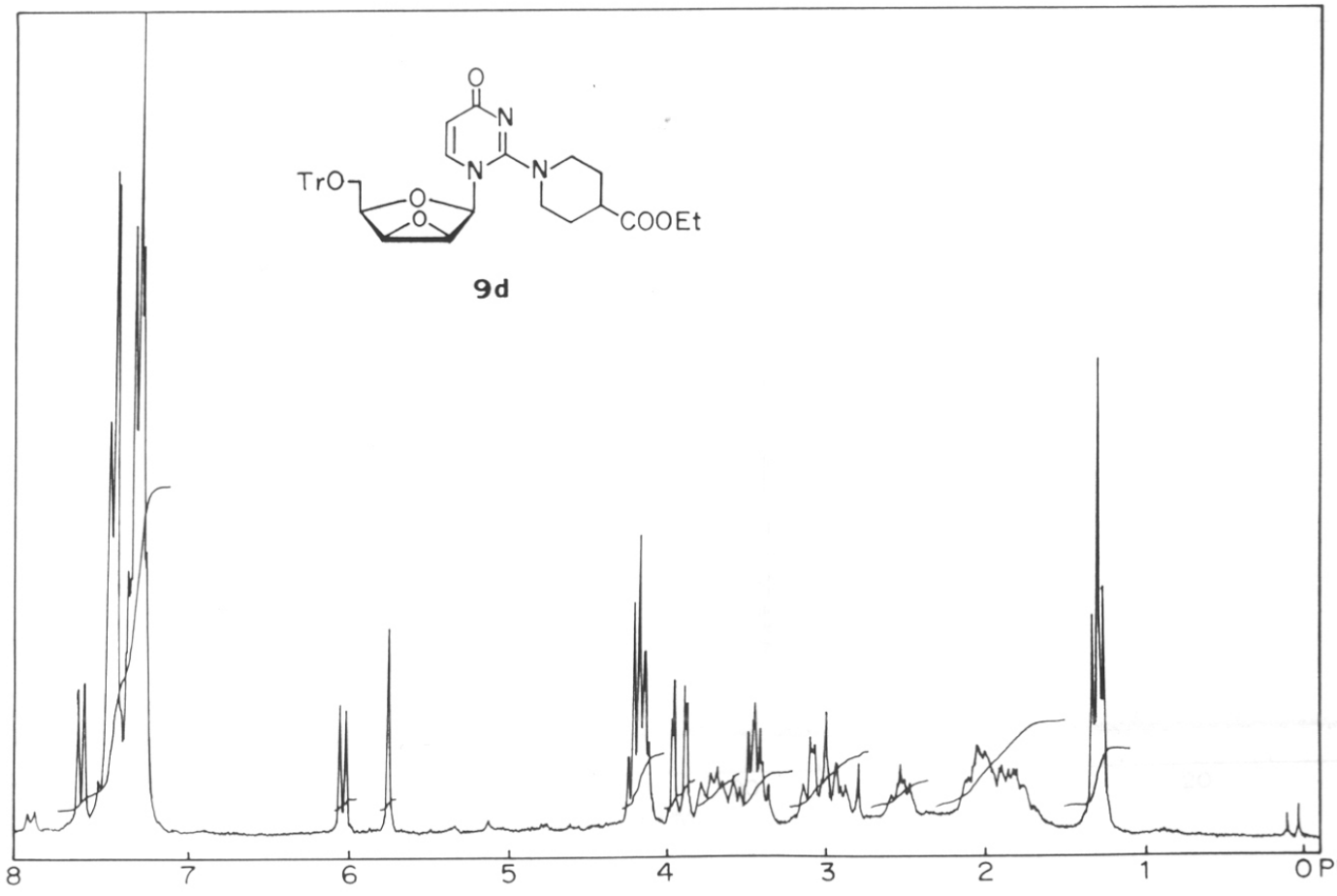

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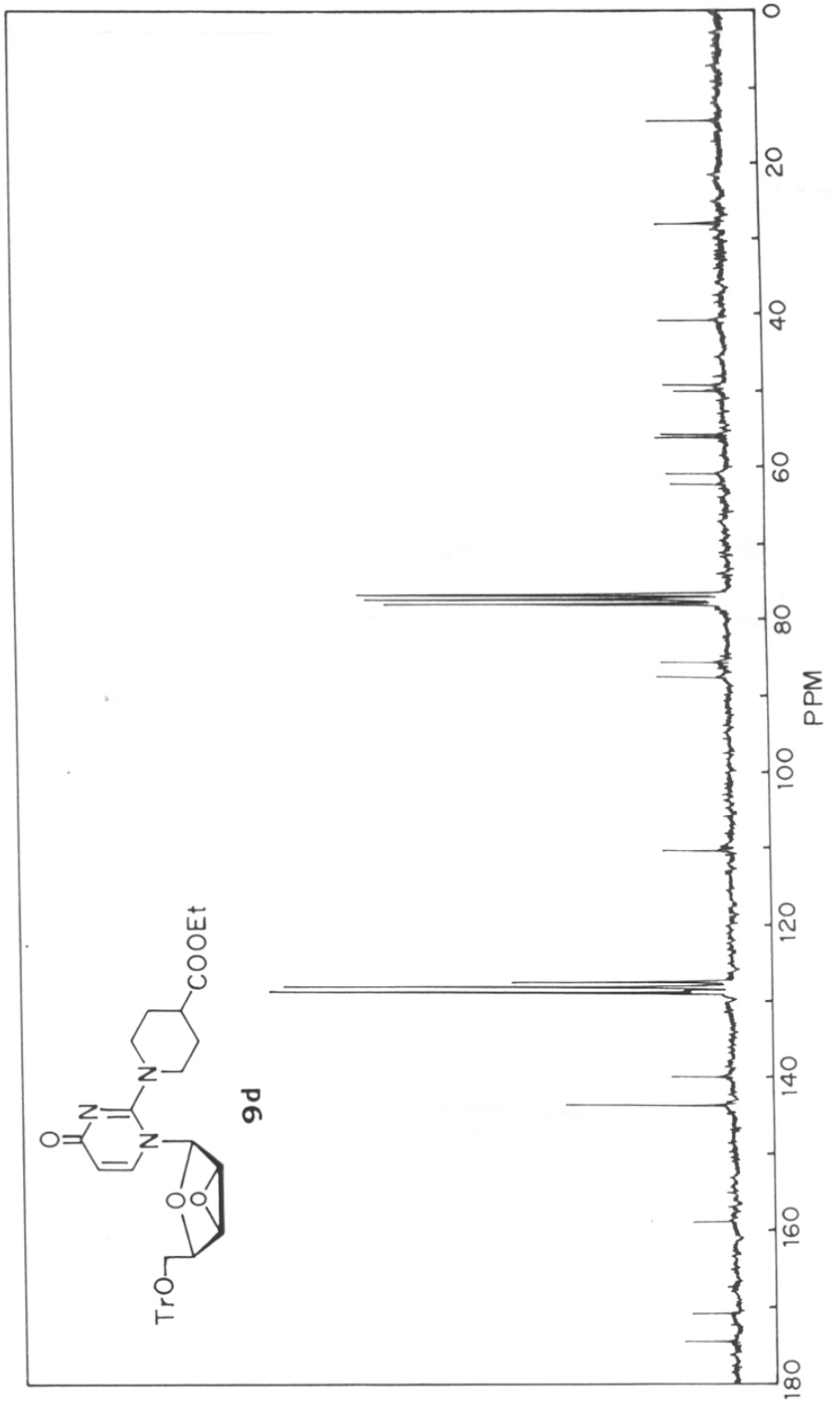
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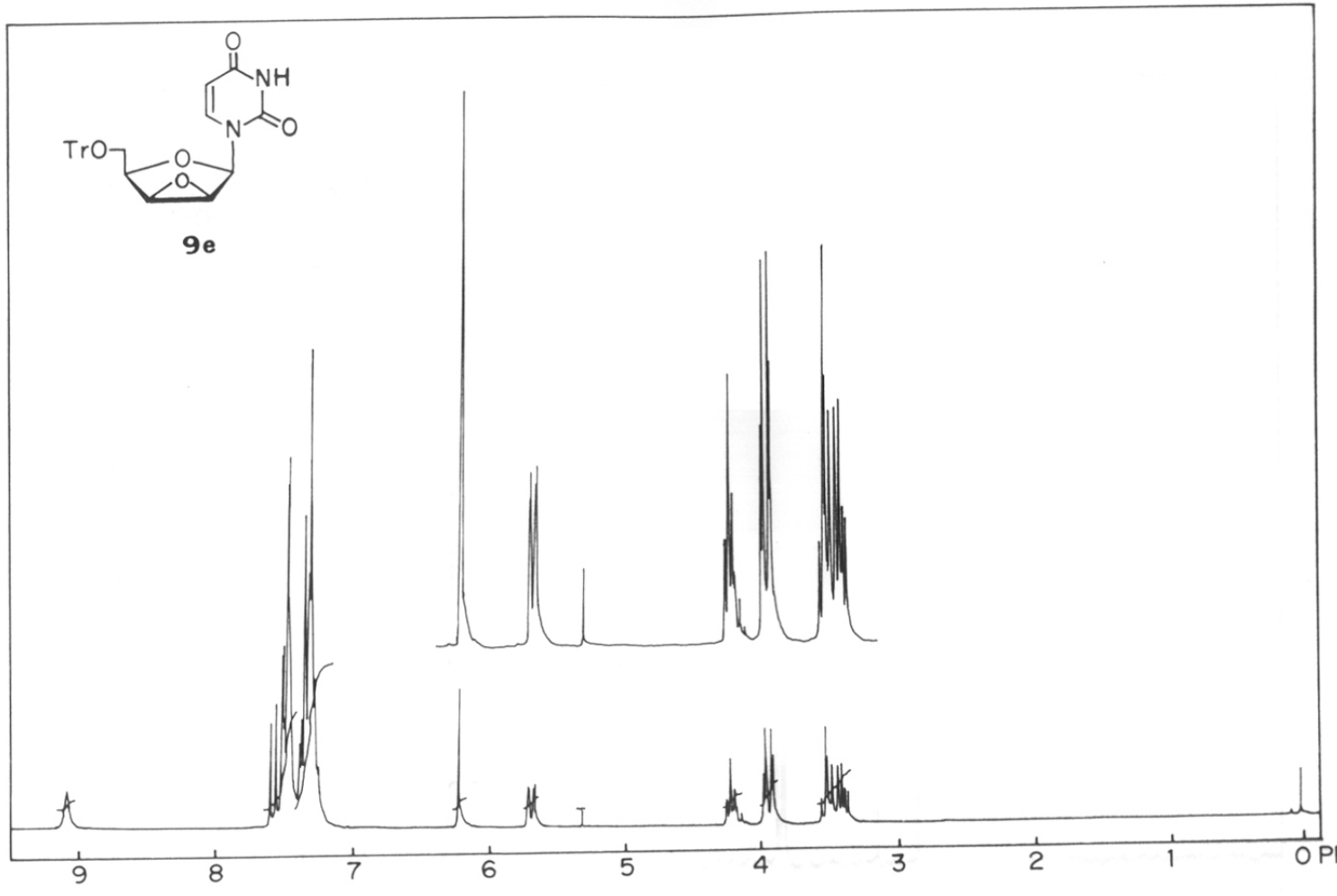
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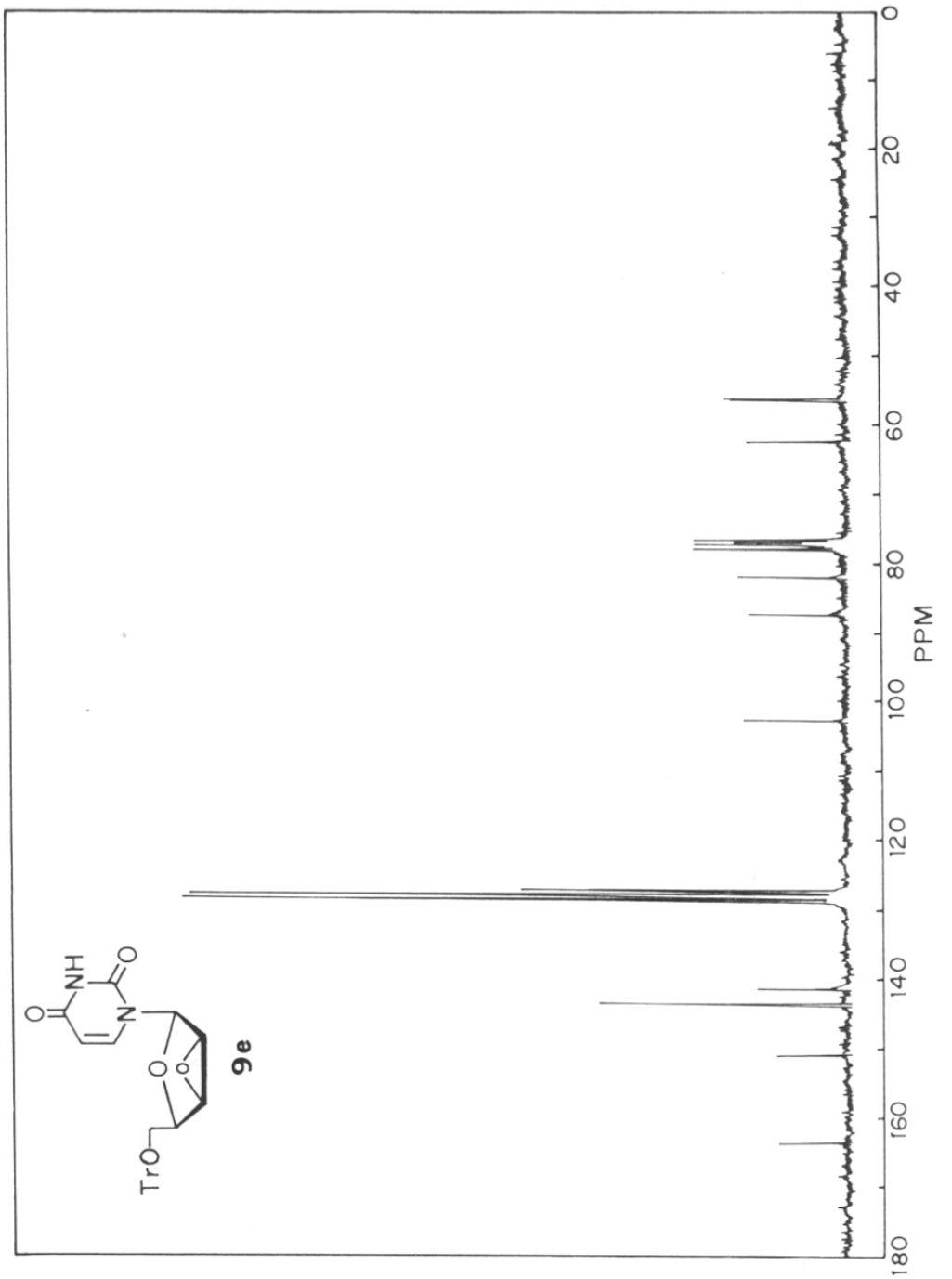
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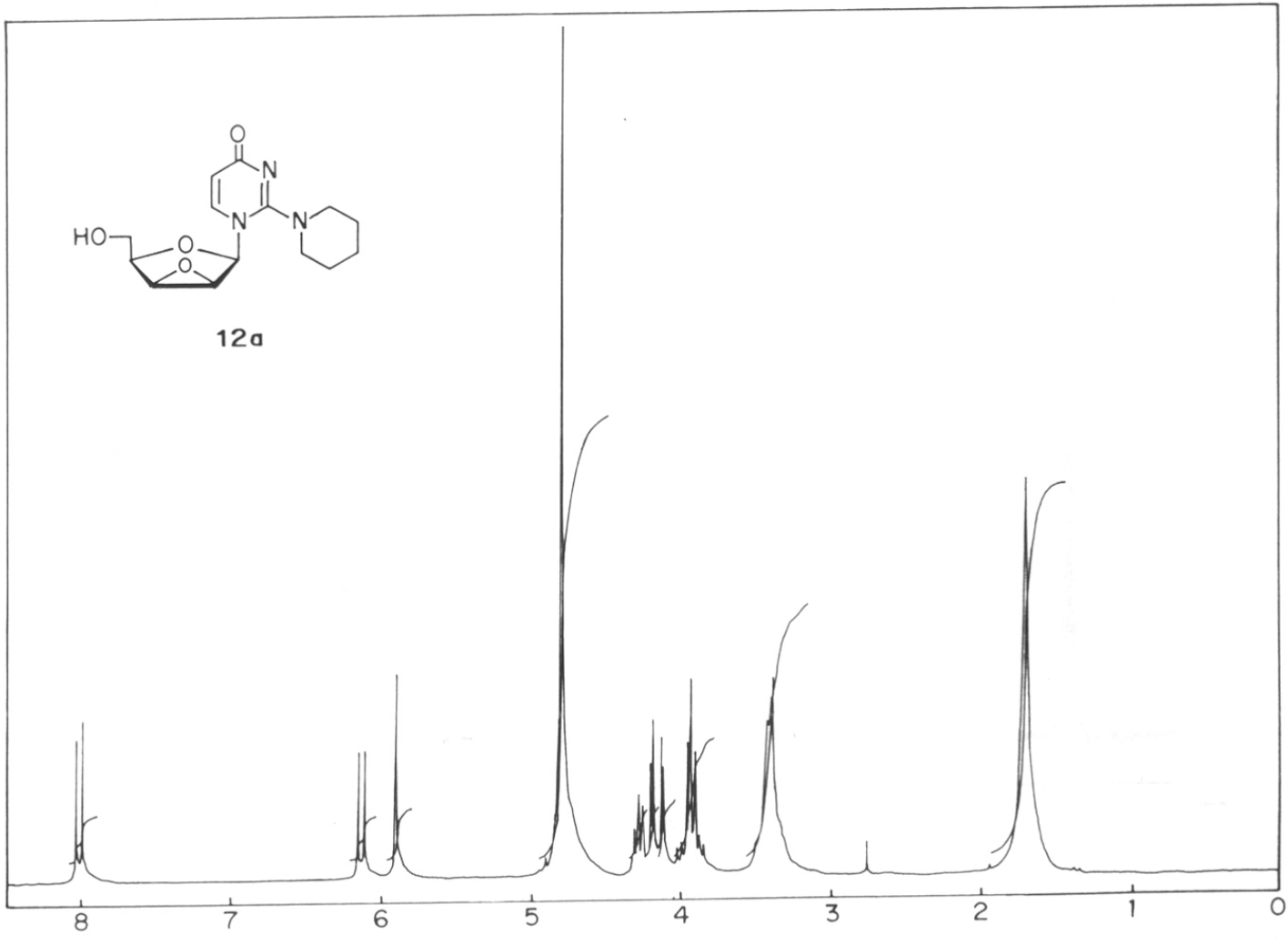

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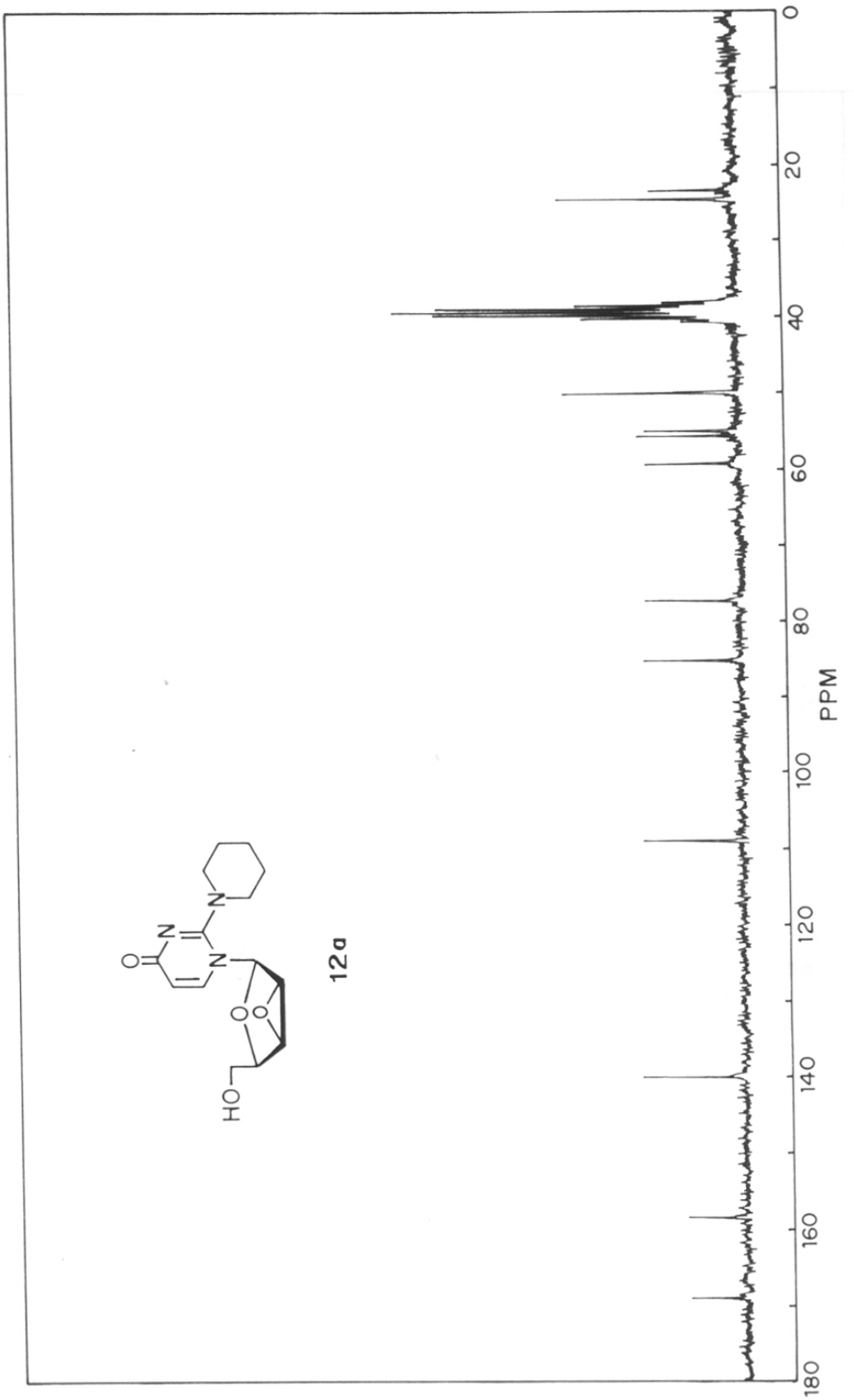

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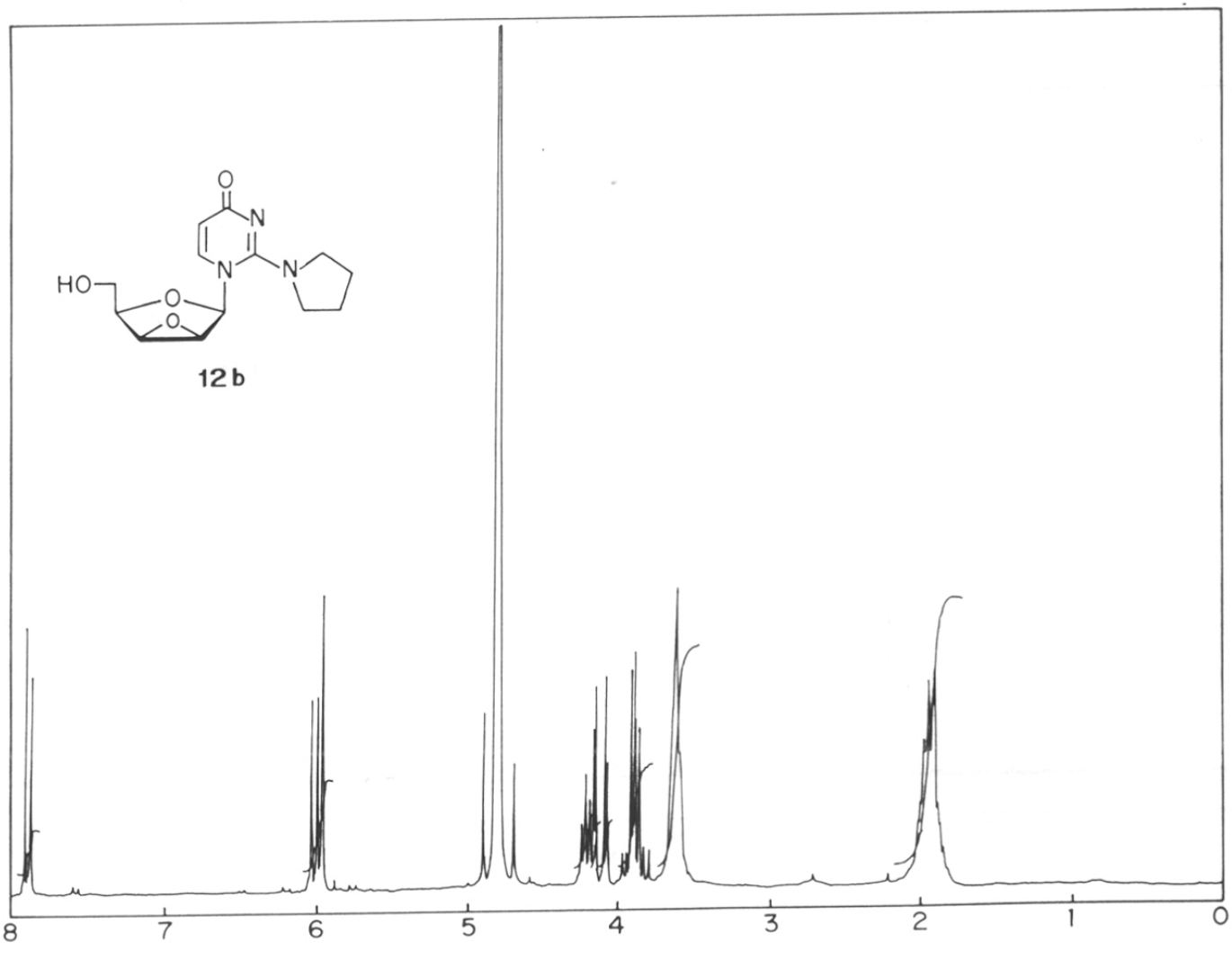

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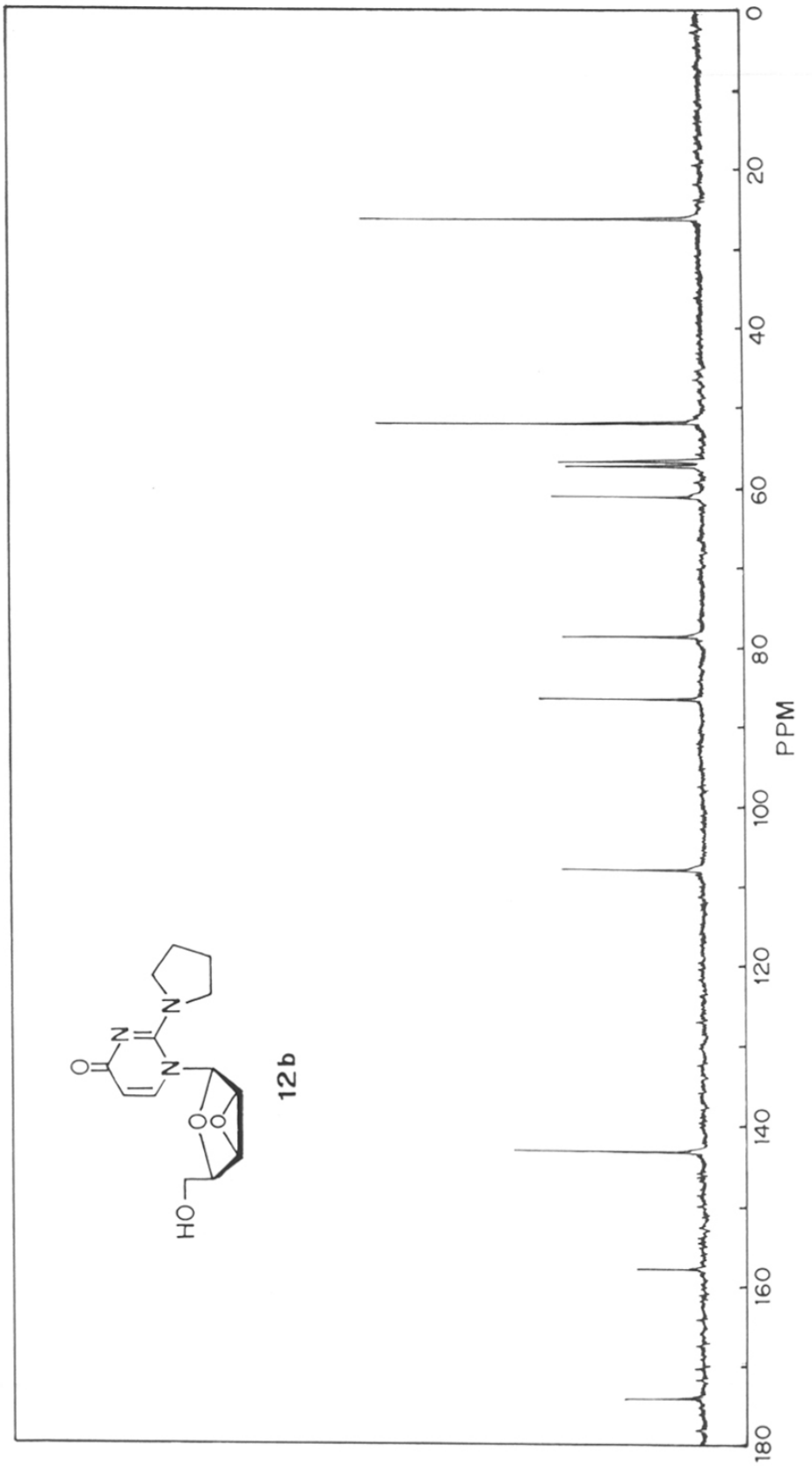
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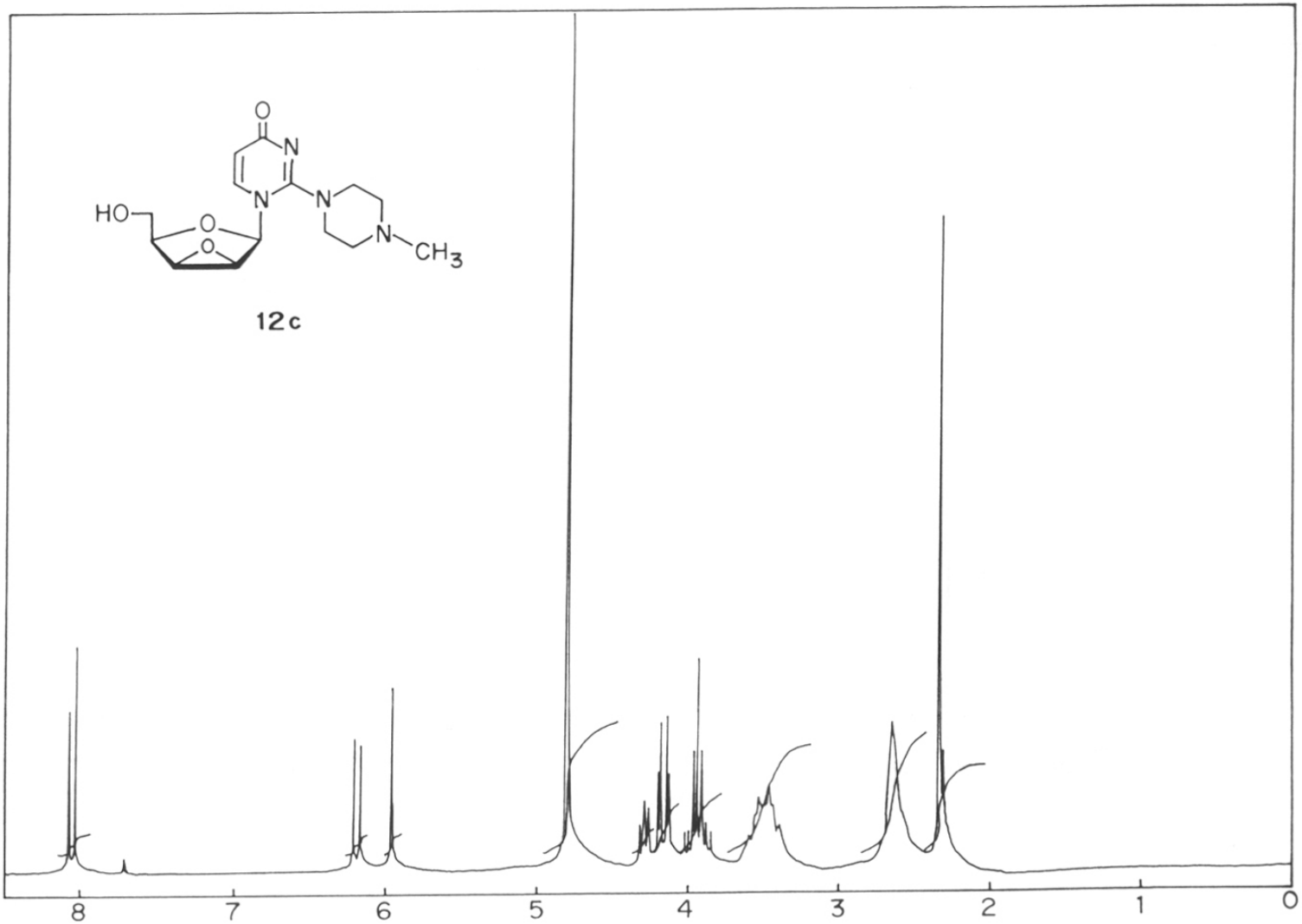

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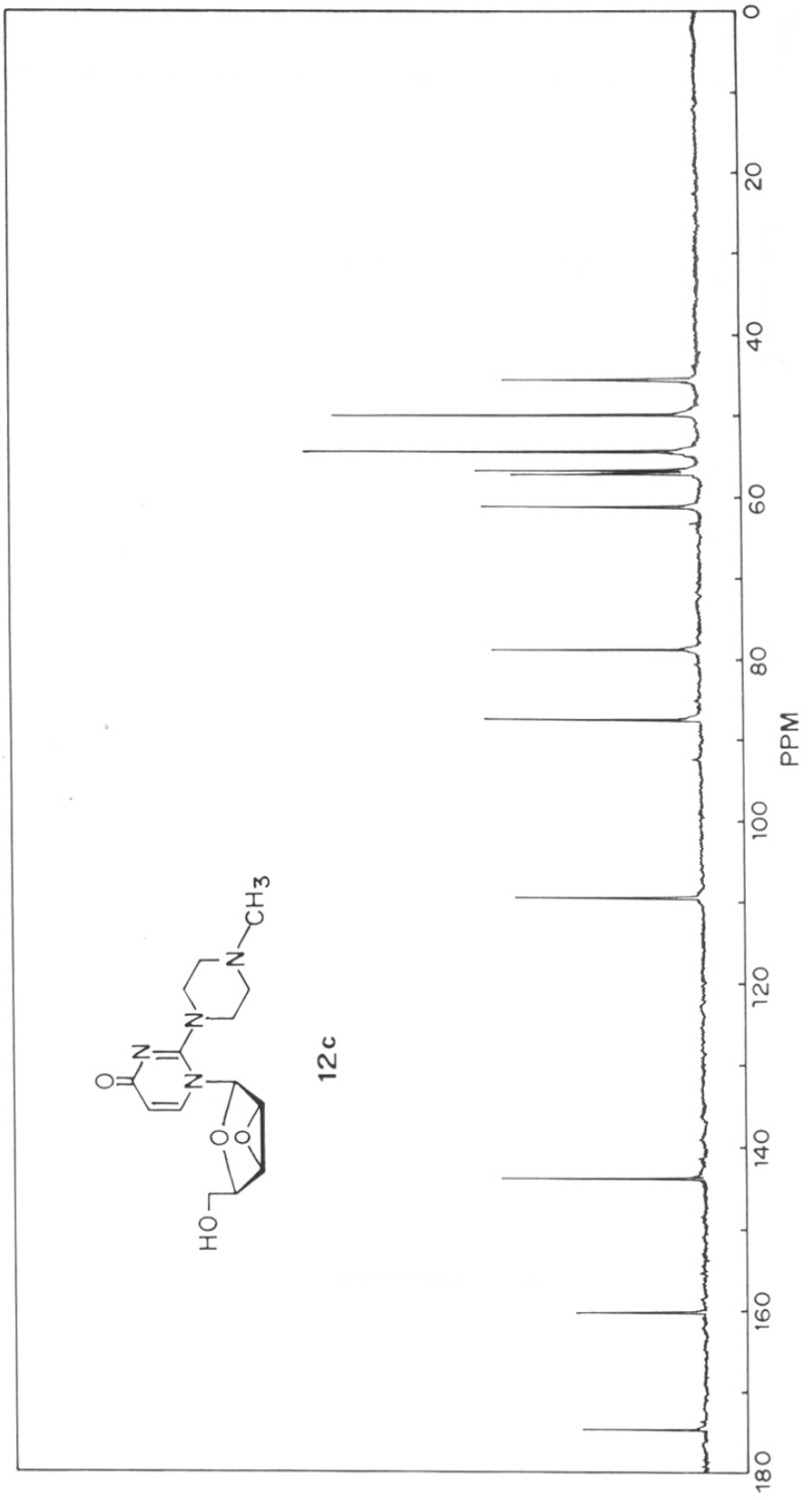
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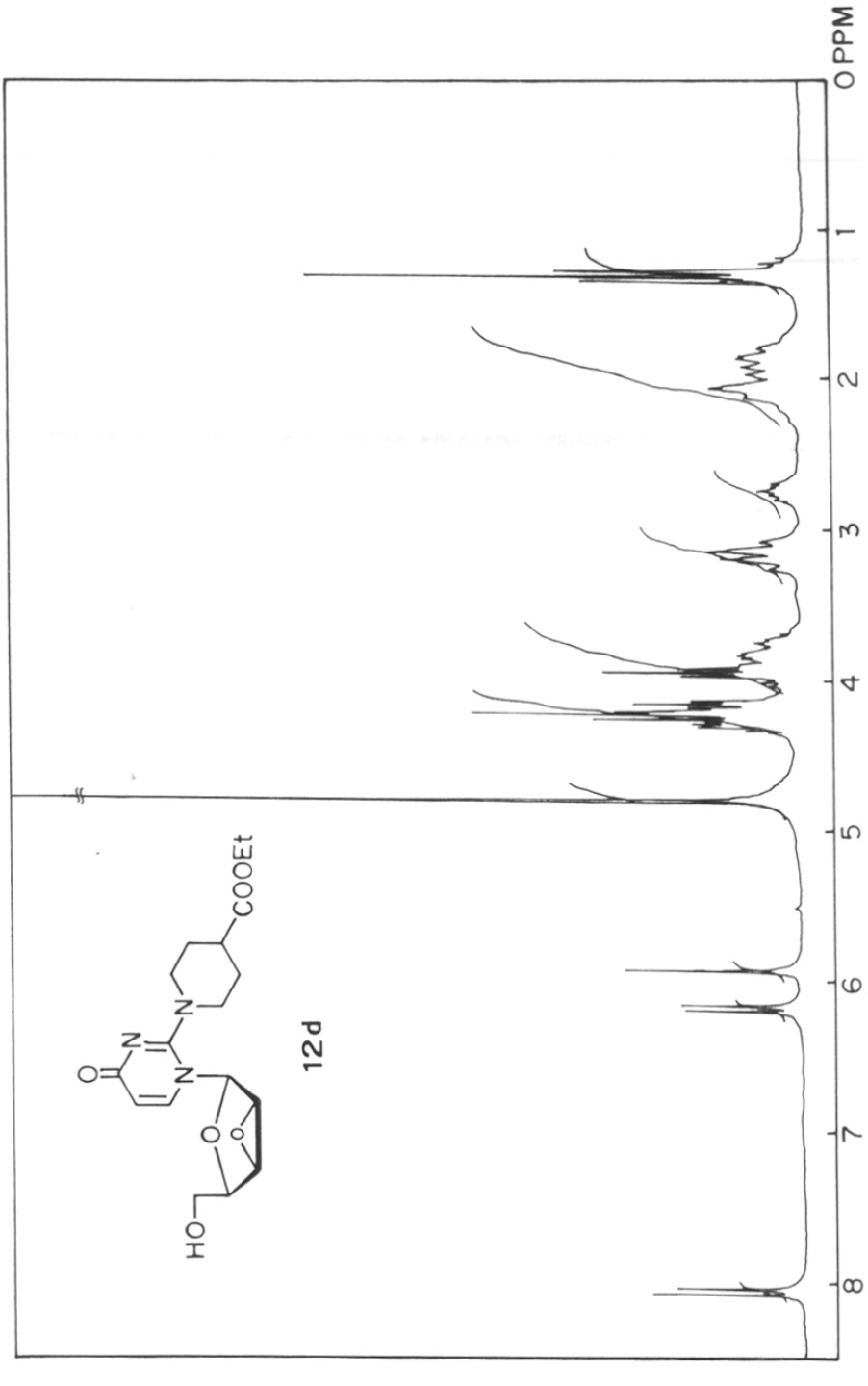
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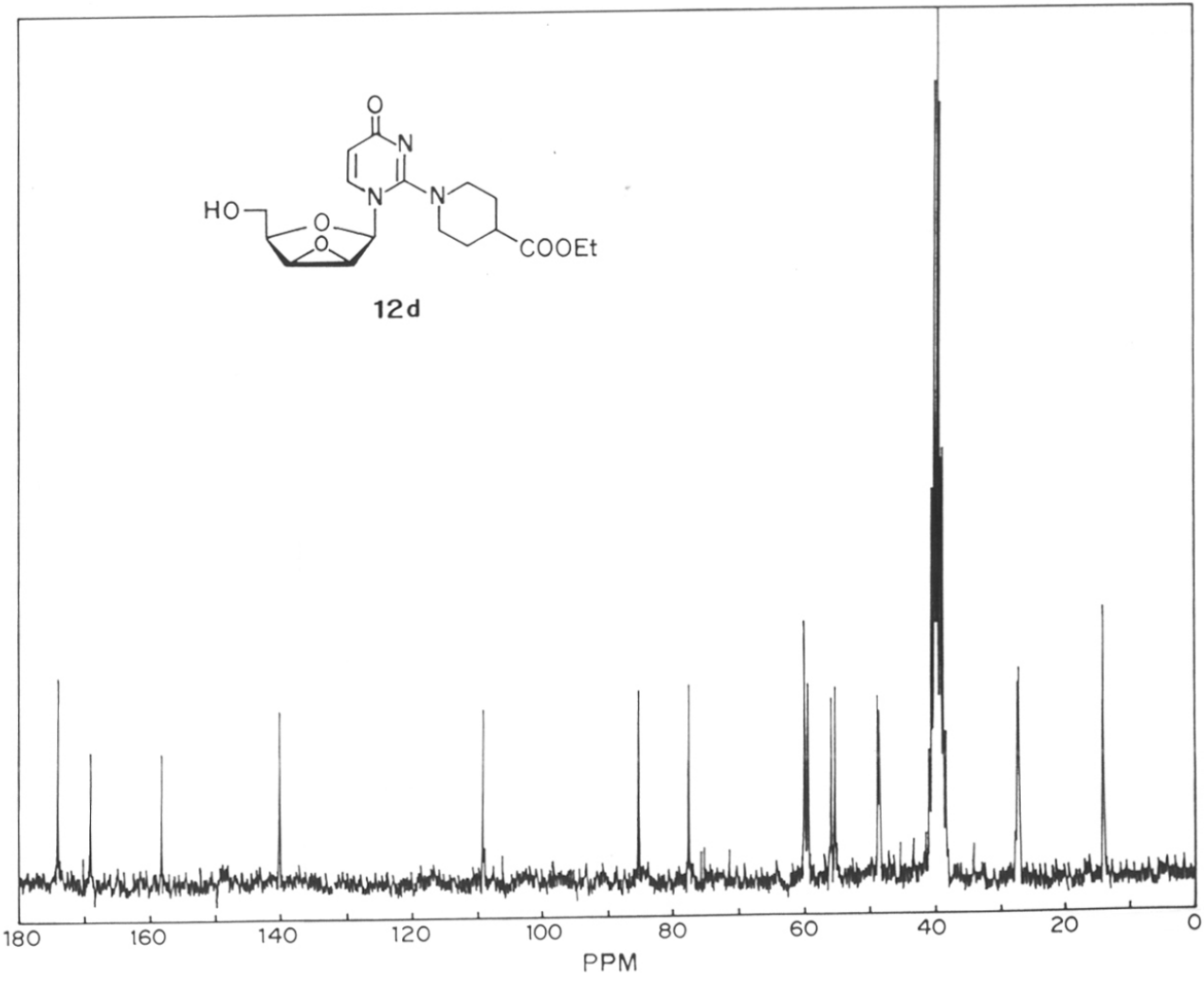
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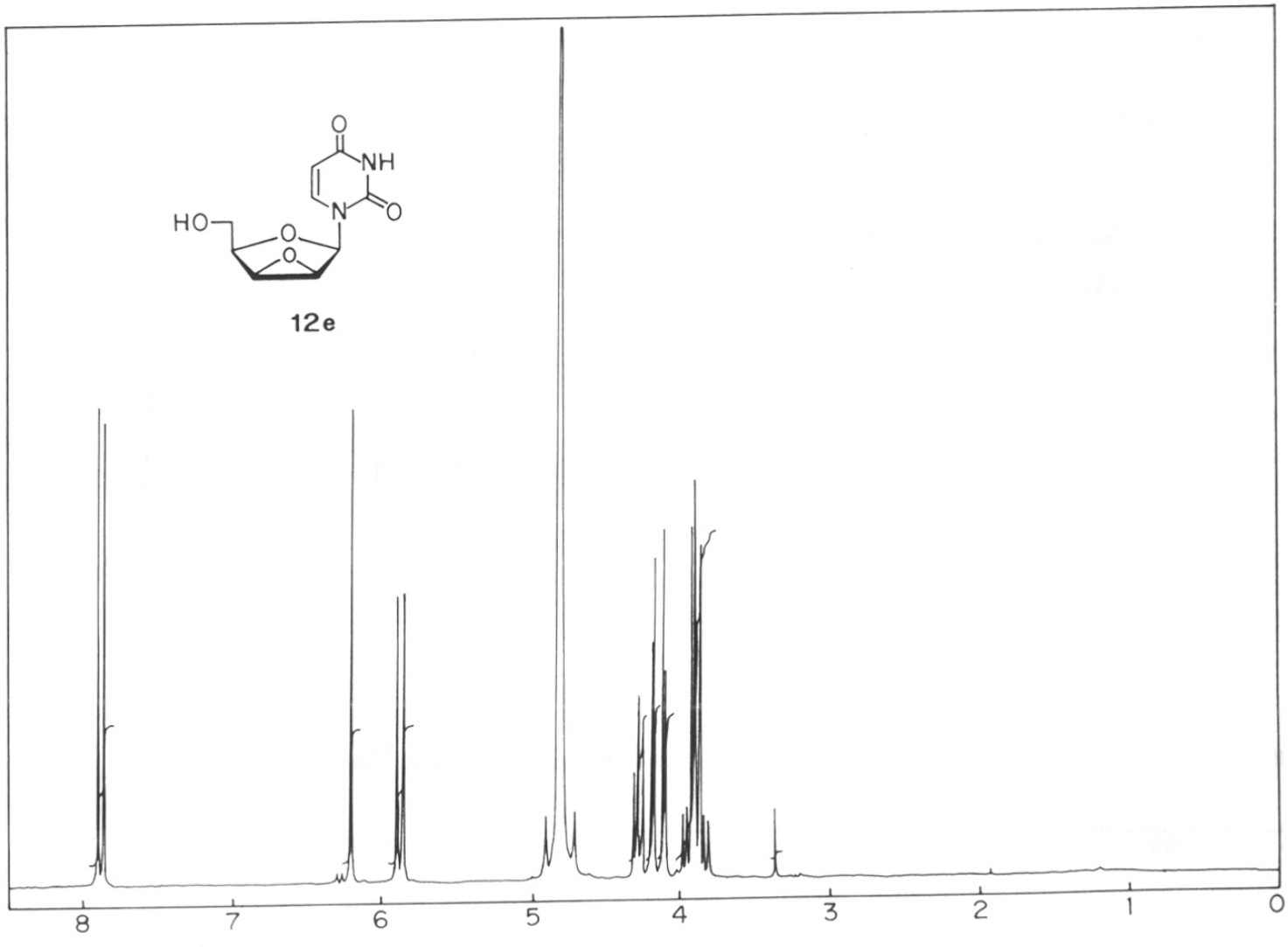
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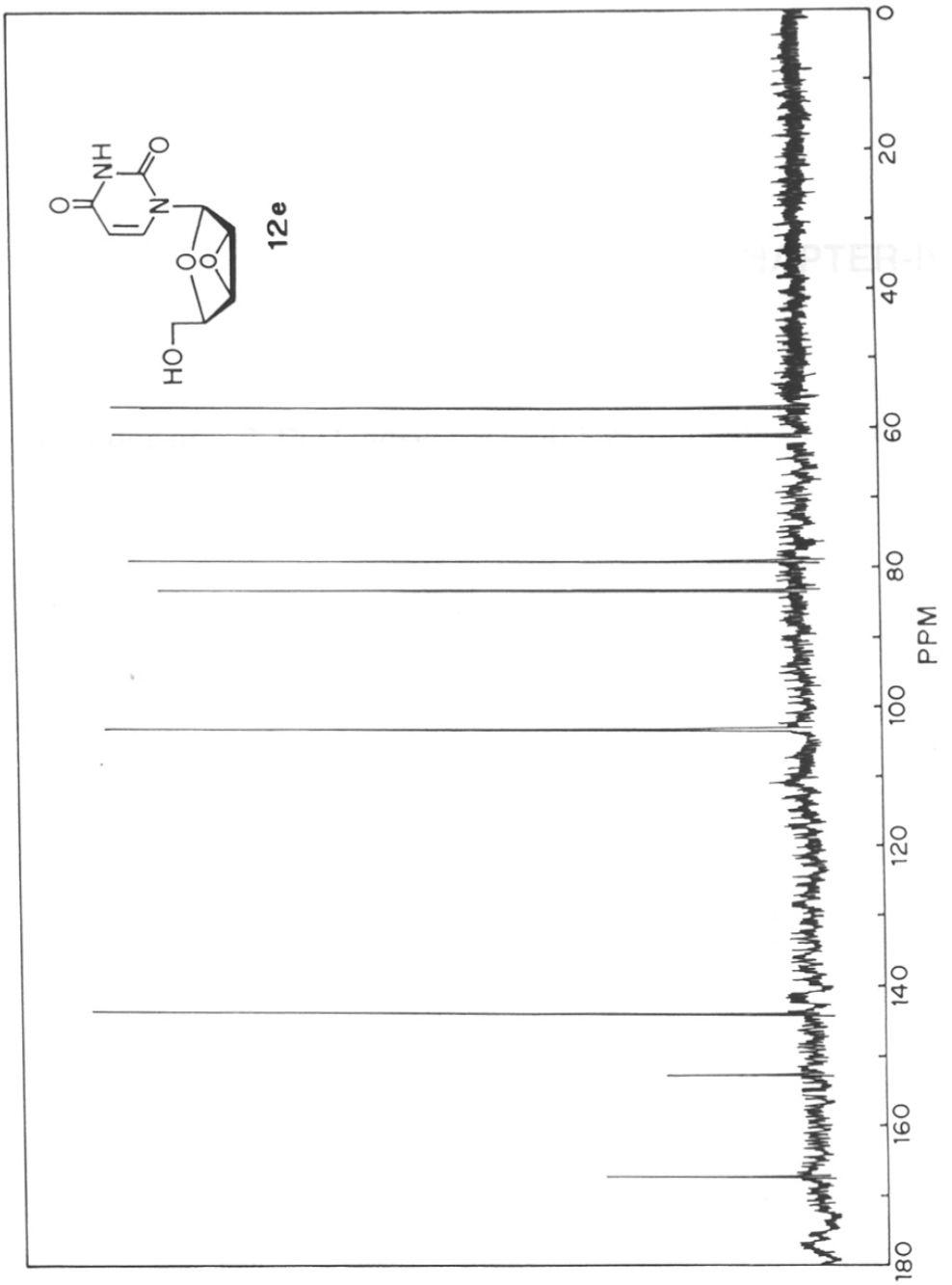
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CHAPTER-IV

*Reactions of 2',3'-Di-O-mesyl-5'-O-trityl-*lyxo*-uridine with Amines*

4.1. Introduction

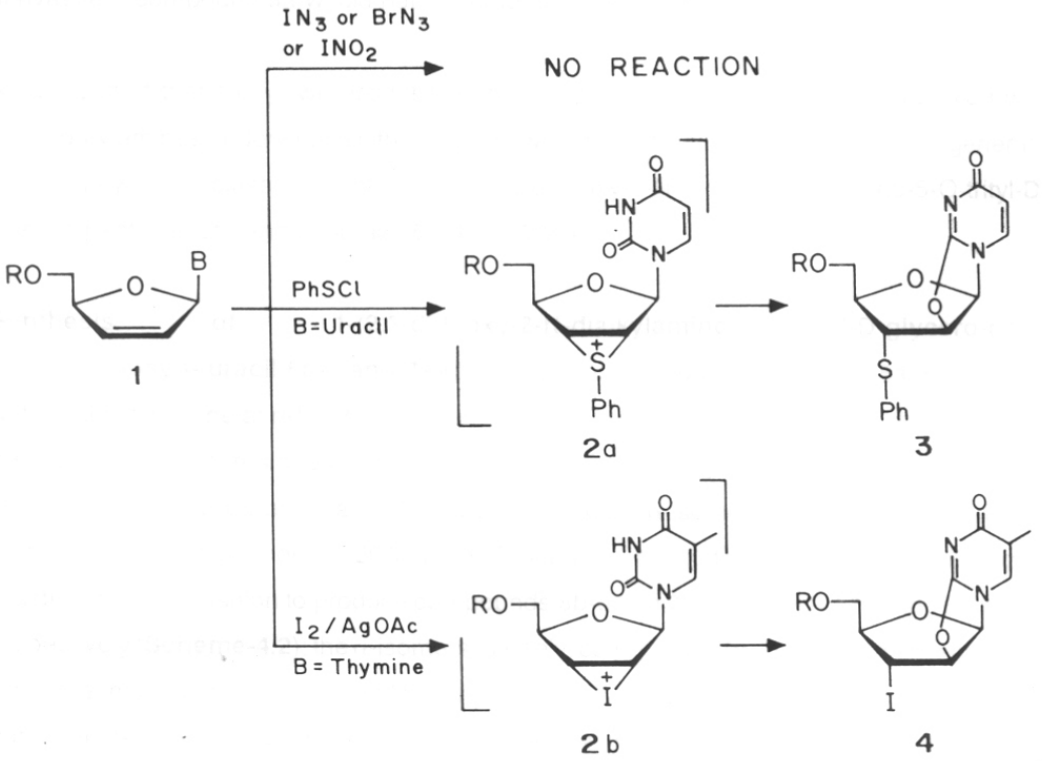
Since the discovery of the anti-HIV activities of AZT, d_4T, ddC and ddI, various attempts have been made to devise newer methods to functionalise the 2'- and 3'-sites of the nucleosides[1,2]. Among them, the functionalisation of the double bond of the 2'-enenucleosides **1** was found to be the most difficult and least useful method because of the unusual inert nature of these double bonds; at least six different reagents (IN_3, BrN_3, INO_2, IOCN, $PhSeNO_2$,$PhSeN_3$), which were supposed to react with double bonds failed to react with 2'-enenucleosides[3]. Phenyl sulphenyl chloride, the only reagent which reacted with the 2'-eneadenosine[4], also reacted with 2'-eneuridine **1** but led to the formation of 2,2'-O-anhydro-3'-deoxy-3'-alkylthiouridine **3** through the formation of the episulphonium intermediate **2a**. It has also been reported[5] that compound **1** on treatment with iodine in silver acetate produced 2,2'-O-anhydro-3'-deoxy-3'-iodouridine **4** *via*, the formation of 2',3'-iodonium intermediate **2b** (**Scheme-4.1**). The problem, however, was circumvented by making use of the electron deficient double bonds which were used as Michael acceptors such as 2',3'-ene-3'- sulphone[6], ene-nitrile[7], ene-phenylselenones[8] (**Schemes-1.44 and 1.32** in Chapter-I), etc.

The synthesis and use of electron-rich double bond such as enamines in nucleoside chemistry, on the other hand, was an area which was studied least-the only reported enaminonucleoside[9] so far, was synthesised from 5'-aldehydo derivative (**Scheme-1.11** in Chapter-I).

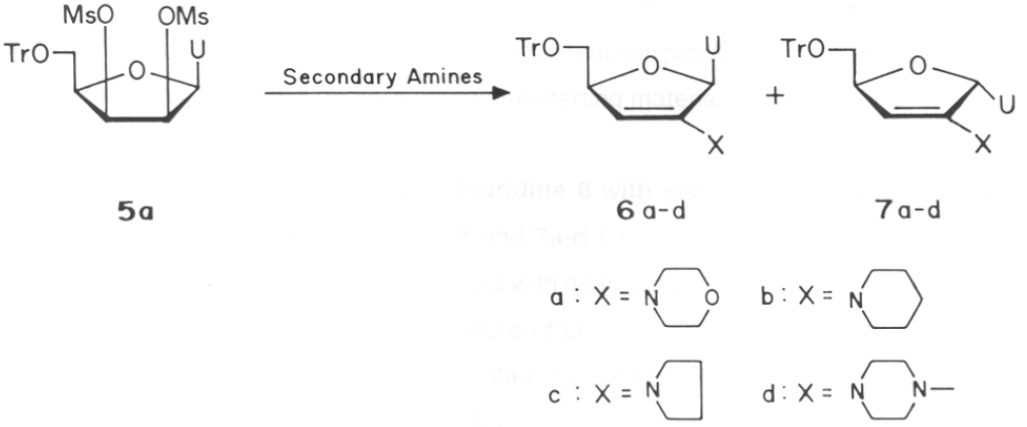
4.2. Present work

We have described in previous chapter that 2',3'-di-O-mesyl-5'-O-trityluridine on reaction with secondary amines produced *iso*cytidine derivatives, 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*furanosyl)-2-dialkylamino-4-pyrimidones, *via* the formation of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine[10] (**Scheme-3.3** in Chapter-III). Although the procedure gave access to hitherto unknown *iso*cytidine derivatives, the starting material was not particularly useful for the functionalisation of the sugar moiety of nucleosides, as the first step, especially in the presence of basic reagents like amines, was always the 2,2'-O-anhydro- ring formation. We, therefore, reasoned that a study on the reactions between

Scheme - 4·1



Scheme - 4·2



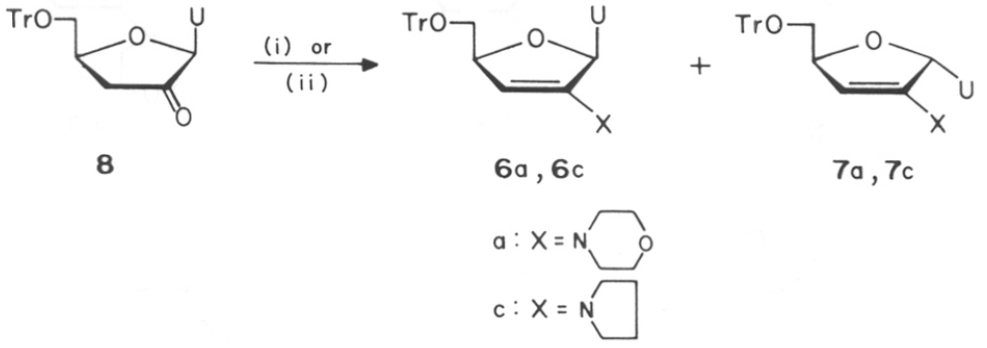
amines and 1-(2, 3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl)- uracil **5a** would give new insight into the area of the functionalisation of the nucleosides, as unlike in the case of the *ribo*-derivative[10], compound **5a** would not undergo any intramolecular cyclisation.

As a result of that study, we describe in this chapter, that compound **5a** on reaction with secondary amines underwent a hitherto unknown "one-pot-multistep" conversion to generate a new class of 1-(2,3-dideoxy-2-N- dialkylamino-5-O-trityl-**D**-glycero-pent-2-enofuranosyl)-uracil **6a-d** and **7a-d**.

Synthesis of 1-(2,3-dideoxy-2-N-dialkylamino-5-O-trityl-D-glycero-pent-2-enofuranosyl)- uracil 6a-d and 7a-d: In a typical procedure, compound **5a** was treated with neat morpholine at reflux temperature for 12h. The amine was removed under reduced pressure and the oily residue was purified by column chromatography to produce an anomeric mixture of isomers **6a** and **7a** in 75% yield. The pure α-isomer **7a** was crystallised from methanol (or isopropanol) in 26% yield. Piperidine, pyrrolidine and N-methylpiperazine reacted in similar fashion to produce compounds **6b-d** and **7b-d** in 71%, 65% and 70% yields respectively (**Scheme-4.2**); the α-isomers, namely, compounds **7b**, **7c** and **7d** were separated from the mixture through crystallisation in 20-25% yields. The β-isomers were always contaminated with varying amounts of α-isomers depending on the amine. In case of pyrrolidine enamines α-anomer was predominant in the mixture; even after crystallisation the mother liquer contained a mixture of both the isomers in a ratio 3:2. Separation of the anomers of pyrrolidine enamine was most difficult to achieve: after repeated crystallisation, the α-anomer **7c** was contaminated with 5-10% of the β-anomer. Attempts to react compound **5a** with a primary amine (benzylamine) failed as the reaction produced an inseparable mixture of compounds indicating the degradation of the starting material.

Reactions of 5'-O-trityl-3'-deoxy-2'-ketouridine 8 with secondary amines: In order to assign the structures of compounds **6a-d** and **7a-d** formed in these reactions, the known 2'-β-ketouridine **8** (ref.11 and 12) was reacted with neat morpholine in the same as was done in case of the dimesyl derivative. The mixture of products obtained from the reaction was identical and similar to the products **6a** and **7a** obtained from the reactions of compound **5a** and morpholine; treatment of compound **8** with 10 equivalents pyrrolidine in a mixture of toluene and benzene (1:1)[9] produced compounds **6c** and **7c** (**Scheme-4.3**). However

Scheme-4·3

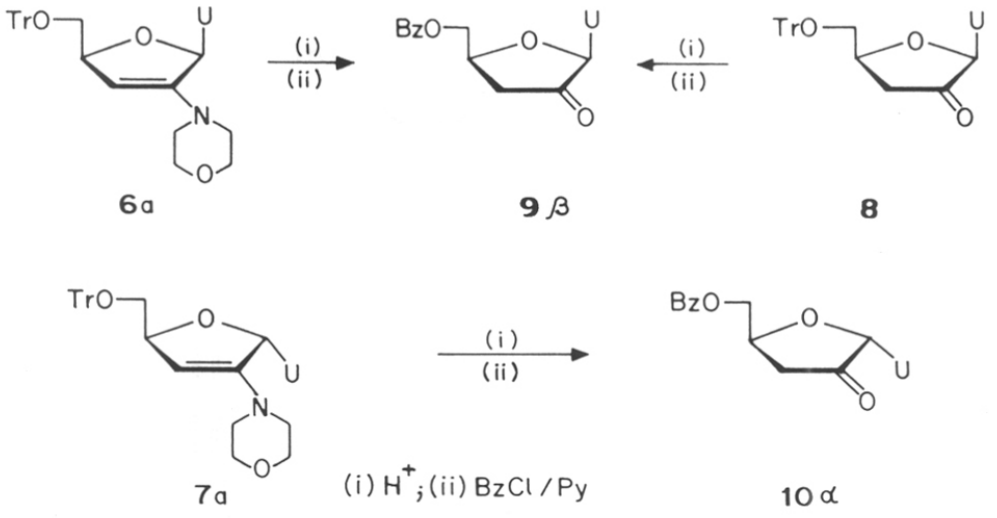


(i) Neat morpholine (ii) Pyrrolidine, toluene-C_6H_6

starting material was recovered when 1-(2, 3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl)- uracil **5a** was treated with 10 equivalents of pyrrolidine in other solvent systems (DMSO, DMF, Pyridine). To achieve this one pot conversion of **5a** to **6** and **7**, use of neat amines was necessary.

Acid hydrolysis of enaminonucleosides 6a and 7a: The identity of the β-isomers present in the mother liquor were established through the hydrolysed product of the representative example **6a**. As, the attempted hydrolysis of the pure crystallined isomer **6a** under neutral conditions (THF-water, 1:1; reflux; 12h) produced an anomeric mixture of the 2'-ketonucleosides and a single 2'-ketonucleoside under acidic conditions, the enamine **6a** was hydrolysed using acid (THF-water 5:1; conc. HCl, 3eqv.; reflux; 12h). The detritylated 2'-ketonucleoside was converted to 5'-O-benzoyl-3'-deoxy-2'-ketouridine **9**β (Benzoyl chloride; pyridine; 0°C to room temp.; 2h). The known[12] 5'-O-trityl-3'-deoxy-2'-keto-β-uridine **8** was detritylated and benzoylated under similar conditions to produce the authentic 5'-O-benzoyl-3'-deoxy-2'-keto-β-uridine **9**β (**Scheme-4.4**). The hydrolysed product **9**β obtained from the enamine **6a** present in the mother liquor was similar to the authentic keto derivative (mixed ^{1}H-NMR).

Scheme - 4.4



The crystallised enamine was established to be the α-anomer with the help of crystal structure analysis (**Fig-4.1**) of a representative example **7d**. In order to prove whether the acid hydrolysis caused any anomerisation or not, the α-enamine **7a** was subjected to the same acidic conditions (THF-water 5:1; conc. HCl, 3eqv.; reflux; 12h); hydrolysis followed by benzoylation produced 5'-O-benzoyl-3'-deoxy-2'-keto-α-uridine **10**α. The structure of compound **10**α was unambiguously assigned by X-ray crystal structure analysis (**Fig-4.2**).

4.3. Structural Assignment

The spectral data were consistent with the structures assigned. A discussion on the ^{1}H-NMR will be pertinent here. The H-1' signals of both the sets of anomers appeared at around 7.0 ppm as doublets; however, H-1' of **6a-d** were always more deshielded than the same of **7a-d**. A perusal of the COSY spectrum of compound **7a** (**Fig-4.3**) revealed that H-1' was coupled with H-4' showing a coupling constant of 4.2 Hz. It was also evident that H-1' was weakly coupled with H-3'. The H-1' of compound **6a**, on the other hand showed a very small coupling constant of 1.7 Hz. H-3' of both the anomers carrying a particular amine appeared at the same ppm values as singlets showing that the difference in anomeric configuration had no bearing on H-3'. It is worth mentioning here that the chemical shift values of the vinyl protons of all the enamines (H-3') followed the expected and reported[13] order, i.e. H-3' protons of

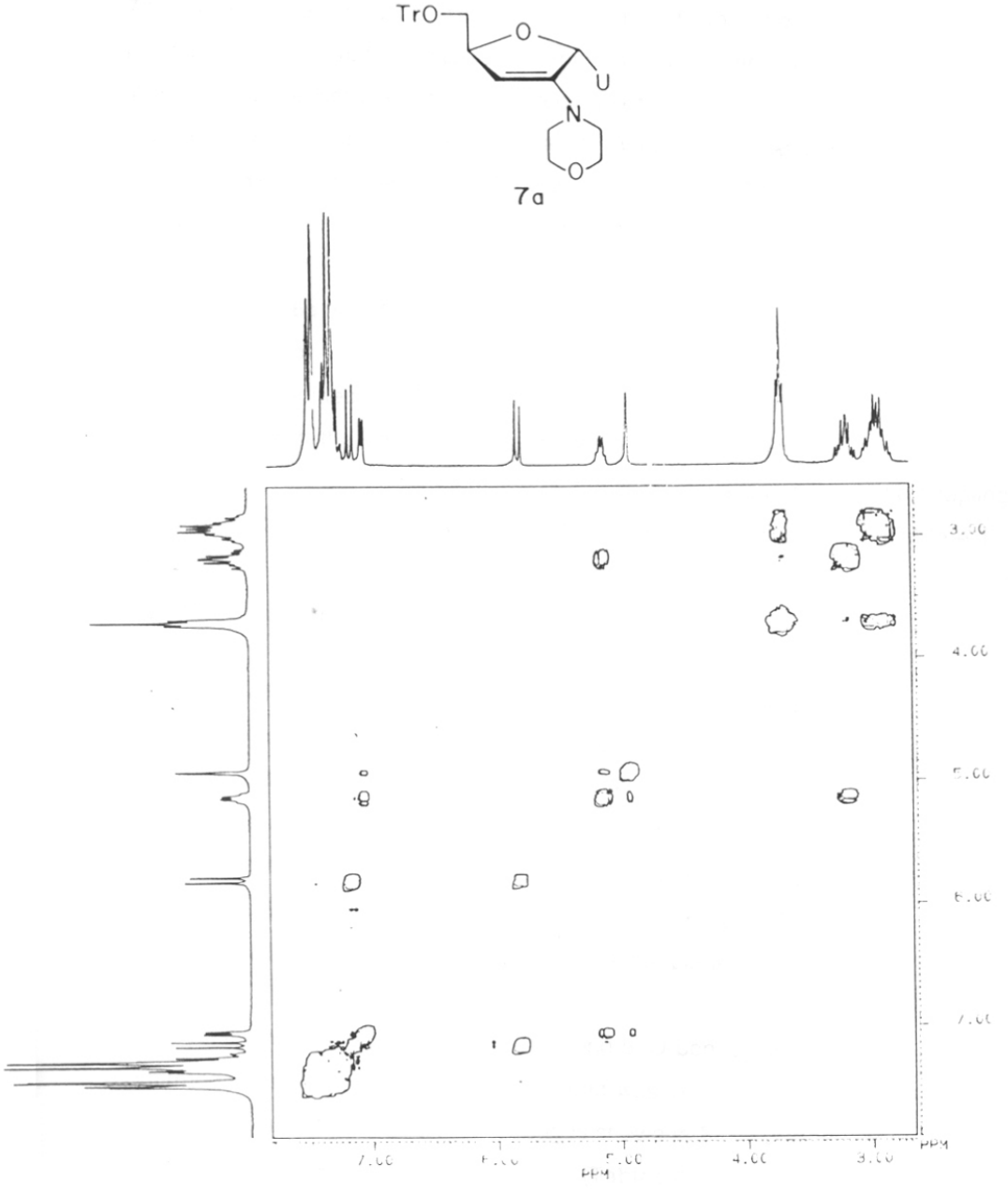


Fig-4.3

pyrrolidine enamines (**6c/7c**, 4.48/4.49 ppm) were shielded most and the same protons of morpholine enamine pair (**6a/7a**, 4.93/4.92 ppm) was least shielded. The H-4' of the α-anomer **7a** were deshielded than that of the β-anomer **6a** but the multiplet arising from the 5'-methylene protons were more upfield in case of compound **6a**. It may be concluded that the difference in the stereochemistry around C-1' affected both C-4' and C-5' centers. The most striking difference was noted when the chemical shift values of H-5 and H-6 protons of compounds **6a** and **7a** were compared. H-6 of **7a** was shielded by 0.46 ppm and H-5 was deshielded by 0.65 ppm when compared with the same sets of signals of compound **6a**. The drastic changes in the positions of H-5 and H-6 signals indicated the difference in the anomeric configurations of compounds **6a** and **7a**. A further comparison of the positions of H-5/H-6 and the splitting pattern of H-5'/H-5'' of compounds **6a-d** and 1-(5-O-trityl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)- uracil[14a] (5'-O-trityld$_4$U) revealed the similarities in the configurations of the C-1' and C-4' centers. In general, the α- and β-enamines could be readily identified by the characteristic positions and coupling patterns of the respective peaks arising from H-1'/H-4' and H-5/H-6 protons (**Table-4.1**). In mass spectrum, all compounds showed peaks corresponds to M^+-uracil and M^+-Ph_3COCH_2 fragments.

Elucidation of the crystal structure of a representative example, compound **7d** (**Fig-4.1**) confirmed unambiguously our assertion that compounds **7a-d** were indeed of α-configuration. A perusal of the selected bond lengths and angles in and around the pentofuranose ring (**Tables 4.2a** and **4.2b**) revealed that C2'-C3' was a double bond. The shortening of the neighbouring bonds indicated the presence of double bond character in them, presumably due to delocalisation of the electron density in C2'-C3' bond. The five membered sugar ring was planar with the piperazine nitrogen lying in the plane.

The crystal structure elucidation of compound 5'-O-benzoyl-3'-deoxy-2'-keto-α-uridine **10**α confirmed unambiguously that the compound was indeed a α-anomer. ORTEP drawing of the molecule along with an atom labelling is shown in **Fig.4.2**. Bond lengths and angles for the pyrimidine base are in expected range (**Tables 4.3a** and **4.3b**). The bond length of the oxygen attached C-2' of the sugar corresponded to those of double bond confirming keto form. Under its influence, presumably, the neighboring bond C-3'-C-4' is shorter and furanosyl intra ring angle at C-2' is wider compared to standard values. The pyrimidine base is in *syn*

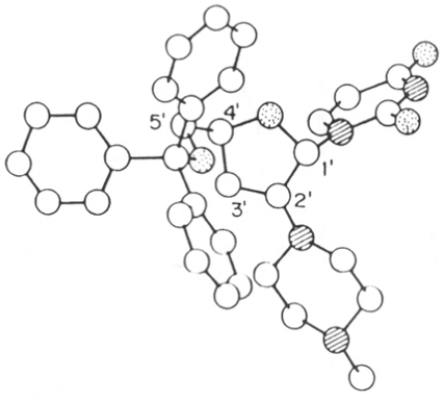


Fig-4.1

Table-4.2a

Selected bond lengths (Å) for compound 7d

O4'-C1'	1.44(3)
O4'-C4'	1.41(2)
C1'-N1	1.46(2)
C1'-C2'	1.48(3)
C2'-C3'	1.34(3)
C2'-Np*	1.37(2)
C3'-C4'	1.48(3)
C4'-C5'	1.53(3)
C5'-O5'	1.42(2)

Table-4.2b

Selected bond angles (deg) for compound 7d

O4'-C1'-C2'	106(1)
C1'-O4'-C4'	109(1)
O4'-C1'-N1	111(3)
C2'-C-1'-N1	112(3)
C1'-C2'-C3'	109(2)
C1'-C-2'-Np*	122(2)
C3'-C2'-Np*	129(2)
C2'-C3'-C4'	109(1)
C3'-C4'-O4'	107(2)
C3'-C4'-C5'	118(1)
O4'-C4'-C5'	111(2)
C4'-C5'-O-5'	104(1)

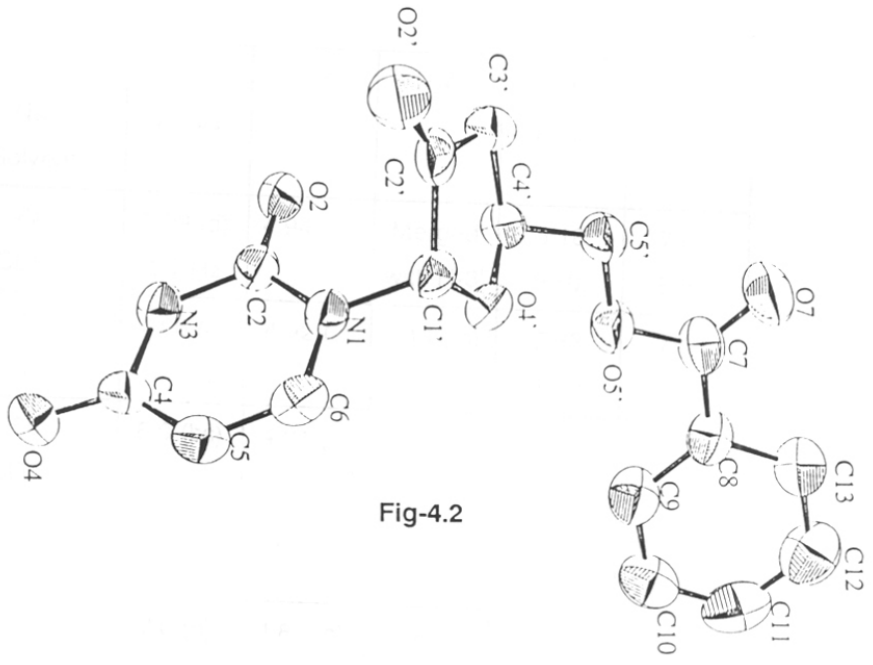


Fig-4.2

Table-4.3a

Selected bond lengths (Å) for compound 10α

O4'-C1'	1.408(6)
O4'-C4'	1.469(7)
C1'-N1	1.452(7)
C1'-C2'	1.517(9)
C2'-O2'	1.221(7)
C2'-C3'	1.485(10)
C3'-C4'	1.518(9)
C4'-C5'	1.480(8)
C5'-O5'	1.446(7)

Table-4.3b

Selected bond angles (deg) for compound 10α

C1'-O4'-C4'	111.1(4)
O4'-C1'-N1	112.3(4)
O4'-C1'-C2'	105.4(5)
N1-C-1'-C2'	113.5(5)
O2'-C2'-C3'	127.2(6)
O2'-C2'-C1'	123.0(7)
C3'-C2'-C1'	109.6(6)
C2'-C3'-C4'	103.9(5)
O4'-C4'-C5'	108.0(5)
O4'-C4'-C3	106.3(5)
C5'-C4'-C3'	112.01(5)

Table - 4.1

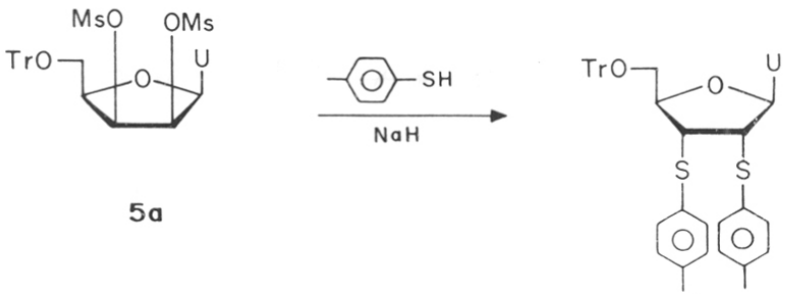
Compound No: (Solvent)	H-1' $J_{H-1',H-4'}$	H-3'	H-4'	H-5 $J_{H-5,H-6}$	H-6 $J_{H-6,H-5}$
6a ($CDCl_3$)	6.99 (d) 1.7 Hz	4.94 (m)	Merged with H-3'	5.18 8 Hz	7.63 8 Hz
7a ($CDCl_3$)	7.06 (d) 4.2 Hz	4.92 (s)	5.14 (m)	5.83 8 Hz	7.17 8 Hz
6b ($CDCl_3$)	6.9 (bs)	4.81 (s)	4.95 (m)	5.16 8 Hz	7.55-7.25 Merged with trityl
7b ($CDCl_3$)	7.0 (d) 4.0 Hz	4.81 (s)	5.08 (m)	5.75 8 Hz	7.2 8 Hz
6c ($CDCl_3$)	6.94 (d) 1.1 Hz	4.48 (s)	4.98 (m)	5.24 8 Hz	7.53 8 Hz
7c ($CDCl_3$)	7.0 (d) 4.1 Hz	4.49(s)	5.19 (m)	5.78 8 Hz	7.51-7.22 Merged with trityl
6d ($CDCl_3$)	6.96 (d) 1.3 Hz	4.87 (s)	4.94 (m)	5.14 8 Hz	7.53 8 Hz
7d ($CDCl_3$)	7.02 (d) 4.3 Hz	4.86(s)	5.13 (m)	5.76 8 Hz	7.12 8 Hz

conformation. This is in contrast to the more common anti-conformation observed in pyrimidine nucleosides[14b]. It may be noted that bulky group at C-1' and C-4' disposed on opposite sides of the furanosyl ring here, was conducive to *syn* conformation.

4.4. Discussion

It was reported in the literature[15] that compound **5a** on direct nucleophilic displacement reaction with thiols produced 2',3'-dideoxy-2',3'-dithiophenyl-uridine **11** (**Scheme-4.5**). Therefore, the first step of our study was to eliminate the possibility of the involvement of the intermediates such as 2'-O-mesyl-3'-deoxy-3'-morpholino-5'-O-trityl-*ara*- and 2'-deoxy-2'-morpholino-3'-O-mesyl-5'-O-trityl-*xylo*-uridines **13b** and **14b** respectively, which could have formed by the direct nucleophilic attack of the amines at the 2'- or 3'-site of compound **5a**.

Scheme-4·5



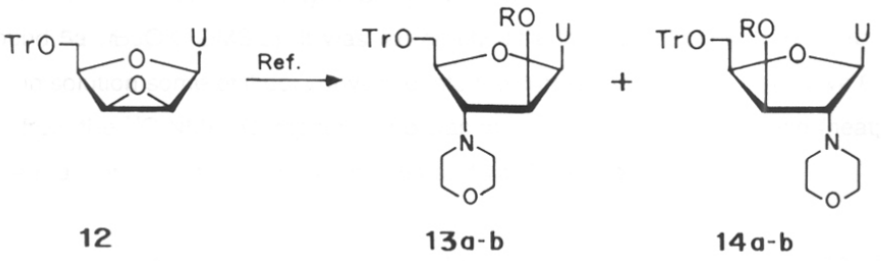
5a

11

We converted compounds **13a** and **14a** (obtained from the reactions between compound **12** and morpholine[16]) separately to the mesylated derivatives **13b** and **14b** (Mesyl chloride; Pyridine; +4°C); a mixture of **13b** and **14b** was then heated under reflux with neat morpholine. The reaction did not furnish the enamines **6a** and **7a**; instead, the starting materials underwent extensive degradation as was evident from tlc (**Scheme-4.6**).

As it was well known that under basic or even nucleophilic conditions, 1-(2,3-di-O-mesyl-5-O-benzoyl- β-D-*lyxo*furanosyl)- uracil **5b** underwent an elimination reaction to form the 1-(2,3-dideoxy-2-O-mesyl-5-O-benzoyl- D-glycero-pent-2-enofuranosyl)- uracil[17] **15a** (**Scheme-4.7**) it could be assumed that similar type of

Scheme - **4·6**



12 **13a-b** **14a-b**

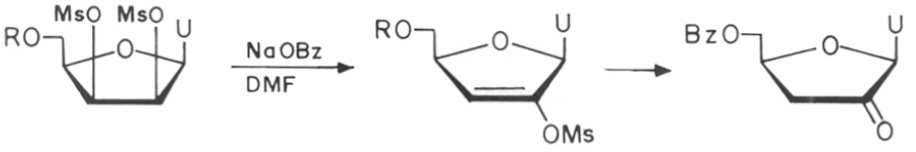
(i) **a** : R = H, **b** : R = Ms

(i) **a** : R = H, **b** : R = OMs

(i) Ms Cl / Py / 0°C

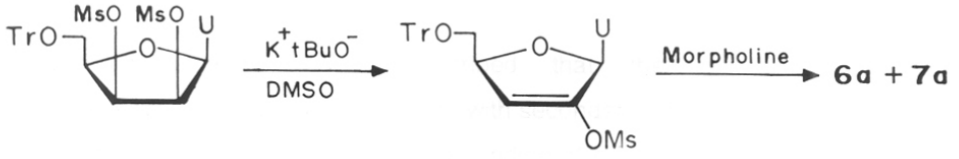
13b + 14b —Morpholine→ **6a + 7a**

Scheme - **4·7**



5b R = Bz **15a** R = Bz **9β**

Scheme - **4·8**



5a **15b** **6a + 7a**

ene-mesylate derivative **15b** was also an intermediate formed in the present case.

To prove that point unambiguously, we synthesised 1-(2,3-dideoxy-2-O-mesyl-5-O-trityl-β-**D**-glycero-pent-2-enofuranosyl)-uracil **15b** from compound **5a** (*t*BuOK, DMSO). It was extremely difficult to obtain compound **15b** in pure form as in solution some of it got converted into the corresponding keto derivative **8** as was evident from the ^{13}C-NMR. Compound **15b** was then reacted with morpholine (neat; reflux; 1h). The reaction did furnish compounds **6a** and **7a** (**Scheme-4.8**).

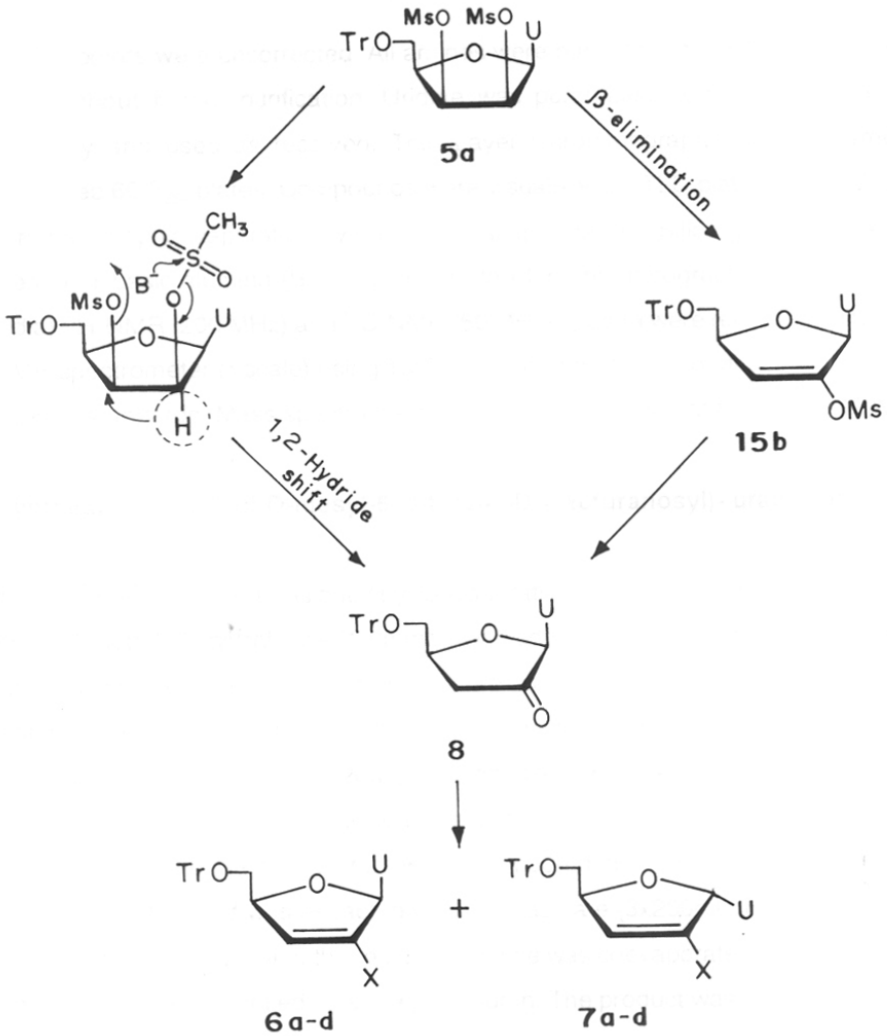
As the formation of the ene-mesylate **15b** as intermediates alone did not explain the formation of the anomers **6a** and **7a**, formation of the 2'-ketonucleoside **8** was thought to be prerequisite for the anomerisation to take place. It is not illogical to assume the formation of the 2'-ketonucleosides as it was well known in the literature that the conversion of the ene-mesylates to the 2'-ketonucleoside was a facile reaction under basic conditions[17-19]. The assumption was further supported by the fact that the pure 2'-ketonucleoside **8** could be converted to the mixture of anomers **6a** and **7a** very easily as described above.

The formation of 3'-deoxy-2'-ketonucleosides **8** from 2',3'-di-O-mesyl-*lyxo*-uridine derivatives **5a** was shown to go through the two mechanistic pathways such as, base catalysed β-elimination reactions[17-19] and 1,2 hydride shift rearrangements[20-23] (This part will be discussed in detail next chapter). In the present system, whether the 2'-ketonucleoside **8** was formed directly from compound **5a** through 1,2-hydride shift[20-23] remained to be established; however, all reports of 1,2-hydride shift in case of nucleosides involved the presence of metal ions[20-23]. The possible two mechanism of this conversion was shown in **scheme 4.9**.

4.5. Conclusion

In this chapter, we have decscribed that the mode of reactions of 2',3'-di-O-mesyl-5'-O-trityl-*lyxo*-uridine **5a** with secondary amines was completely different than that of 2',3'-di-O-mesyl-5'-O-trityl-*ribo*-uridine. We have also described an interesting and distinct difference in behaviour of 2',3'-di-O-mesyl-*lyxo*-uridine **5a** towards basic

Scheme - **4·9**



nucleophiles (amines) as compared to other nucleophiles such as thiols; the amines reacted as bases first to modulate the course of reactions whereas the thiols produced the expected substitution products.

4.6. Experimental

Melting points were uncorrected. All amines were purchased from Aldrich, U.S.A. and were used without further purification. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS, solvent chloroform-d or dioxane (in case of D_2O) as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

Synthesis of 1-(2,3-di-O-mesyl-5-O-trityl-β-D-*lyxo*furanosyl)- uracil 5a:

*Lyxo*uridine[15] (10mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (60ml). Trityl chloride (13 mmol) was added and the solution was kept for overnight at room temperature. The reaction mixture was then heated at 100°C for 3 hours. After completion of the tritylation (tlc), the reaction mixture was cooled to 0°C. Methanesulphonyl chloride (30 mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 20 hours. The reaction mixture was then poured in to the saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column. The product was crystalised from methanol.

Yield : 75%

M.P : 227°C (229°C)[15]

^{1}H-NMR : ($CDCl_3$): δ 9.3 (bs, 1H) NH; 7.48-7.24 (m, 16H) trityl, H-6; 6.38 (d, 6.3 Hz, 1H) H-1'; 5.7 (d, 8 Hz, 1H) H-5; 5.41 (m, 1H) / 5.33 (m, 1H) H-2'/H-3'; 4.28 (m, 1H) H-4'; 3.71-3.44 (m, 2H) H5', 5''; 3.09 (s, 3H) / 2.95 (s, 3H) 2',3', mesyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 163.7, C-4; 150.9, C-2; 143.3, trityl; 140.3, C-6; 128.8, 128.2, 127.6, trityl; 102.4, C-5; 87.8, trityl; 82.0, C-1'; 77.9/77.1, C-2'/C-3'; 74.9, C-4'; 61.7, C-5'; 38.9, 38.6, 2'/3'mesyl CH_3.

Synthesis of 1-(2,3-dideoxy-2-N-morpholino-5-O- trityl-β-D-glycero- pent-2-enofuranosyl)- uracil 6a and 1-(2,3-dideoxy-2-N- morpholino-5-O-trityl-α-D-glycero-pent-2- enofuranosyl)- uracil 7a:

A solution of compound **5a** (1mmol) in neat morpholine (2ml) was heated under reflux for 12h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina.

Total yield: 75%

Compound 6a:

^{1}H-NMR : ($CDCl_3$): δ 7.63 (d, 8 Hz, 1H) H-6; 7.49-7.22 (m, 15H) trityl; 6.99 (d, 1.7 Hz, 1H) H-1'; 5.18 (d, 8 Hz, 1H) H-5; 4.95-4.93 (m, 2H) H-4', H-3'; 3.72 (t, 4H) H_2C-O-CH_2; 3.4-3.23 (m, 2H) H-5', 5''; 3.06-2.94 (m, 4H) H_2C-N-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 163.9, C-4; 151.3, C-2; 145.1, C-2'; 143.5, trityl; 141.4, C-6; 128.9, 127.9, 127.4, trityl; 102.8/101.3, C-5/C-3'; 87.2/86.1/84.1, trityl/C-1'/C-4'; 66.2, C-5'and H_2C-O-CH_2; 48.7, H_2C-N-CH_2

Mass (EI) : m/z 426 (M^+-uracil, 20%); 264 (M^+-Ph_3COCH_2, 40%).

Compound 7a: (Compound **7a** was crystallised from methanol)

Yield : 26%

M.P : 193°C

^{1}H-NMR : ($CDCl_3$): δ 7.49-7.22 (m, 15H) trityl; 7.17 (d, 8 Hz, 1H) H-6; 7.06 (d, 4.2 Hz, 1H) H-1'; 5.83 (d, 8 Hz, 1H) H-5; 5.14 (m, 1H) H-4'; 4.92 (s, 1H) H-3'; 3.7 (t, 4H) H_2C-O-CH_2; 3.25-3.09 (m, 2H) H-5', 5''; 3.03-2.81 (m, 4H) H_2C-N-CH_2.

^{13}C-NMR : ($CDCl_3$): δ 163.9, C-4; 151.2, C-2; 145.7, C-2'; 144.1, trityl; 140.2, C-6; 128.9, 128.1, 127.3, trityl; 103.6/103.1, C-5/C-3'; 86.9/86.5/84.8, trityl/C-1'/C-4'; 67.4, C-5'; 66.3, H_2C-O-CH_2; 48.8, H_2C-N-CH_2.

Mass (EI) : m/z 426 (M^+-uracil, 20%); 264 (M^+-Ph_3COCH_2, 40%).

Synthesis of 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)- uracil 6b and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-glycero-pent-2-eno-furanosyl)- uracil 7b:

A solution of compound **5a** (1mmol) in neat piperidine (2ml) was heated at 80°C for 12h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina.

Total yield: 71%

Compound 6b:

^{1}H-NMR : ($CDCl_3$): δ 7.55-7.25 (m, 16H) trityl, H-6; 6.90 (bs, 1H) H-1'; 5.16 (d, 8 Hz, 1H) H-5; 4.95 (m, 1H) H-4'; 4.81 (s, 1H) H-3'; 3.40-3.10 (m, 2H) H-5', 5''; 2.95 (bs, 4H) H_2C-N-CH_2; 1.55 (bs, 6H) H_2C-CH_2-CH_2

^{13}C-NMR : ($CDCl_3$): δ 164.1, C-4; 151.3, C-2; 145.0, C-2'; 143.5, trityl; 141.7, C-6; 128.6, 127.9, 127.2, trityl; 102.4/99.3, C-5/C-3'; 87.0/86.4/84.0, trityl/C-1'/C-4'; 66.7, C-5'; 49.3, H_2C-N-CH_2; 25.1, 24.0, H_2C-CH_2-CH_2.

Mass (EI) : m/z 423 (M^+-uracil, 10%); 262 (M^+-Ph_3COCH_2, 10%).

Compound 7b: (Compound **7b** was crystallised from methanol)

Yield : 20%

M.P : 193°C

^{1}H-NMR : ($CDCl_3$): δ 7.48-7.22 (m, 15H) trityl; 7.20 (d, 8 Hz, 1H) H-6; 7.00 (d, 4.0Hz, 1H) H-1'; 5.75 (d, 8 Hz, 1H) H-5; 5.08 (m, 1H) H-4'; 4.81 (s, 1H) H-3'; 3.20-3.04 (m, 2H) H-5', 5''; 2.88 (bs, 4H) H_2C-N-CH_2; 1.53 (bs, 6H) H_2C-CH_2-CH_2.

^{13}C-NMR : (DMSO-d_6): δ 163.4, C-4; 151.2, C-2; 144.9, C-2'; 144.1, trityl; 140.8, C-6; 128.7, 128.3, 127.4, trityl; 103.2/99.0, C-5/C-3'; 86.2/84.3, trityl/C-1'/C-4'; 67.4, C-5'; 49.0, H_2C-N-CH_2; 24.9, 23.9, H_2C-CH_2-CH_2.

Mass (EI) : m/z 423 (M^+-uracil, 10%); 262 (M^+-Ph_3COCH_2, 10%).

Synthesis of 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)- uracil 6c and 1-(2,3-dideoxy-2-N- pyrrolidino-5-O-trityl-α-D-glycero-pent-2- enofuranosyl)- uracil 7c:

A solution of compound 5a (1mmol) in neat pyrrolidine (2ml) was heated at 60°C for 10h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina.

Total yield: 65%

Compound 6c:

^{1}H-NMR : ($CDCl_3$): δ 7.53 (d, 8 Hz, 1H) H-6; 7.48-7.22 (m, 15H) trityl; 6.94 (d, 1.1 Hz, 1H) H-1'; 5.24 (d, 8 Hz, 1H) H-5; 4.98 (m, 1H) H-4'; 4.48 (s, 1H) H-3'; 2.94-3.11 (m, 6H) H_2C-N-CH_2, H-5', 5''; 1.87 (m, 4H) H_2C-CH_2

^{13}C-NMR : ($CDCl_3$): δ 164.0, C-4; 151.1, C-2; 143.6, C-2'; 141.7, trityl; 141.2, C-6; 128.8, 127.9, 127.2, trityl; 102.8/93.7, C-5/C-3'; 87.0/85.2/84.7, trityl/C-1'/C-4'; 66.9, C-5'; 48.6, H_2C-N-CH_2; 25.2, H_2C-CH_2

Mass (EI) : m/z 248 (M^+-Ph_3COCH_2, 5%)

Compound 7c: (Compound **7c** was crystallised from methanol)

Yield : 20%

M.P : 158°C

^{1}H-NMR : ($CDCl_3$): δ 7.51-7.22 (m, 16H) trityl; H-6; 7.0 (d, 4.1 Hz, 1H) H-1'; 5.78 (d, 8 Hz, 1H) H-5; 5.19 (m, 1H) H-4'; 4.49 (s, 1H) H-3'; 3.20-2.94 (m, 6H) H-5', 5''; H_2C-N-CH_2; 1.86 (m, 4H) H_2C-CH_2.

^{13}C-NMR : (DMSO-d_6+$CDCl_3$): δ 163.43, C-4; 151.22, C-2; 144.1, C-2'; 142.0, trityl; 140.2, C-6; 128.66, 128.1, 127.3, trityl; 103.37/93.55, C-5/C-3'; 86.84/86.27/84.78, trityl/C-1'/C-4'; 68.28, C-5'; 48.46, H_2C-N-CH_2; 25.08, H_2C-CH_2

Mass (EI) : m/z 248 (M^+-Ph_3COCH_2, 5%)

Synthesis of 1-[2,3-dideoxy-2-N-(N-methylpiperazino)-5-O-trityl-β-D-glycero-pent-2-enofuranosyl]- uracil 6d and 1-[2,3-dideoxy-2-N-(N-methylpiperazino)-5-O-trityl-α-D-glycero-pent-2- enofuranosyl]- uracil 7d:

A solution of compound 5a (1mmol) in neat N-methylpiperazine (2ml) was heated at 80°C for 24h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina.

Total Yield: 70%

Compound 6d:

^{1}H-NMR : ($CDCl_3$): δ 7.53 (d, 8 Hz, 1H) H-6; 7.47-7.20 (m, 15H) trityl; 6.96 (d, 1.3 Hz, 1H) H-1'; 5.14 (d, 8 Hz, 1H) H-5; 4.94 (m, 1H) H-4'; 4.87 (s, 1H) H-3'; 3.37-3.20 (m, 2H) H-5', 5''; 3.10-2.94 (m, 4H) $_2$C-N-CH_2; 2.43-2.32 (m, 4H) H_2C-N(CH_3)-CH_2; 2.29 (s, 3H) N-CH_3

^{13}C-NMR : ($CDCl_3$): δ 163.1, C-4; 151.4, C-2; 144.7, C-2'; 143.5, trityl; 141.3, C-6; 128.8, 127.9, 127.3, trityl; 102.6/100.7, C-5/C-3'; 87.1/86.2/84.0, trityl/C-1'/C-4'; 66.5, C-5'; 54.7, H_2C-N(CH_3)-CH_2; 48.0, H_2C-N-CH_2; 45.8, N-CH_3

Mass (EI) : m/z 549 (M^+, 2%) 437 (M^+-uracil, 20%); 277 (M^+-Ph_3COCH_2, 10%)

Compound 7d: (Compound **7d** was crystallised from methanol)

Yield : 22%

M.P : 220°C

^{1}H-NMR : ($CDCl_3$): δ 9.25 (bs, 1H) N3-H; 7.48-7.22 (m, 15H) trityl; 7.12 (d, 8 Hz, 1H) H-6; 7.02 (d, 4.3 Hz, 1H) H-1'; 5.76 (d, 8 Hz, 1H) H-5; 5.20-5.07 (m, 1H) H-4'; 4.86 (s, 1H) H-3'; 3.23-3.08 (m, 2H) H-5', 5''; 3.02-2.88 (m, 4H) H_2C-N-CH_2; 2.42-2.37 (m, 4H) H_2C-N(CH_3)-CH_2; 2.84 (bs, 3H) N-CH_3.

^{13}C-NMR : ($DMSO-d_6$): δ 163.4, C-4; 151.1, C-2; 144.7, C-2'; 144.0, trityl; 140.4, C-6; 128.6, 128.1, 127.3, trityl; 103.1/100.0, C-5/C-3'; 86.2/85.9/84.2, trityl/C-1'/C-4'; 67.5, C-5'; 54.1, H_2C-N(CH_3)-CH_2; 47.9, H_2C-N-CH_2; 46.1, N-CH_3.

Mass (EI) : m/z 549 (M^+, 2%) 437 (M^+-uracil, 20%); 277 (M^+-Ph_3COCH_2, 10%)

Synthesis of 5'-O-benzoyl-3'-deoxy-2'-ketouridine 9β from compound 6a:

A solution of compound **6a** (0.5mmol) and conc. HCl (1.5mmol) in THF/H_2O (6ml, 5:1) was heated under reflux for 12 h. After completion of the reaction, solvents were evaporated under reduced pressure. The oily residue was coevaporated with pyridine and redissolved in the same solvent (6ml). the solution was cooled at 0°C and benzoyl chloride in pyridine was added to it. After the addition, the reaction mixture was stirred at room temperature for 2h. the reaction mixture was poured into the saturated sodium bicarbonate solution and was extracted with ethyl acetate. Organic layer was dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified on silica gel column. Yield: 65 %.

Synthesis of 5'-O-trityl-3'-deoxy-2'-ketouridine 8:

Compound **8** was synthesised using reported procedure[11,12].

Synthesis of authentic 5'-O-benzoyl-3'-deoxy-2'-ketouridine 9β from compound 8:

A solution of compound **8** (1mmol) and conc. HCl (3mmol) in THF (5ml) was heated under reflux. After completion of the reaction, solvents were evaporated under reduced pressure. The oily residue was coevaporated with pyridine and redissolved in the same solvent (6ml). The solution was cooled at 0°C and benzoyl chloride in pyridine was added to it . After the addition, the reaction mixture was stirred at room temperature for 2h. The reaction mixture was poured into the saturated sodium bicarbonate solution and was extracted with ethyl acetate. Organic layer was dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified on silica gel column.

Yield : 70%

M.P : 191°C

^{1}H-NMR : (DMSO-d_6): δ 11.57 (bs, H) N-H; 8.02-7.49 (m, 6H) benzoyl, H-6 ; 5.65 (d, 7.9 Hz 1H) H-5; 5.52 (s, 1H) H-1'; 4.75 (m, 1H) H-4'; 4.49 (m, 2H) H-5', 5''; 2.77 (d, 7.9 Hz, 2H) H-3', 3''

^{13}C-NMR : (DMSO-d_6): δ 207.4, C-2'; 166.1, benzoyl keto; 163.7, C-4; 150.6, C-2; 145.2, C-6; 133.9, 129.8, 129.2, phenyl; 102.6, C-5; 86.5, C-1'; 73.7, C-4'; 66.4, C-5'; 36.7, C-3'.

Mass (EI) : 330 (M^+, 10%); 219 (M^+-uracil, 15%); 208 (M^+-BzOH, 25%); 195 (M^+-$BzOCH_2$, 5%).

Synthesis of 5'-O-benzoyl-3'-deoxy-2'-keto-α-uridine 10α from enamine 7a:

A solution of compound **7a** (1mmol) and conc. HCl (3mmol) in THF/H_2O (6ml, 5:1) was heated under reflux for 12 h. After completion of the reaction, solvents were evaporated under reduced pressure. The oily residue was coevaporated with pyridine and redissolved in the same solvent (6ml). The solution was cooled at 0°C and benzoyl chloride in pyridine was added to it . After the addition, the reaction mixture was stirred at the same temperature for 2h. The reaction mixture was poured into saturated sodium bicarbonate solution and was extracted with ethyl acetate. Organic layer was dried over sodium sulphate and evaporated under reduced pressure. The oily residue was purified on silica gel column.

Yield : 67 %,

M.P : 195°C

^{1}H-NMR : (DMSO-d_6): δ 11.62 (bs, H) N-H; 7.99-7.46 (m, 6H) benzoyl, H-6 ; 5.65 (d, 7.9 Hz 1H) H-5; 5.59 (s, 1H) H-1'; 4.97 (m, 1H) H-4'; 4.54-4.35 (m, 2H) H-5', 5''; 2.97-2.63 (m, 2H) H-3', 3''.

^{13}C-NMR : (DMSO-d_6): δ 206.5, C-2'; 166.0, benzoyl keto; 163.8, C-4; 151.2, C-2; 145.6, C-6; 133.9, 129.7, 129.2, phenyl; 102.3, C-5; 86.67, C-1'; 76.9, C-4'; 66.85, C-5'; 37.6, C-3'

Mass (EI) : 330 (M^+, 10%); 219 (M^+-uracil, 15%); 208 (M^+-BzOH, 25%); 195 (M^+-$BzOCH_2$, 5%).

Synthesis of 2'-O-mesyl-3'-deoxy-3'-morpholino- 5'-O- trityl-*ara*-uridine 13b:

Compound **13a** (0.5mmol) was dried by coevaporation with dry pyridine and redissolved in the same solvent (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (1.5mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the solution was left at +4°C overnight. The reaction mixture was then poured in to the ice-cold water. The white precipitate was filtered and the residue was washed thoroughly with water. The residue was redissolved in ethyl acetate, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness. The residue thus obtained was purified on silica gel column.

Yield : 68%

M.P : 155°C

^{1}H-NMR : ($CDCl_3$): δ 9.18 (bs, 1H) NH; 7.69 (d, 8 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 6.14 (d, 4.6 Hz, 1H) H-1'; 5.68 (d, 8 Hz, 1H) H-5; 5.38 (m, 1H) H-2'; 4.13 (m, 1H) H-4'; 3.67 (m, 4H) H_2C-O-CH_2; 3.59-3.36, (m, 3H) H-5', 5'', H-3'; 2.95 (s, 3H) 2'-mesyl CH_3; 2.71-2.58, H_2C-N-CH_2

^{13}C-NMR : ($CDCl_3$): δ 163.5, C-4; 150.5, C-2; 143.4, trityl; 140.8, C-6; 128.7, 128.1, 127.5, trityl; 102.7, C-5; 87.3, trityl; 83.7, C-1'; 77.4/76.9, C-2'/C-4'; 70.8, C-3'; 66.9, H_2C-O-CH_2; 63.2, C-5'; 50.6, H_2C-N-CH_2; 38.5, 2'-mesyl CH_3.

Synthesis of 2'-deoxy-2'-morpholino-3'-O- mesyl-5'-O-trityl-*xylo*-uridine 14b:

Compound **14b** was prepared[16] from **14a** and purified as described in case of compound **13b**.

Yield : 70%

M.P : 134°C

^{1}H-NMR : ($CDCl_3$): δ 9.1 (bs, 1H) NH; 7.45-7.25 (m, 16H) trityl, H-6; 6.19 (d, 4.4 Hz, 1H) H-1'; 5.63 (d, 8 Hz, 1H) H-5; 5.29 (m, 1H) H-3'; 4.32 (m, 1H) H-4'; 3.75 (m, 4H) H_2C-O-CH_2; 3.67-3.6, 3.38-3.26 (m, 3H) H-5', 5'', H-2'; 2.83 (s, 3H) 3'-mesyl CH_3; 2.72 (m, 4H) H_2C-N-CH_2

^{13}C-NMR : ($CDCl_3$): δ 162.3, C-4; 149.4, C-2; 142.3, trityl; 138.7, C-6; 127.6, 127.0, 126.4, trityl; 102.2, C-5; 86.5, trityl; 83.2, C-1'; 77.9, 77.2, 74.7, C-2'/C-3'/C-4'; 65.6, H_2C-O-CH_2; 60.6, C-5'; 50.3, H_2C-N-CH_2; 37.5, 3'-mesyl CH_3.

Synthesis of 1-(5-O-trityl-3-deoxy-2-O-mesyl-β-D-glycero- pent-2- eno-furanosyl)-uracil 15b:

A solution of compound **5a** (1mmol) in DMSO (3ml) was treated with pottassium *t*-butoxide (2mmol). After 12h, the reaction mixture was poured in to the water which was substiquently extracted with ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to dryness. The product obtained was purified on silica gel column.

Yield : 30%

M.P : 134°C

^{1}H-NMR : ($CDCl_3$): δ 9.00 (bs, 1H) NH; 8.05 (d, 8 Hz, 1H) H-6; 7.4-7.28 (m, 15H) trityl; 6.93-6.9 (m, 1H) H-1'; 6.17 (t, 1H) H-3'; 5.03-4.97 (m, 2H) H-5, H-4'; 3.6-3.4 (m, 2H) H-5', 5''; 3.24 (s, 3H) mesyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 163.6, C-4; 151.2, C-2; 143.0, trityl; 140.82/140.73, C-6/C-2'; 128.9, 128.7, 128.2, trityl; 115.7, C-3'; 103.1, C-5; 87.8, trityl; 84.9/82.9, C-1'/C-4'; 64.4, C-5'; 38.7, CH_3.

Reaction of morpholine with compound 15b.

A solution of compound **15b** (0.28mmol) in neat morpholine (2ml) was heated under reflux for 1h. After the completion of the reaction, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina to produce a mixture of compounds **6a** and **7a**. Yield 60 %.

Reaction of morpholine with 5'-O-trityl-3'-deoxy-2'-ketouridine 8:

A solutiun of compound **8** (1mmol) in neat morpholine (2ml) was heated under reflux. After 1 h, the amine was evaporated under reduced pressure. The oily residue was purified by column chromatography on basic alumina to produce a mixture of compounds **6a** and **7a**. Yield. 70 %.

Reaction of pyrrolidine with 5'-O-trityl-3'-deoxy-2'-ketouridine 8:

A mixture of compound **8** (1mmol) and pyrrolidine (10 mmol) in toluene and benzene (1:1, 20 ml) was heated under reflux for 20 hours. The reaction mixture was evaporated to dryness and the residue was purified on basic alumina column to produce a mixture of enamines **6c** and **7c**. Yield: 63%.

Reactions of morpholine with compounds 13b and 14b:

A solution of a mixture of compounds **13b** and **14b** (1 mmol, 0.5 mmol each) in neat morpholine (5ml) was heated under reflux for 6h. The reaction did not produce any isolable compounds; instead the starting materials underwent extensive degradation (tlc).

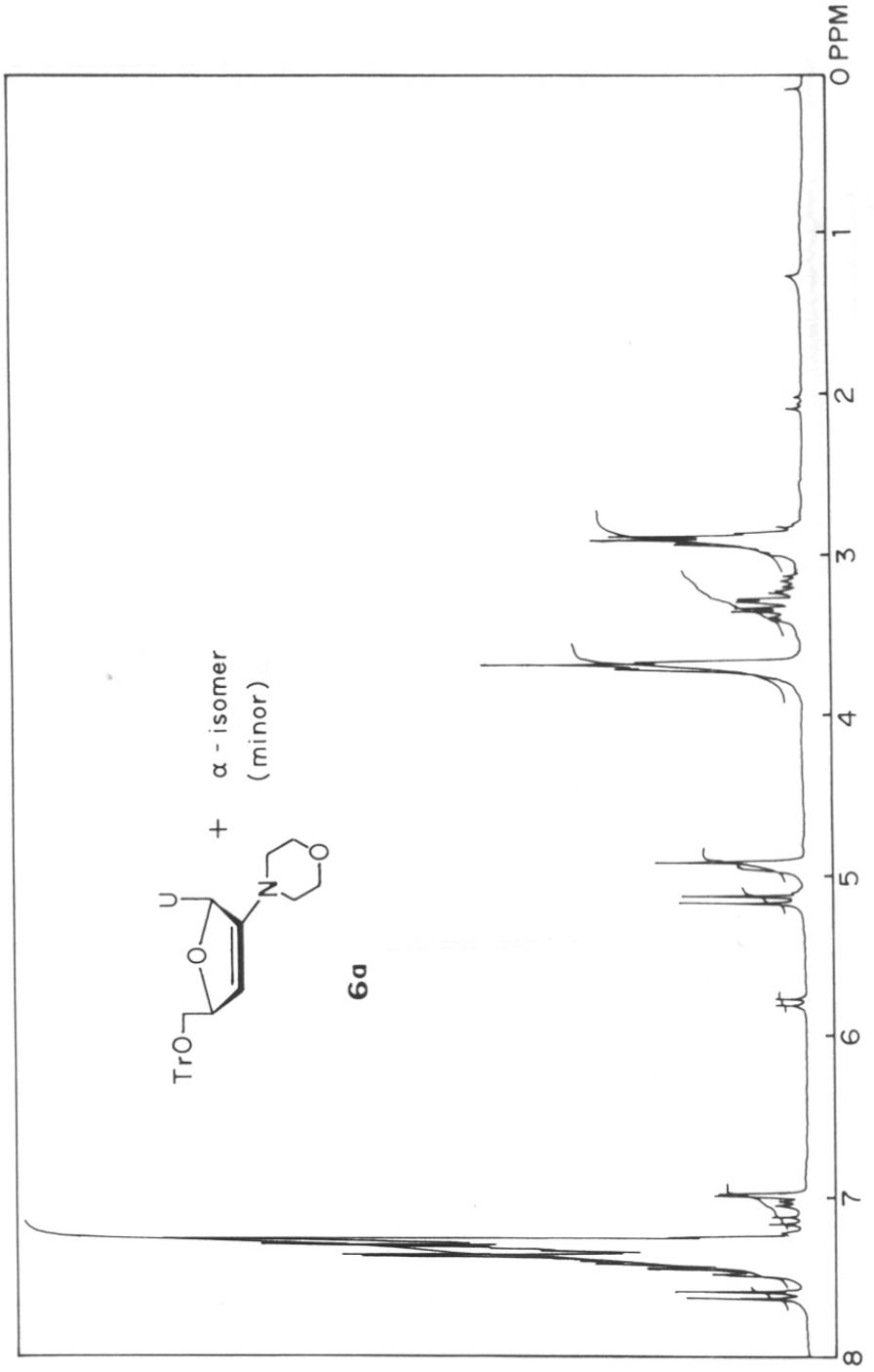
4.7. References

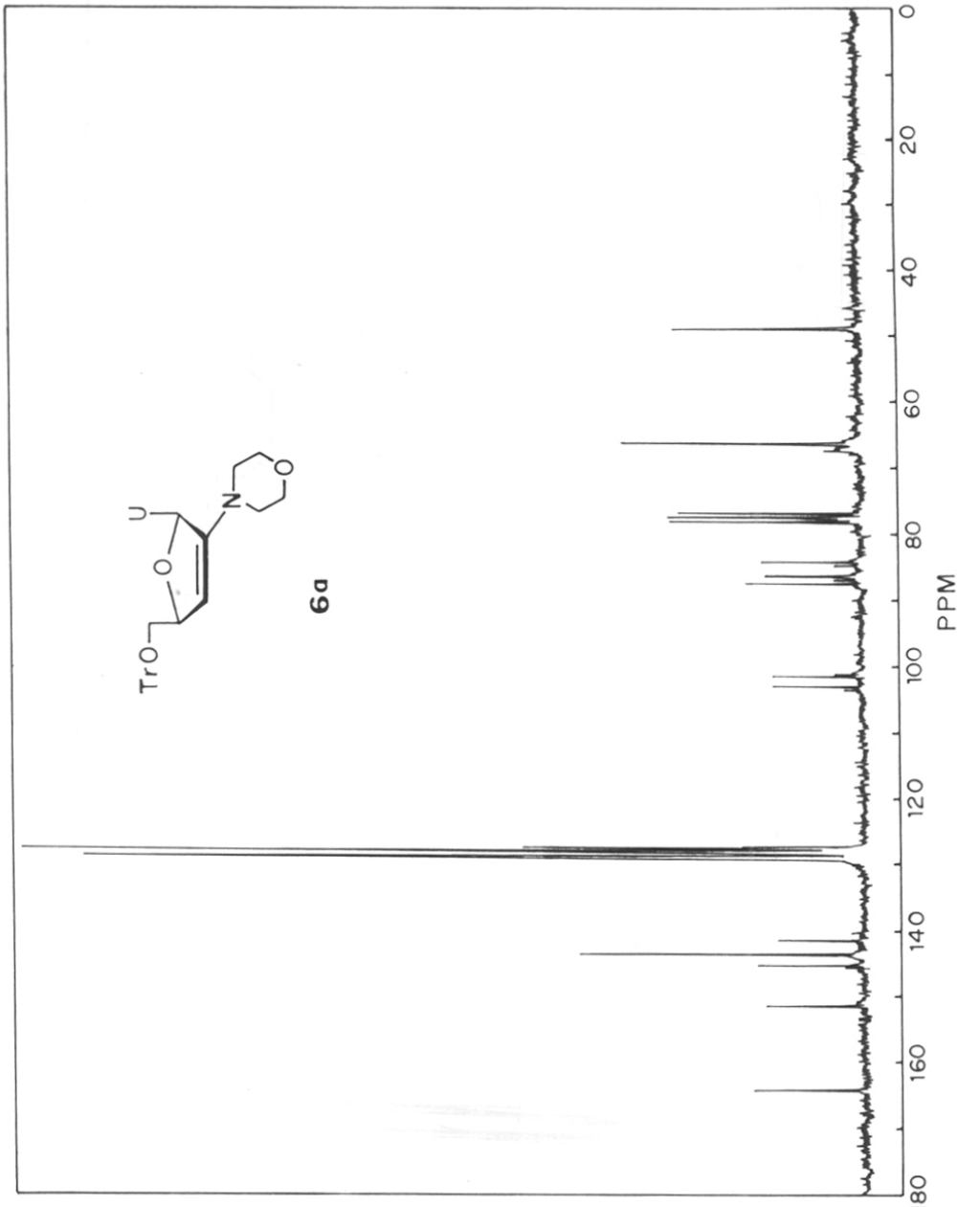
1. Mitsuya, H.; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Nusinoff-Lehrman, S.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S. *Proc. Natl. Acad. Sci. USA*, **1985**, 82, 7096-100.
2. For a review, see: Huryn, D.M.; Okabe, M. *Chem. Rev.* **1992**, 92, 1745-68 and the references cited therein.
3. Pathak, T. *PhD Thesis*, **1988**, Uppsala University, Sweden.
4. Welch, C.J.; Bazin, H.; Chattopadhyaya, J. *Acta, Chem. Scand.* **1986**, B40, 343-57.
5. Minamoto, K.; Hamano, Y.; Matsuoka, Y.; Watanab, K.; Hirota, T.; Eguchi, S.; *Nucleosides Nucleotides*, **1992**, 11, 457-71.
6. Wu, J-C.; Pathak, T.; Tong, W.; Vial, J-M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron*, **1988**, 44, 6705-22.
7. Wu, J-C.; Chattopadhyaya, J. *Tetrahedron*, **1989**, 45, 4507-22.
8. Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J. *Tetrahedron*, **1991**, 47, 3431-50.
9. Secrist III, J.A.; Winter, Jr., W. J. *J. Am. Chem. Soc.* **1977**, 100, 2554-5.
10. Sakthivel, K.; Bera, S.; Pathak, T. *Tetrahedron*, **1993**, 49, 10387-92.
11. Kawana, M.; Nishikawa, M.; Yamasaki, N.; Kuzuhara, H. *J. Chem. Soc. Perkin Trans I*, **1989**, 1593-6.
12. Lin, T-S.; Luo, M-Z. Liu, M-C. *Nucleosides Nucleotides*, **1992**, 329-40.
13. Nagarajan, K.; Rajappa, S. *Tetrahedron Lett.* **1969**, 2293-6.
14. a) Lin, T-S.; Yang, J-H.; Liu, M-C.; Zhu, J-L. *Tetrahedron Lett.* **1990**, 3829-32. b) Altona, C.; Sundaralingam, M.; *J. Am. Chem. Soc.* **1972**, 94, 8205-12.
15. Johnson, R.; Joshi, B.V.; Neidle, S.; Reese, C.B.; Snook, C.F. *Tetrahedron Lett.*, **1992**, 33, 8151-4.
16. Bera, S.; Pathak, T. Langley, G; *Tetrahedron*, **1995**, 51, 1459-70.
17. Sasaki, T.; Minamoto, K.; Suzuki, H. *J. Org. Chem.*, **1973**, 38, 598-607.
18. Sasaki, T.; Minamoto, K.; Hattori, K. *J. Org. Chem.*, **1973**, 38, 1283-6.
19. Sasaki, T.; Minamoto, K.; Hattori, K. *Tetrahedron*, **1974**, 30, 2689-94.
20. Grouiller, A.; Essadiq, H.; Pacheco, H.; Juntunen, S.; Chattopadhyaya, J. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 52-3.
21. Kawana, M.; Kuzuhara, H. *Tetrahedron Lett.*, **1987**, 28, 4075-8.

22. Kawana, M.; Yamasaki, N.; Nishikawa, M.; Kuzuhara, H. *Chemistry Lett.*, **1987**, 2419-22.

23. Hansske, F.; Robins, M. J.; *J. Am. Chem. Soc.*, **1983**, 105, 6736-7.

4.8. Spectra

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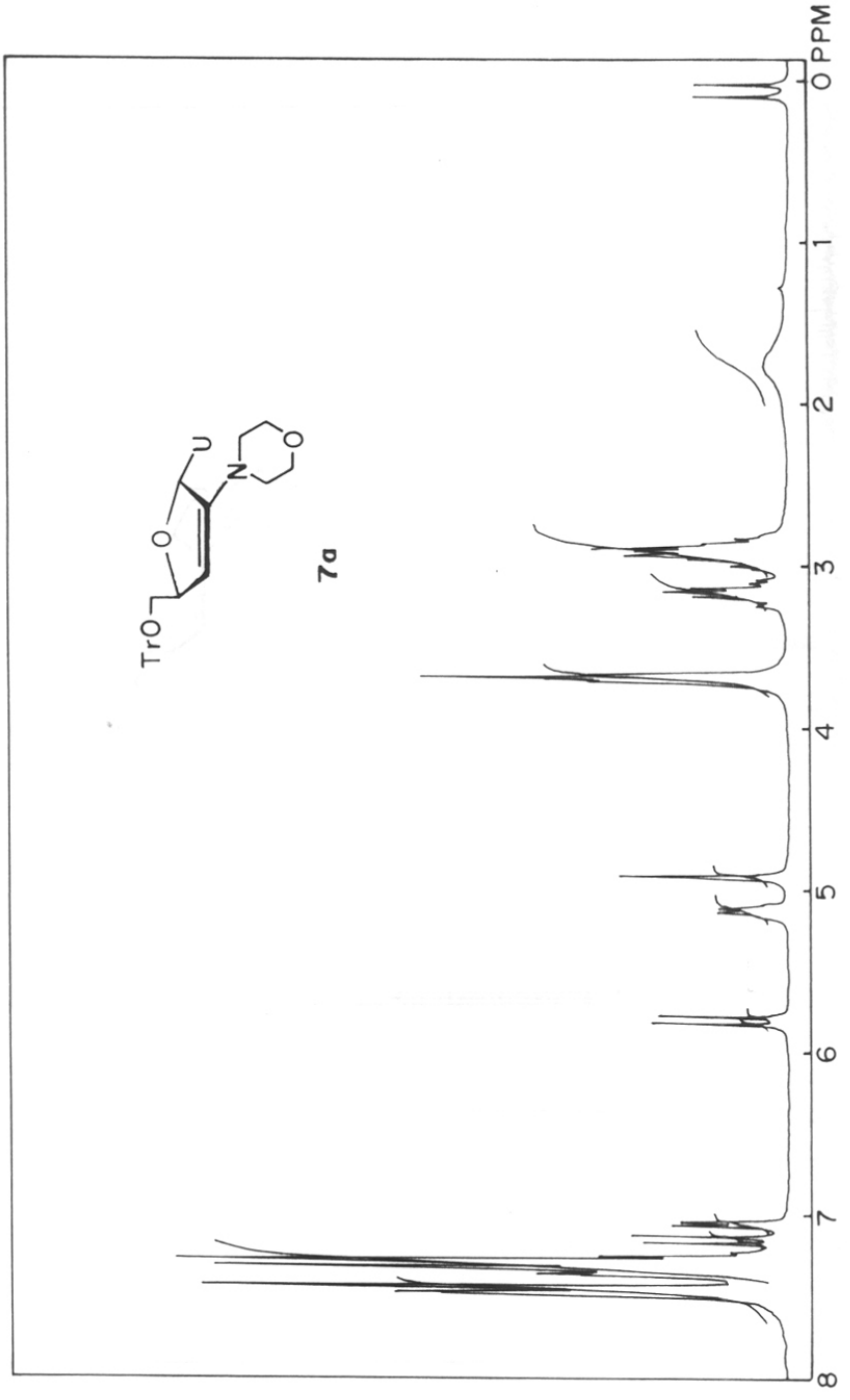
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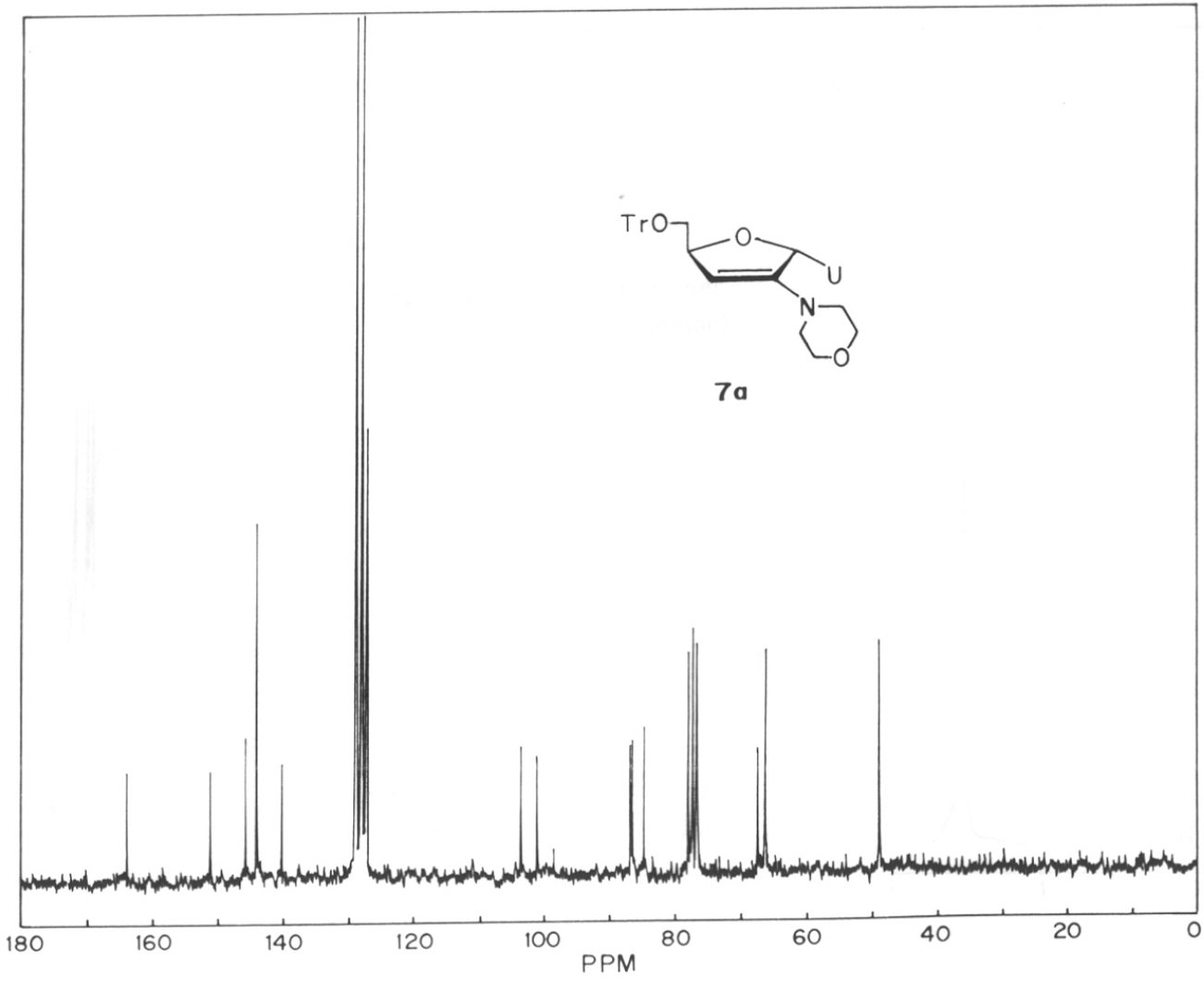

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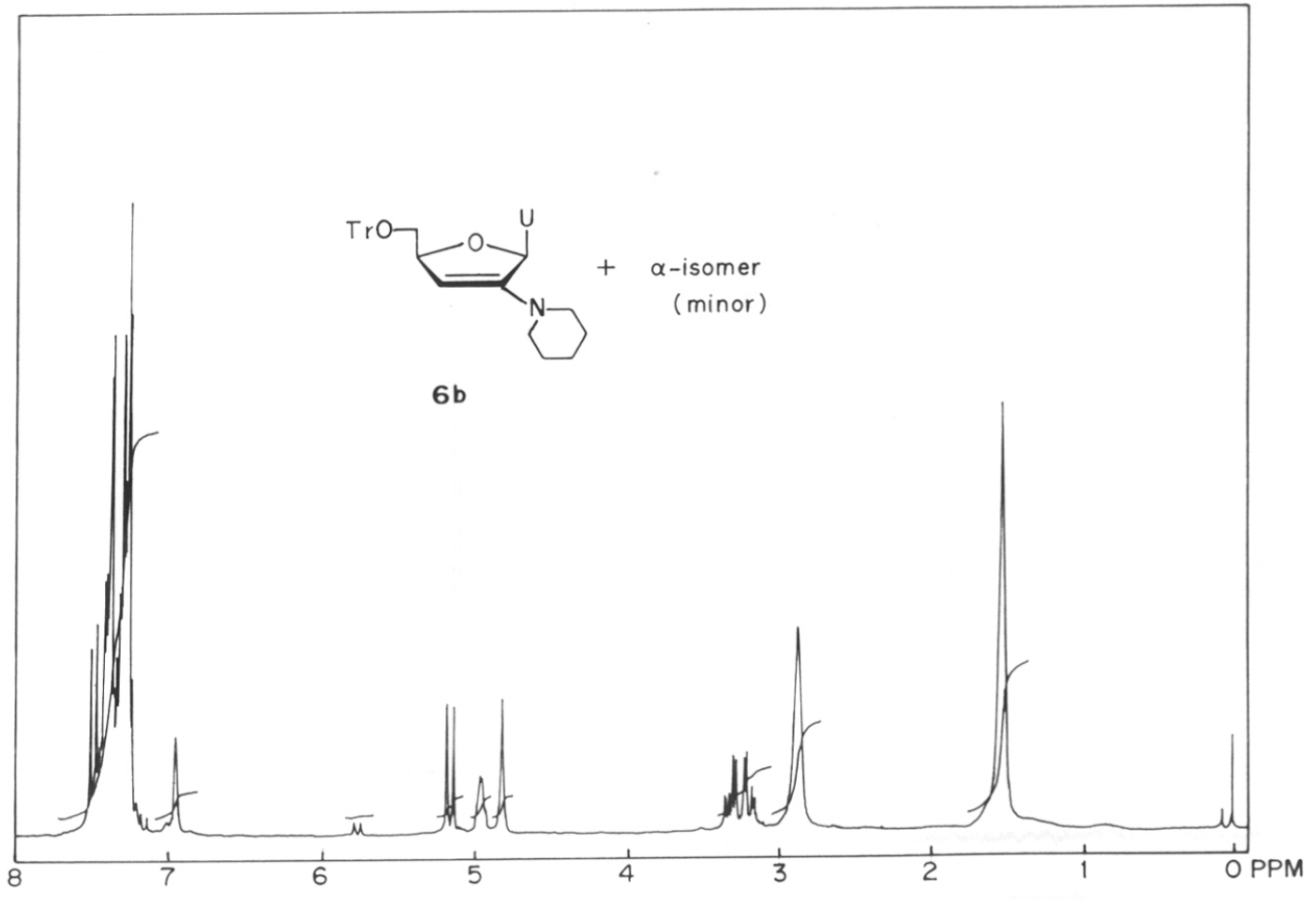
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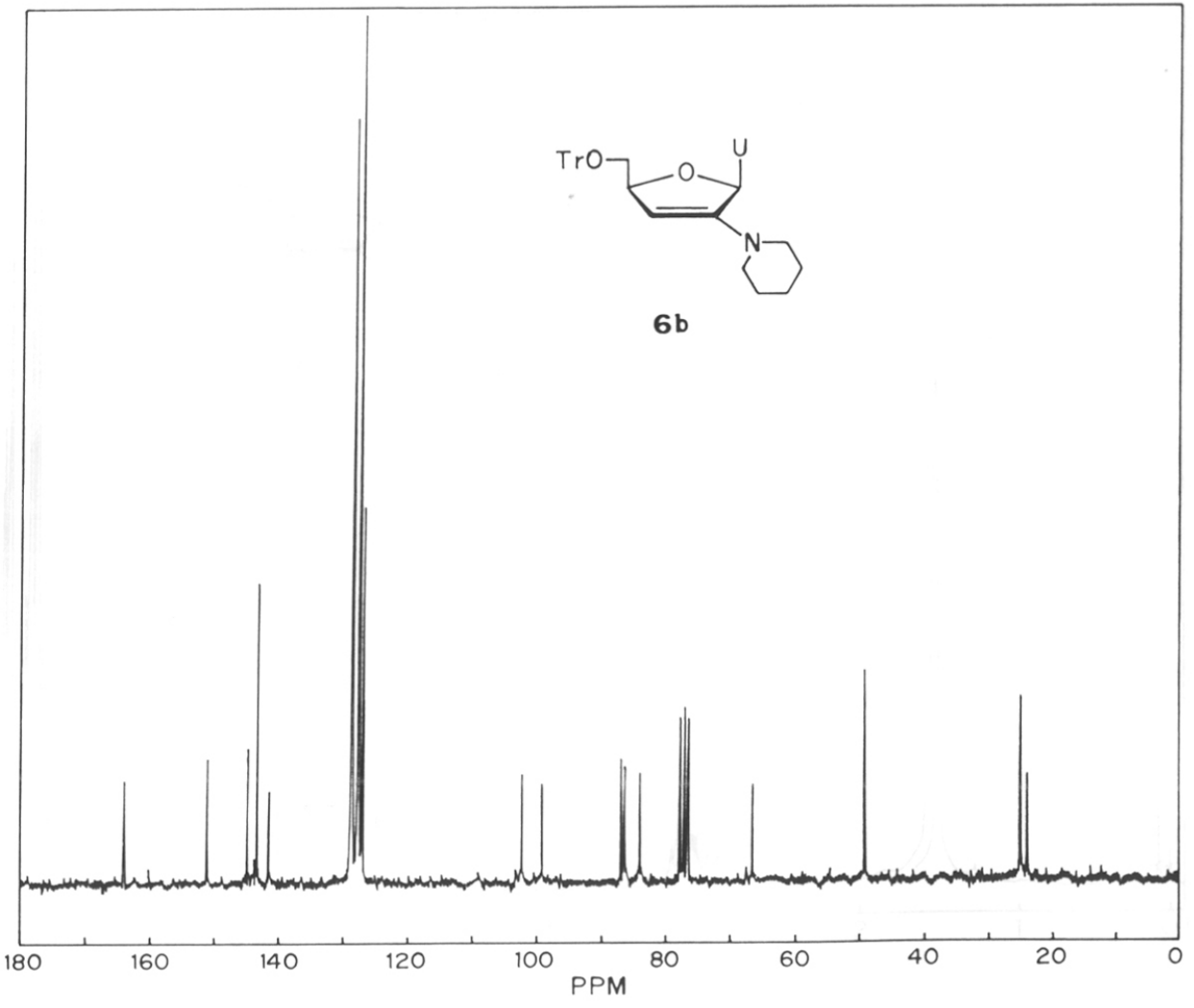
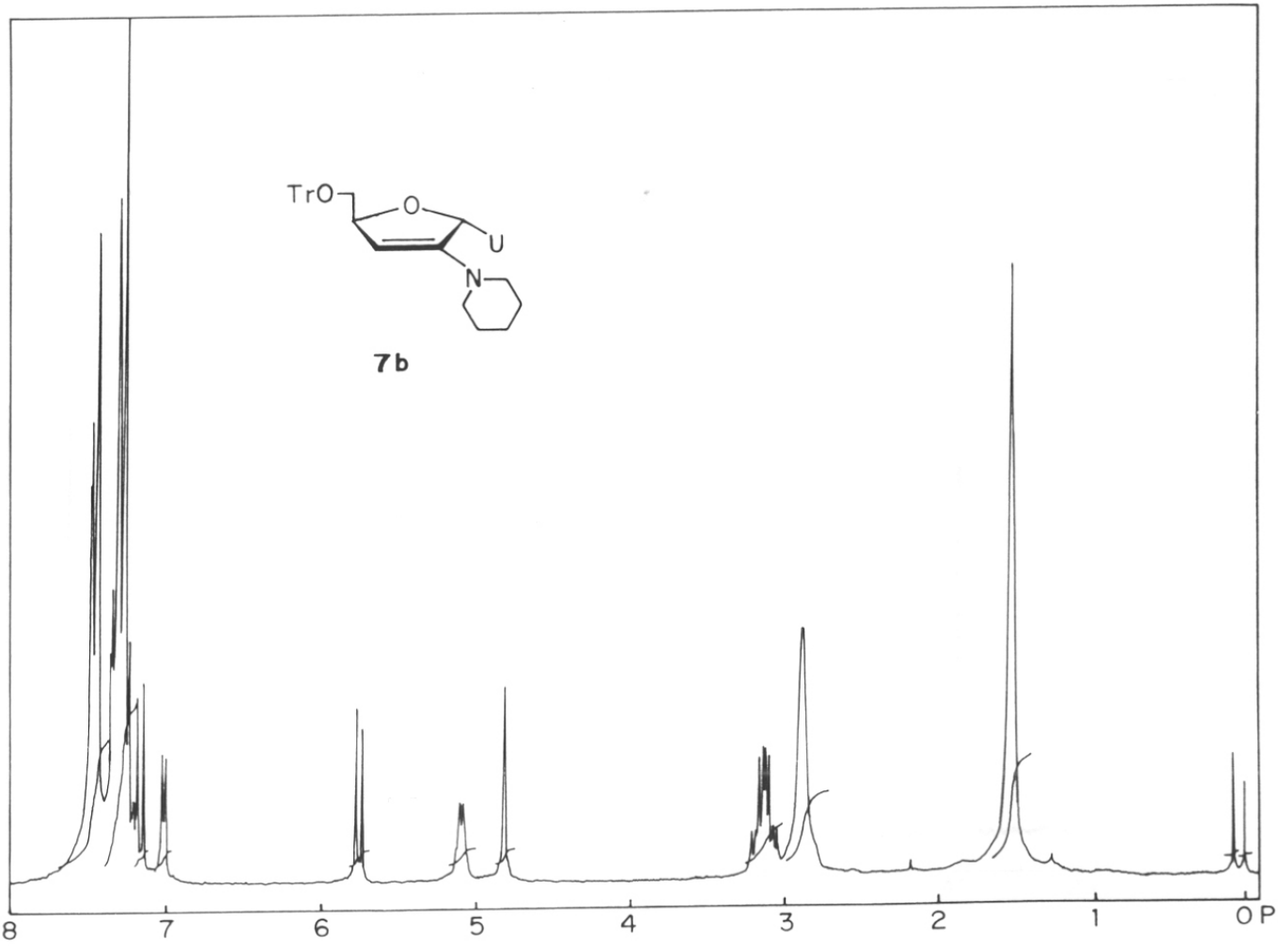
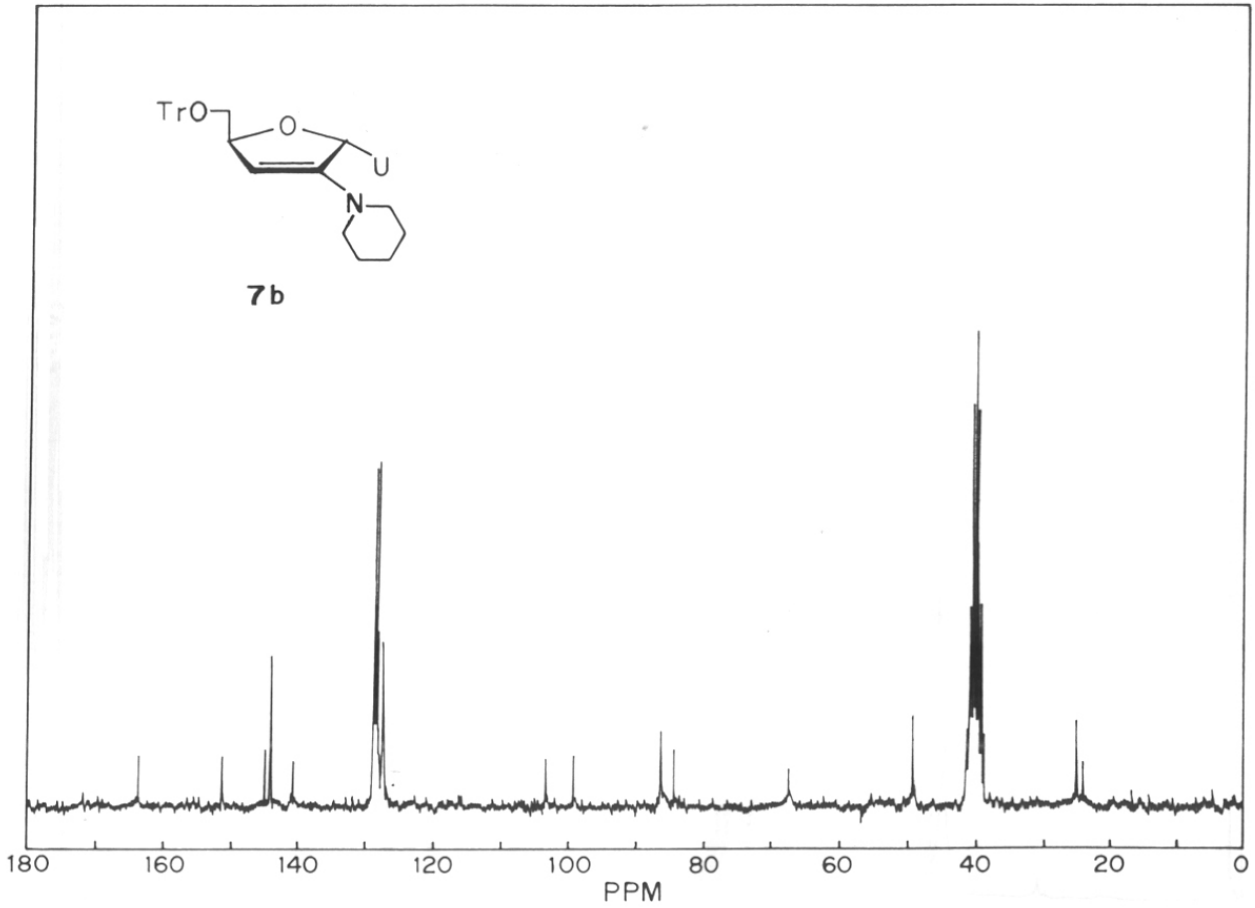
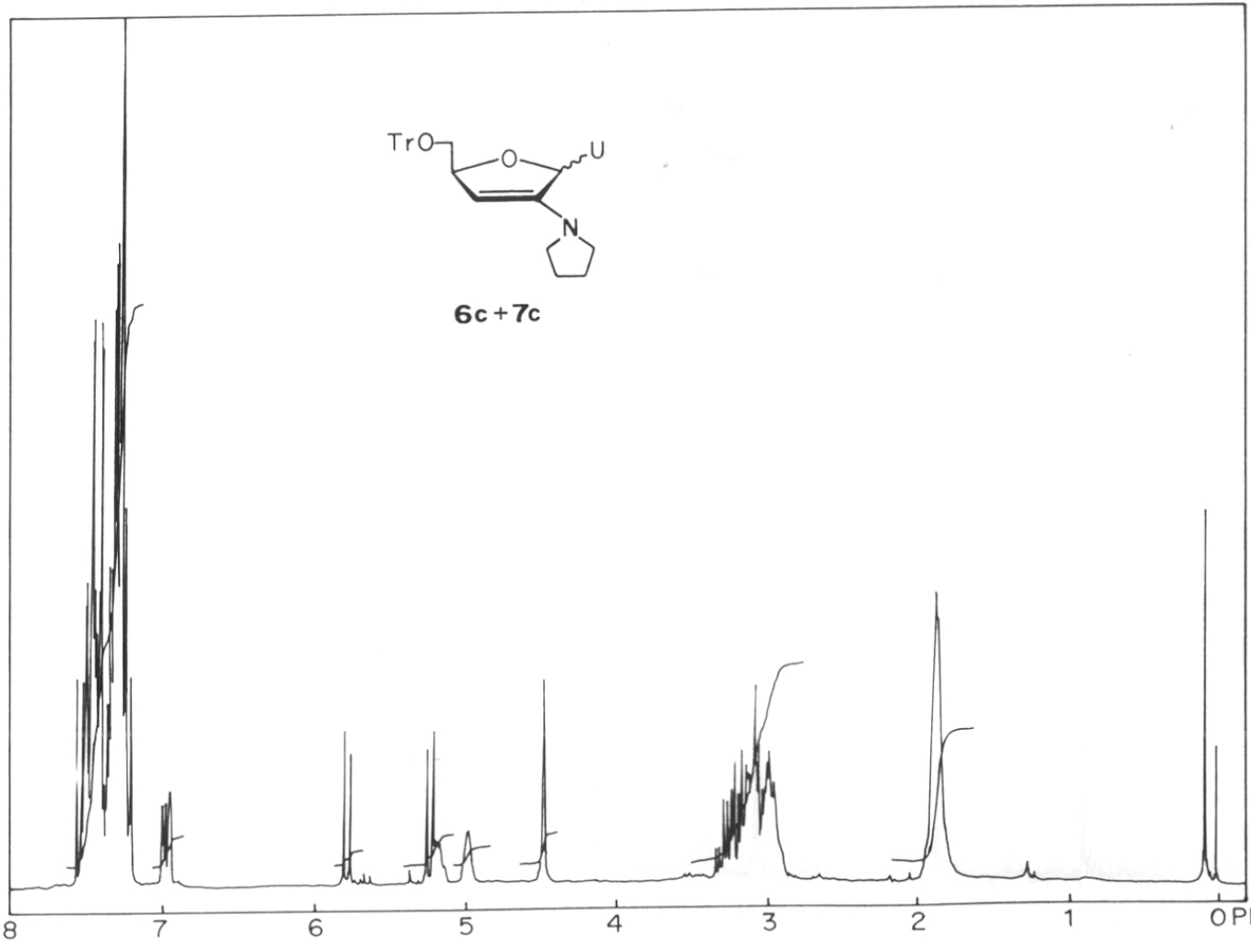


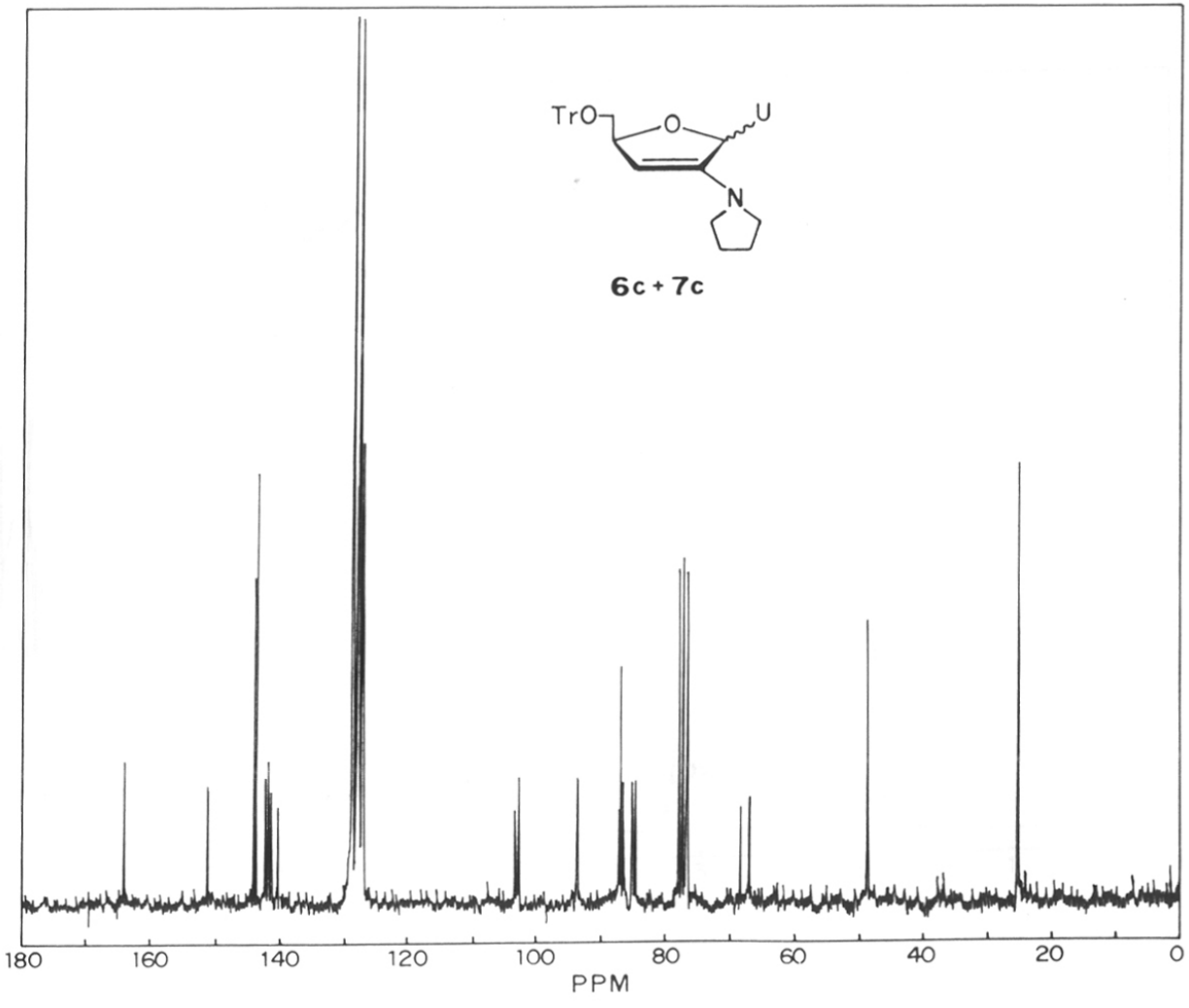
6b

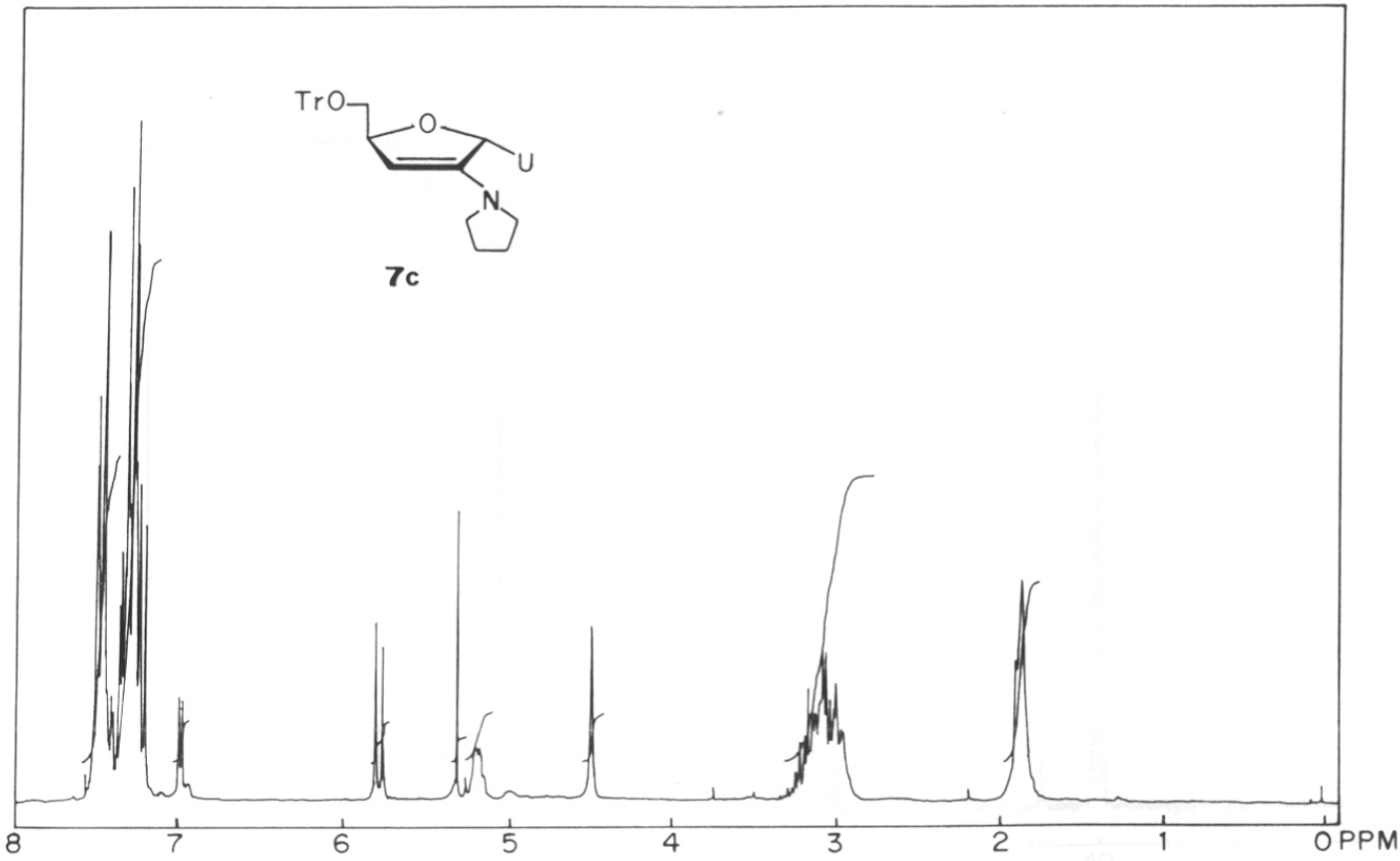


7b

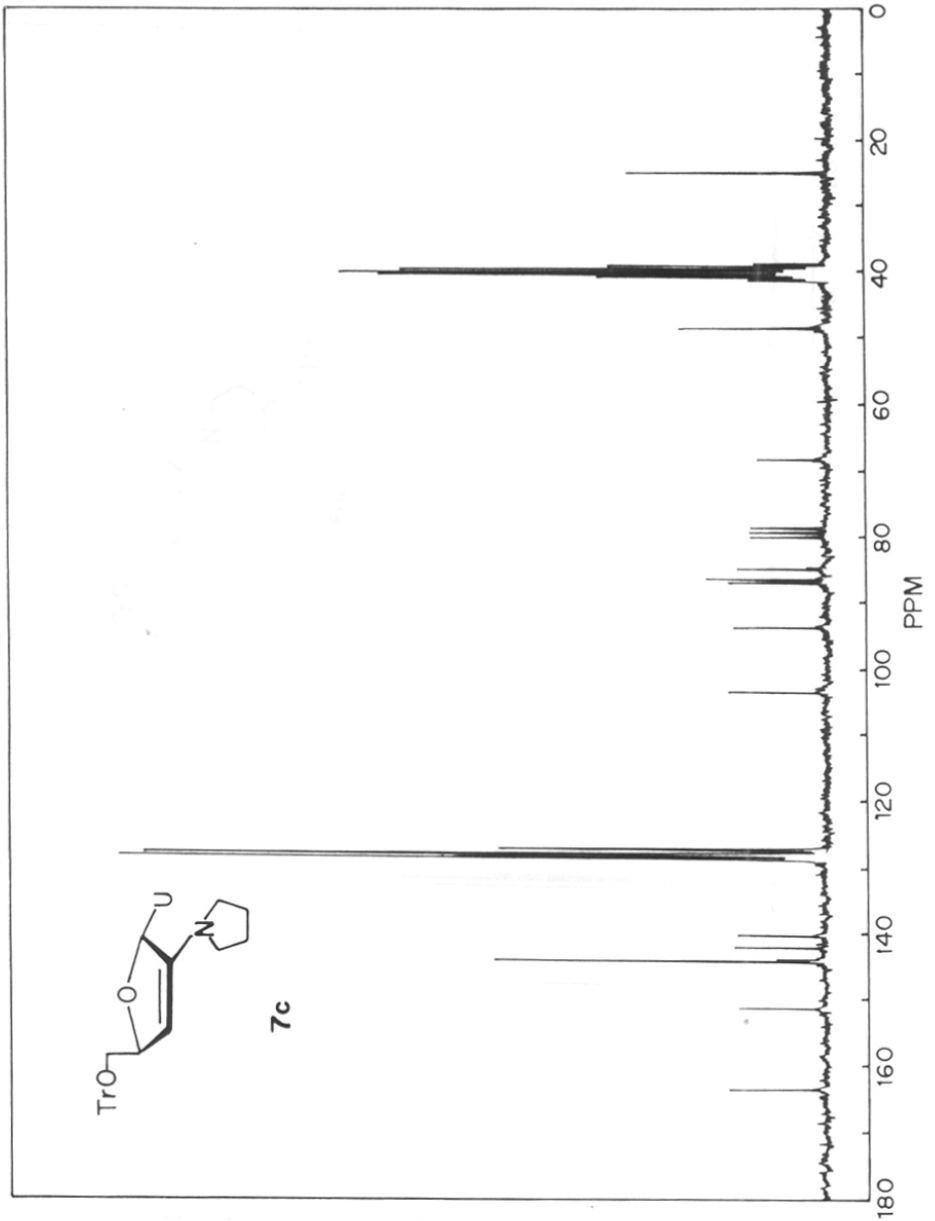

TrO
O
U
N
7b
180
160
140
120
100
80
60
40
20
0
PPM


TrO
O
U
N
6c + 7c
8
7
6
5
4
3
2
1
0 PPM


TrO
O
U
N
6c + 7c
180
160
140
120
100
80
60
40
20
0
PPM



7c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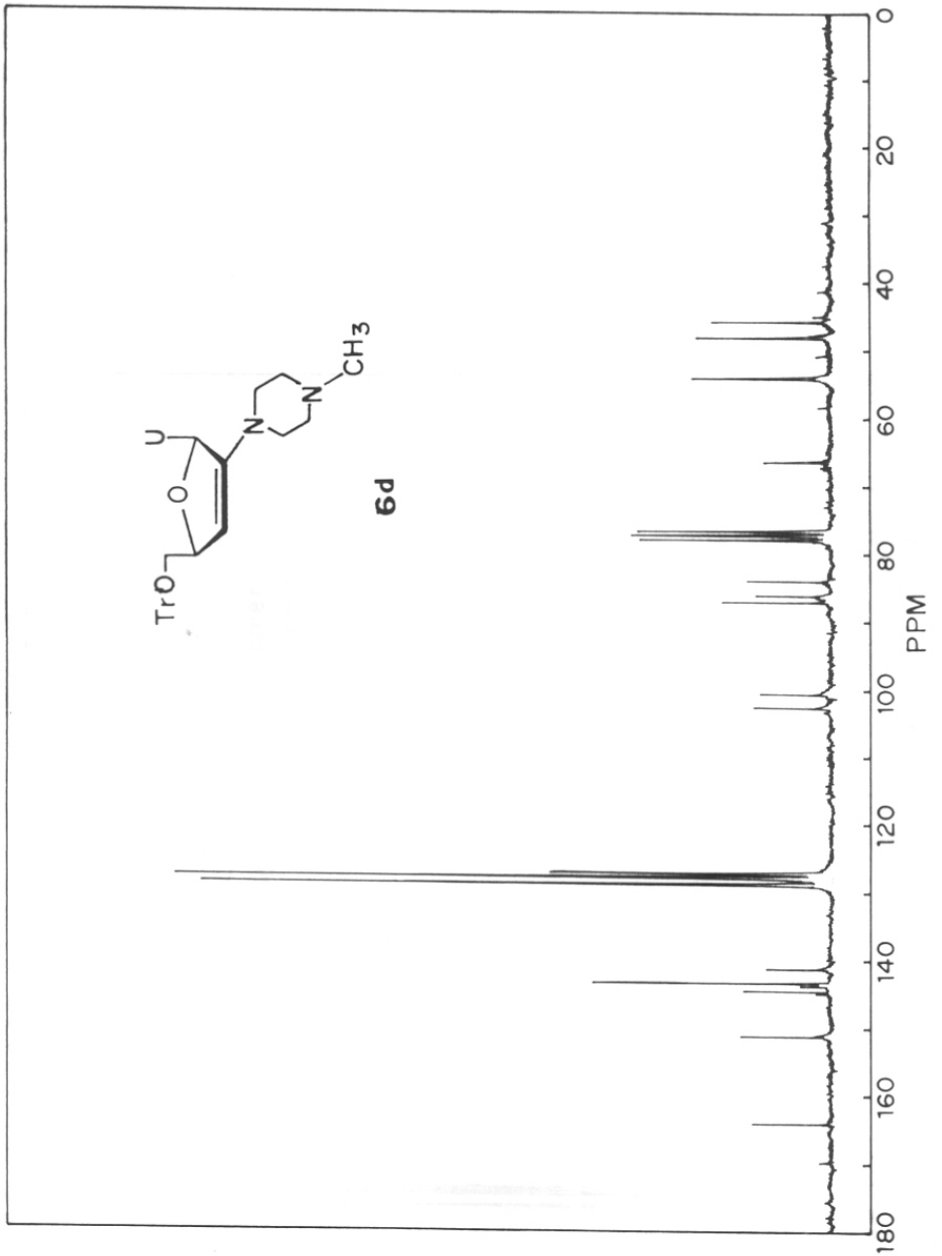
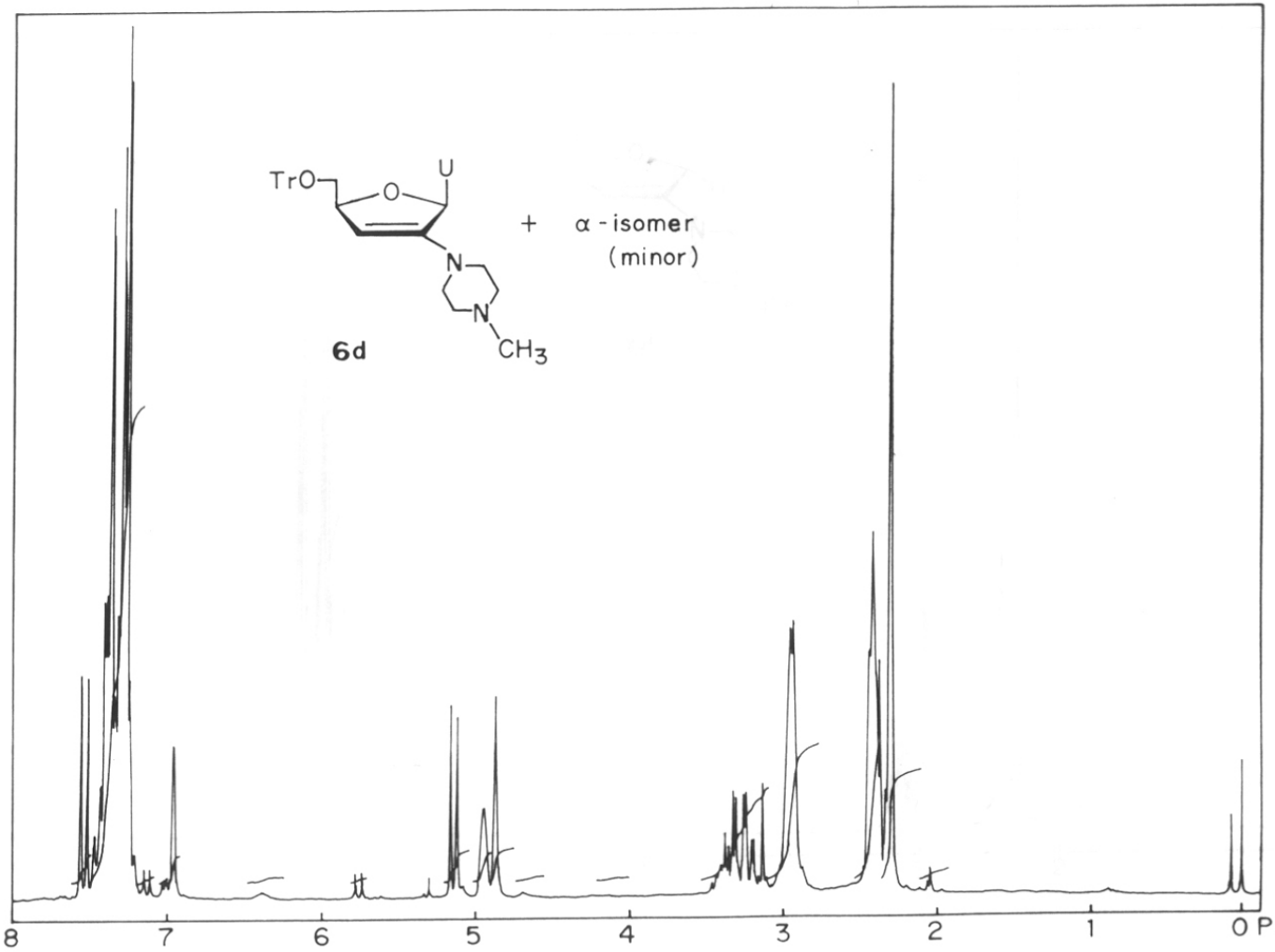
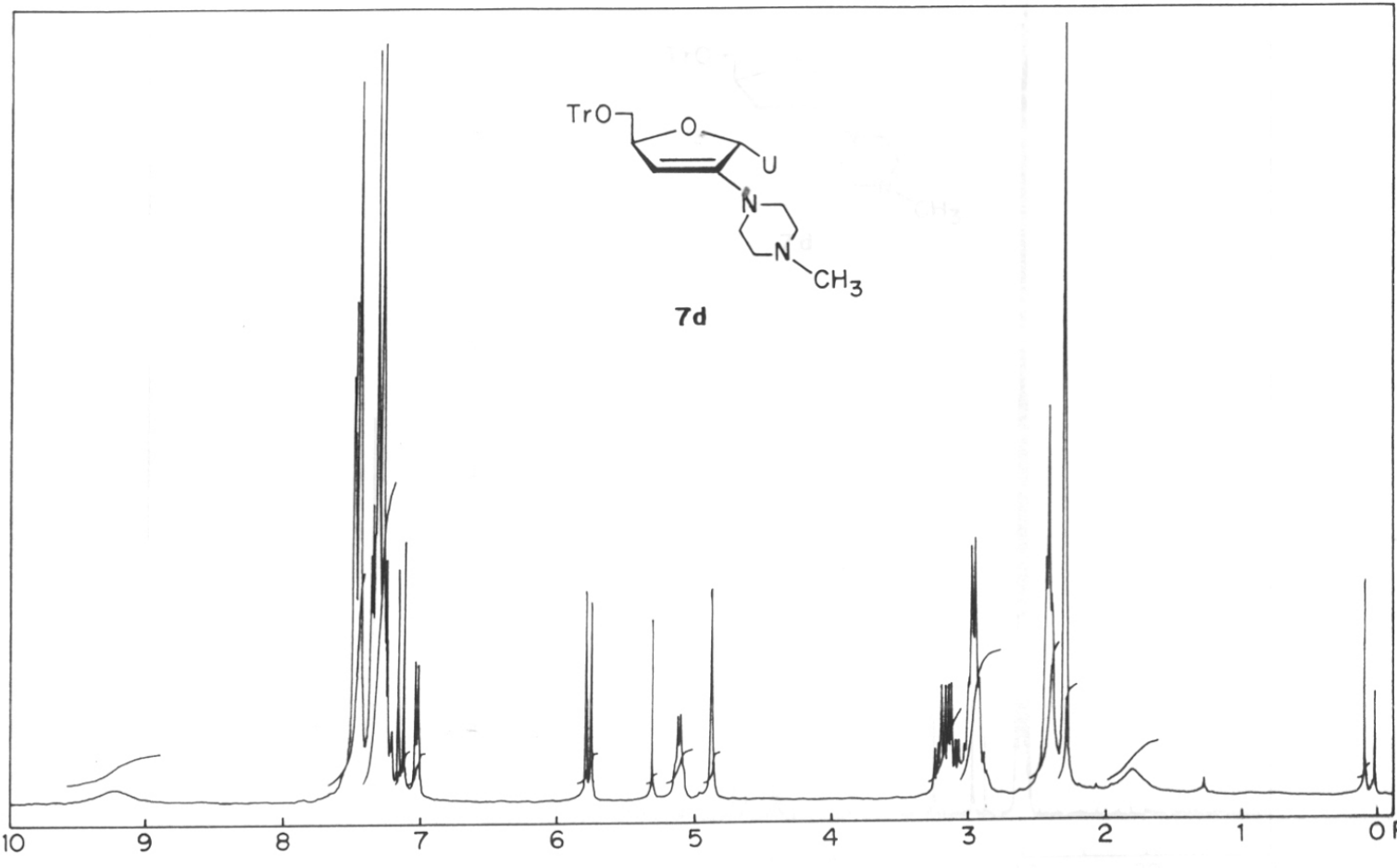
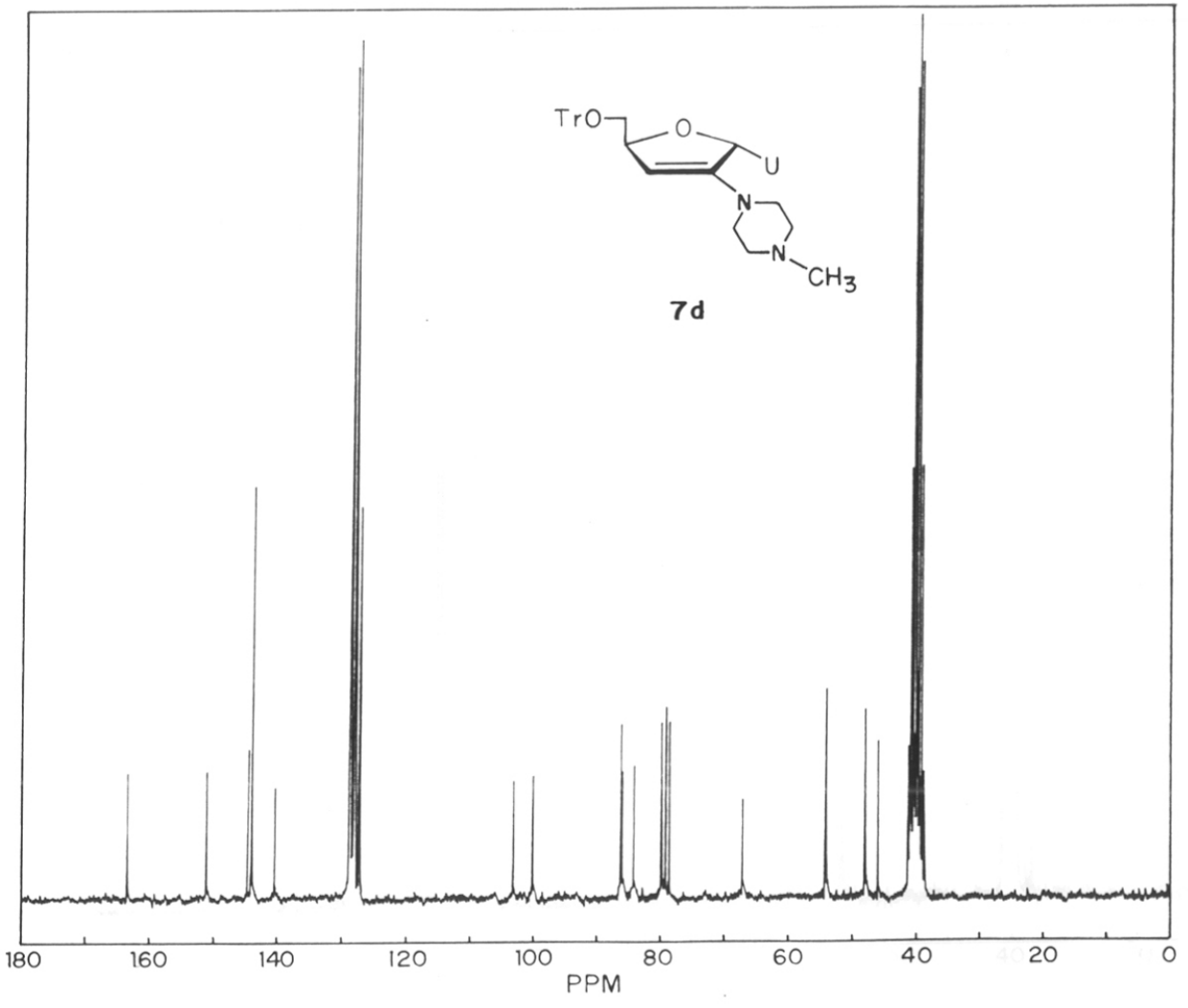
O
U
N
7c
0
20
40
60
80
100
120
140
160
180
PPM

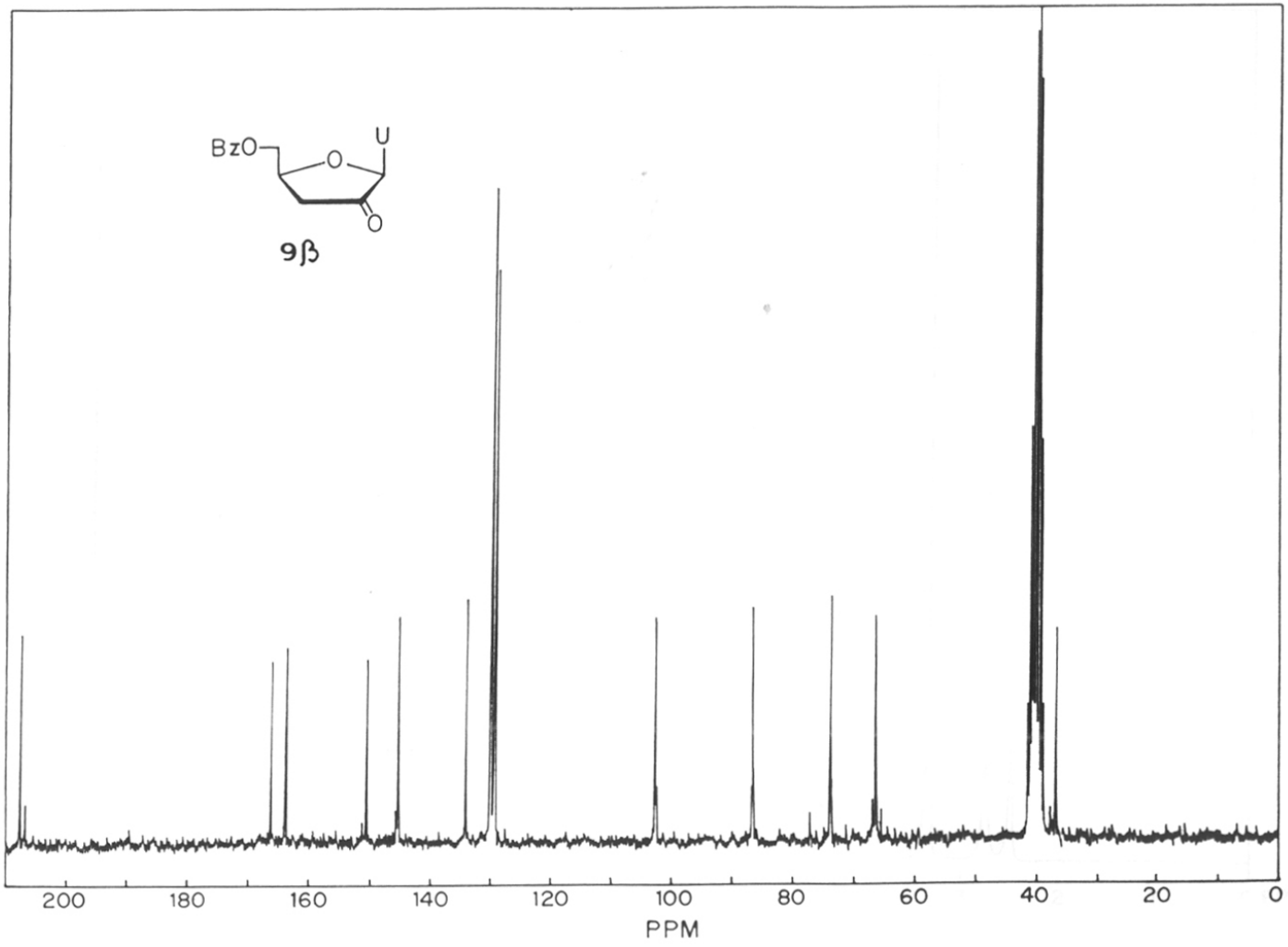

TrO
O
U
N
N
CH3
6d
0
20
40
60
80
100
120
140
160
180
PPM

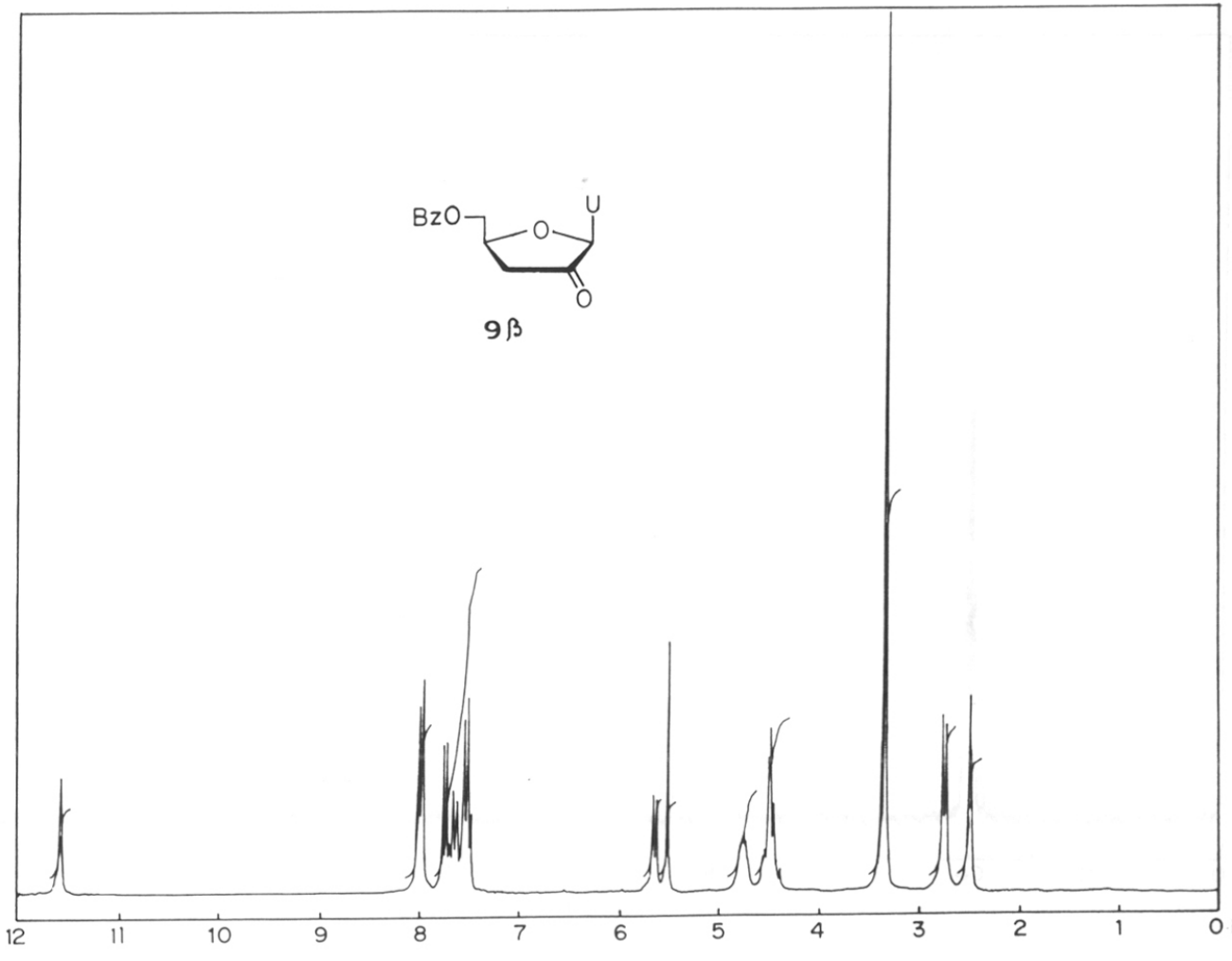

TrO
O
U
N
N
CH3
6d
+ α-isomer
(minor)
8
7
6
5
4
3
2
1
0 PPM



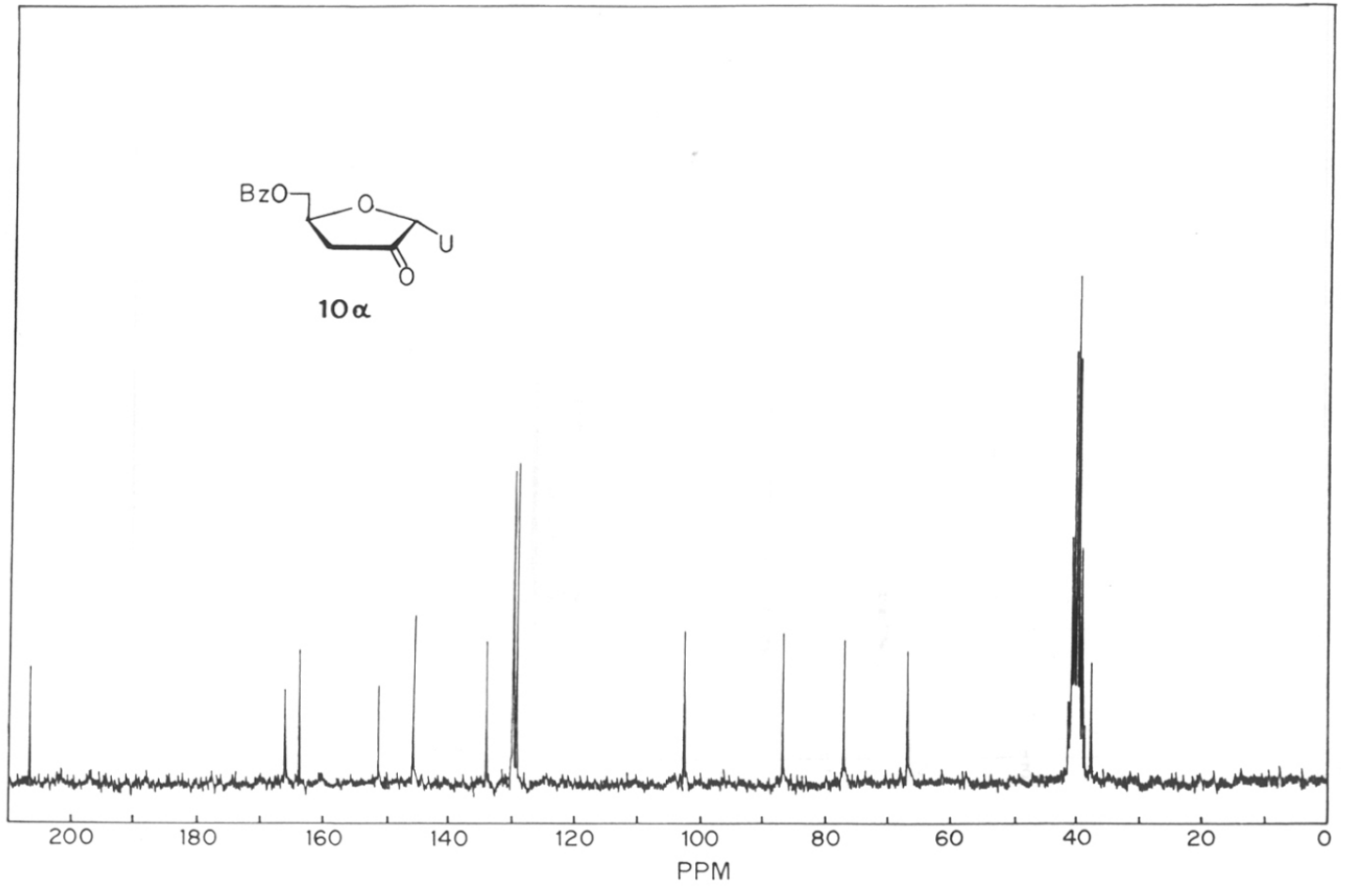
7d

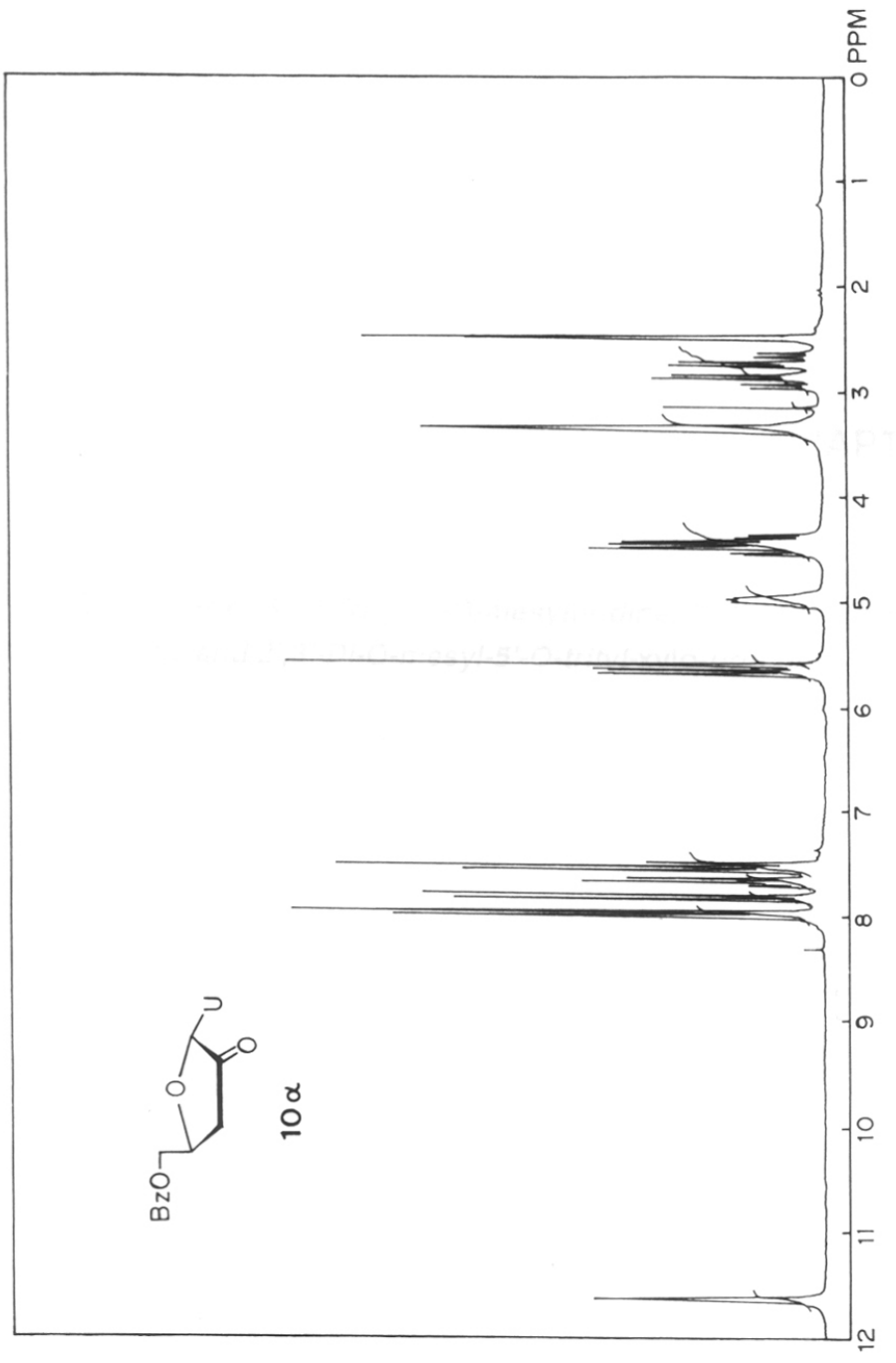

TrO
O
U
N
N
CH3
7d
180
160
140
120
100
80
60
40
20
0
PPM


BzO
O
U
O
9β
200
180
160
140
120
100
80
60
40
20
0
PPM



9β


BzO
O
U
O
10α
200
180
160
140
120
100
80
60
40
20
0
PPM


BzO
O
U
O
10α
0 PPM
1
2
3
4
5
6
7
8
9
10
11
12

CHAPTER-V

*Reactions of 5'-O-Trityl-3'-O-mesyluridine, 2',3'-Di-O-mesyl-5'-O-trityl-*ara*-uridine and 2',3'-Di-O-mesyl-5'-O-trityl-*xylo*-uridine with Amines*

5.1. Introduction

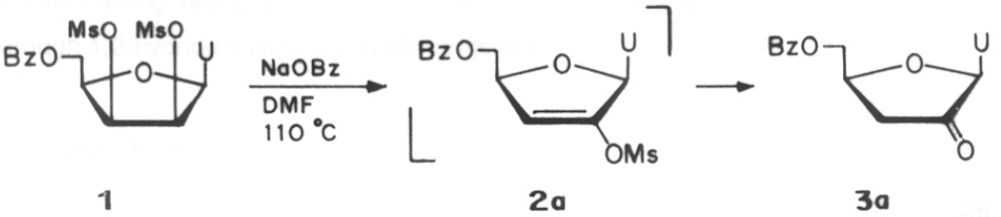
We have described[1] in Chapter-III that 2',3'-di-O-mesyl-5'-O-trityluridine on reaction with secondary amines produced *iso*cytidine derivatives, 1-(2,3-O-anhydro-5-O-trityl-β-D-*lyxo*-furanosyl)-2- dialkylamino- 4-pyrimidones, *via* the formation of 2,2'-O-anhydro-3'-O-mesyl-5'-O-trityluridine (**Scheme-3.3** in Chapter-III). As already discussed in Chapter-IV, the procedure gave access to new *iso*cytidine derivatives; but the methodology was not particularly useful for the functionalisation of the sugar moiety as the first step, was always the 2,2'-O-anhydro ring formation. We, therefore, decided to study the reactions between amines and 1-(2,3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl)- uracil, as unlike in the case of the *ribo*- derivative, it would not undergo any intramolecular cyclisation. Compound 1-(2,3-di-O-mesyl-5-O-trityl-β-D-*lyxo*- furanosyl)- uracil on reaction with secondary amines generated a new class of enaminonucleosides[2] (**Scheme-4.2** in Chapter-IV). On the basis of the above observations, we envisaged that if the presence or absence of the intramolecular cyclisation was the key feature of the reactions between various sulphonylated pyrimidines and secondary amines, then even a properly functionalised *ribo*nucleoside with no leaving group at the C-2' position would also form the enaminonucleosides.

As we have established in the previous chapter that the generation of 2'-ketouridines *in situ* was a prerequisite for the formation of enaminonucleosides, we envisaged that any nucleoside derivative capable of forming 2'-ketouridines in the reaction medium under basic or nucleophilic conditions would be the substrate of choice for the synthesis of enaminonucleosides.

A persual of literature established that the 2'-ketouridine could be obtained *in situ* from two different kind of reactions namely, base catalysed elimination reactions[3-5] and 1,2-hydride shift rearrangements[6-15].

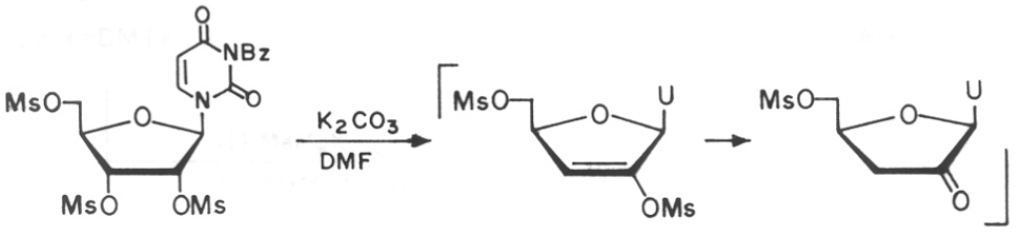
Base catalysed elimination reactions[3-5]: Sasaki and coworkers developed the base catalysed β-elimination reactions directed towards the synthesis of 2'-ketouridines from 2',3'-di-O-mesyl derivatives. 5'-O-Benzoyl-2',3'-di-O-mesyl-*lyxo*-uridine **1** on treatment with sodium benzoate in hot DMF produced 1-(5-O-benzoyl-2,3-dideoxy-2-O-mesyl-β-D-pent-

Scheme-5·1



1 2a 3a

Scheme-5·2



4 2b 3b

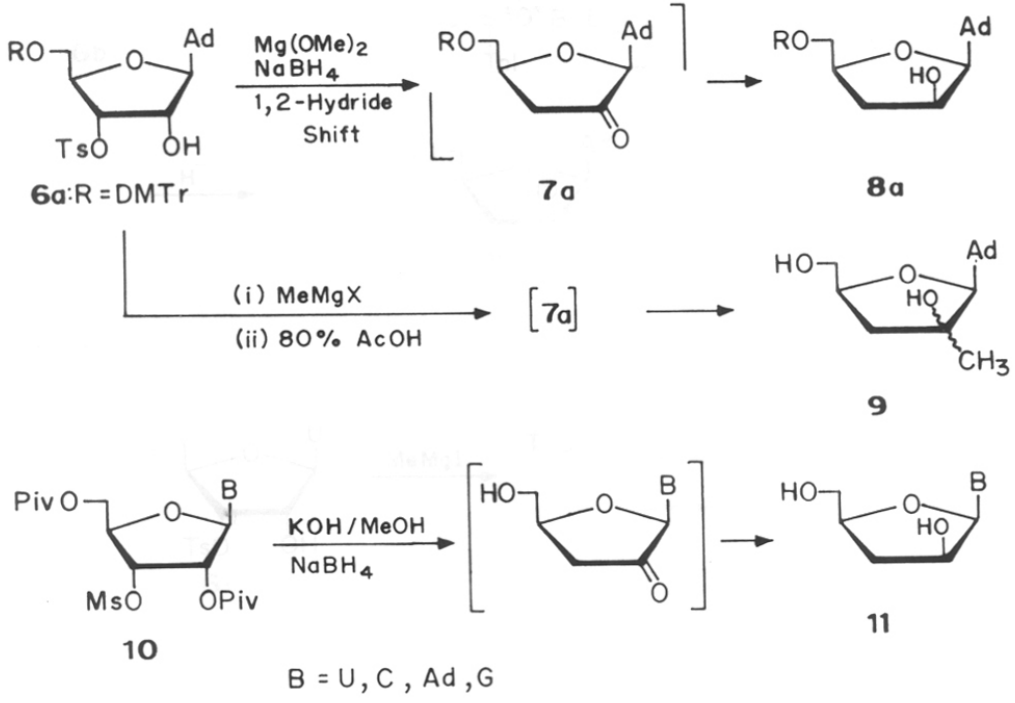
5

enofuranosyl)-uracil **2a** which got transformed into 2'-ketouridine derivative **3a** (ref.3) (**Scheme-5.1**). It was also reported[4] that 2',3',5'-tri-O-mesyl-3-N-benzoyl-uridine **4** on reaction with sodium carbonate in DMF produced 3',5'-cyclopropane derivative of 2'-ketouridine **5** *via* a base catalysed elimination reaction (**Scheme-5.2**).

1,2-Hydride shift reactions in nucleosides[6-16]**:** A stereoselective deoxygenation of *ribo*furanose derivatives involving 1,2-hydride shift was reported by Kawana and coworkers[6-14]. The synthetic utility of this method was demonstrated later by various groups[15,16,21] by synthesising novel carbohydrates or nucleoside derivatives. The derivatives having a 3'-O-sulphonyl group alongwith either a 2'-free hydroxyl function **6a** or a 2'-O-pivaloyl group **10** produced 2'-ketonucleosides **7** under various reaction conditions through 1,2-hydride shift reaction. Compound **6a** on reaction with Grignard reagent followed by acid

treatment produced compounds **9** through the keto derivative **7a**. To show the usefulness of this interesting rearrangement, 3'-deoxy-*ara*-nucleosides **8a** and **11** were synthesised through 1,2-hydride shift reaction (**Scheme-5.3**).

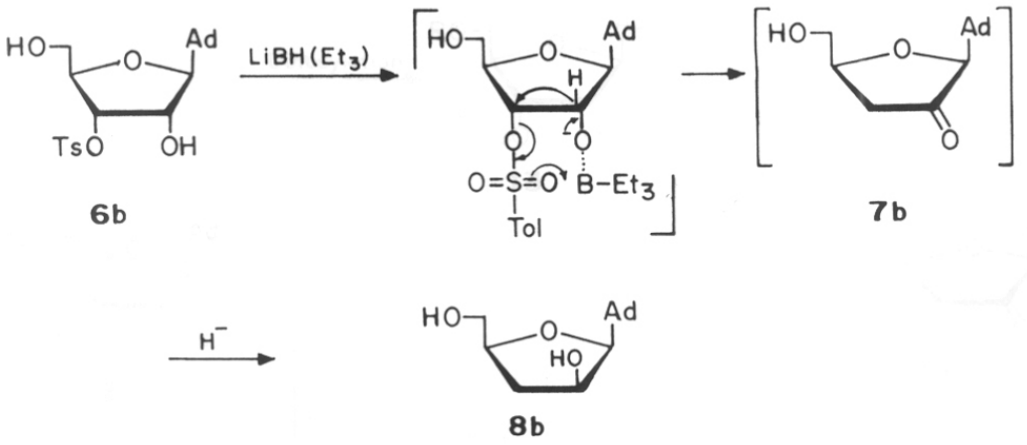
Scheme-5·3



Robins and coworkers reported[15] that 3'-O-tosyl-adenosine **6b** on reaction with triethylborohydride in THF produced 3'-deoxy-*ara*-adenosine **8b** through 1,2-hydride shift. This transformation was well studied using deuteriated nucleosides to estabilish the hydride shift. Boron coordinated with the 2'-hydroxyl group which ultimately underwent 1,2-hydride shift. The resulting 2'-ketone **7b** simultaneously got reduced by hydride to yield -*ara*-nucleoside **8b** (**Scheme-5.4**).

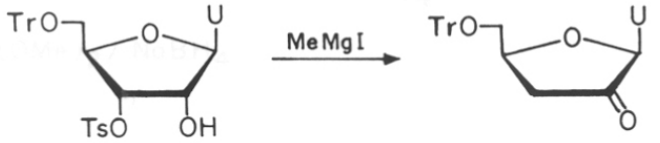
Chattopadhyaya and coworkers described[16] that 3'-O-tosyl-5'-O-trityluridine **6c** on controlled treatment with Grignard reagent produced 5'-O-trityl-3'-deoxy-2'-ketouridine **3c** (**Scheme-5.5**). In this case, the possibility of formation of a 2'-magnesium enol-ether complex

Scheme-5·4



6b 7b 8b

Scheme-5·5

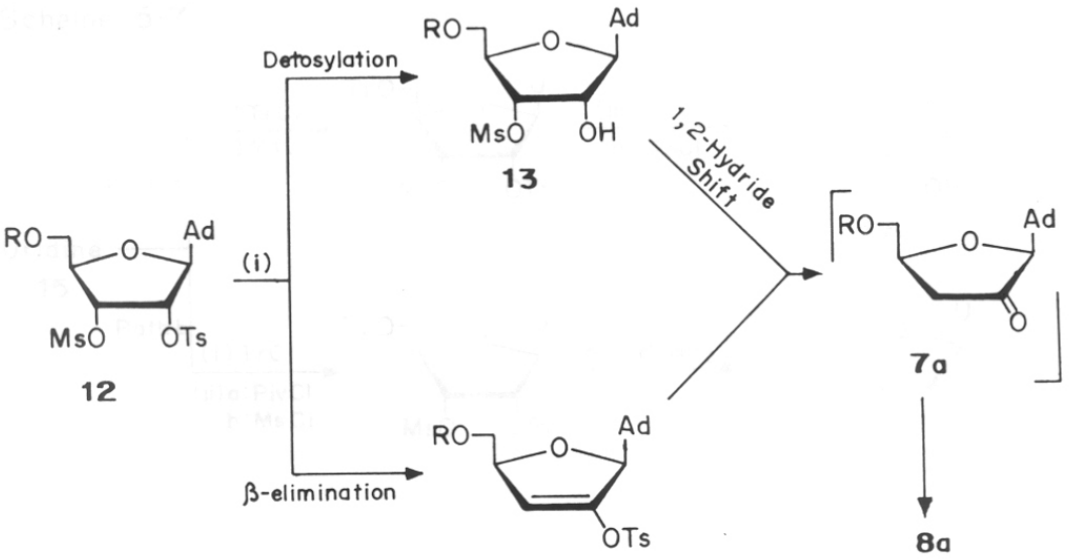


6c 3c

was also proposed.

Base catalysed elimination and 1,2-Hydride shift reactions[17]: Kawana and coworkers described[17] that compound **12** having sulphonyl group at the 2'-position underwent both kind of reactions. Compound **12** on treatment with magnesium methoxide and sodium borohydride underwent elimination reaction to produce ene-tosylate **14** which eventually produced the keto derivative **7a**. Under the same reaction conditions, the simple 2'-detosylation of compound **12** to **13** led to the formation keto derivative **7a** through 1,2-hydride shift rearrangement (**Scheme-5.6**). The resulting ketonucleoside was reduced to its *ara*-derivative **8a**. The incorporation of a deuterium atom at the C-3' of **8a** throughβ-elimination was examined by the use of methanol-d_1 instead of methanol. The ^{1}H-NMR spectrum of the product **8a**

Scheme-**5·6**



R = DMTr

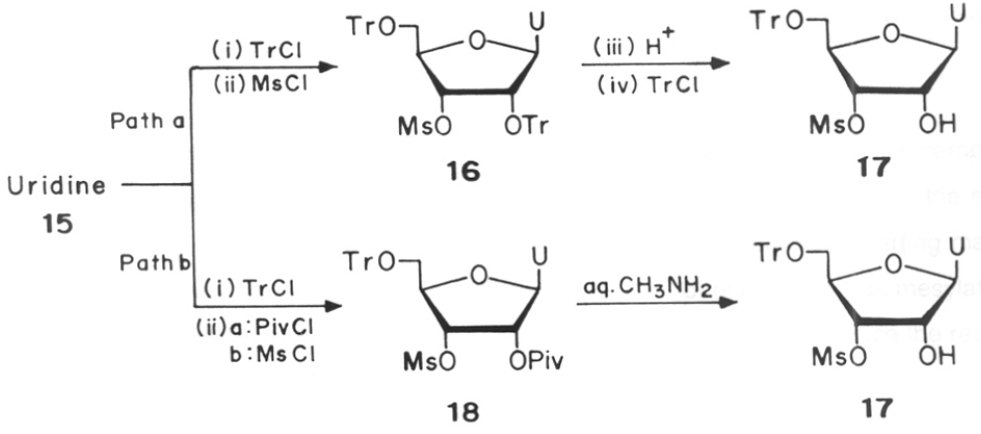
(i) $Mg(OMe)_2$ / $NaBH_4$

obtained from **12** showed that the content of the deuterium at C-3' position was 37.5%. From this observation, it was suggested that about 75% of the reaction proceeded through elimination reaction path.

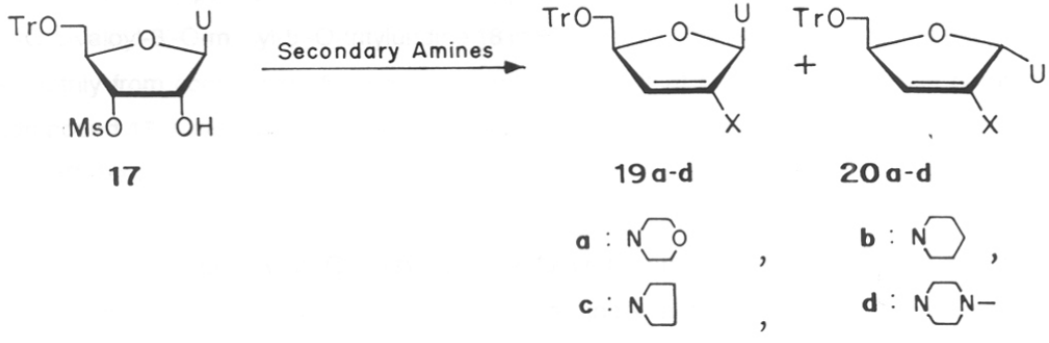
5.2. Present Work

The above mentioned literature[6-16] established that nucleoside derivatives having a 3'-O-sulphonyl group alongwith either a 2'-free hydroxyl function **6a-c** or a 2'-O-pivaloyl group, such as **10** produced 2'-ketonucleosides under various reaction conditions. Moreover, it was established earlier[18] that 3'-O-mesyluridine **17** did not undergo any 2,3'-O-anhydro ring formation under various reaction conditions; this observation was important for our work because formation of 2,3'-O-anhydro derivative from compound **17** would lead, through an intramolecular reaction, to the formation of 2,2'-O-anhydro derivative and not the intended ketone **3c**. These results warranted us to use the 5'-O-trityl-3'-O-mesyluridine **17** as a substrate for the synthesis of enaminonucleosides.

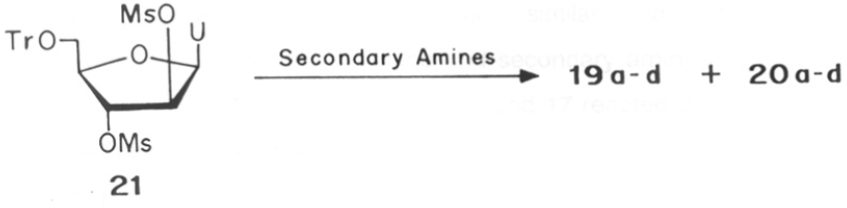
Scheme-5·7



Scheme-5·8



Scheme-5·9



We also decided to study the reactions of 5'-O-trityl-2',3'-di-O-mesyl-*ara*-uridine **21** (ref.19) with secondary amines, as compound **21** would not undergo any intramolecular cyclisation. In order to complete the studies on the reactions of sulphonylated pyrimidine nucleosides with amines, we have also described the reactions of 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine **22** (ref.19) with amines in this chapter.

The improved synthesis of 5'-O-trityl-3'-O-mesyl-uridine 17: In order to use compound **17** as starting material, we had to develop a better method for its synthesis. In the earlier method[20] for the preparation of **17**, 5',2'-O-ditrityluridine was used as the starting material which was obtained from uridine **15** in 32% yield[18]; 5',2'-O-ditrityluridine was mesylated to compound **16** , detritylated and retritylated selectively at the 5'-site to produce the required product **17**. The overall yield of this conversion was less than 15% (**Scheme-5.7, path-a**) which was unacceptable to us as we needed compound **17** in large amount. Therefore, we decided to improve the overall yield of compound **17** by using an alternative route. 5'-O-Trityluridine was reacted with pivaloyl chloride at -20°C followed by methanesulphonyl chloride in one-pot fashion; usual work-up followed by column purification furnished 2'-O-pivaloyl-3'-O-mesyl-5'-O-trityluridine **18** in 80% yield[21]. The pivaloyl group was removed smoothly from compound **18** by aqueous methylamine[22] at room temperature to produce compound **17** in 68% yield. The overall yield of compound **17** in this case was greater than 40% (**Scheme-5.7**, **path-b**).

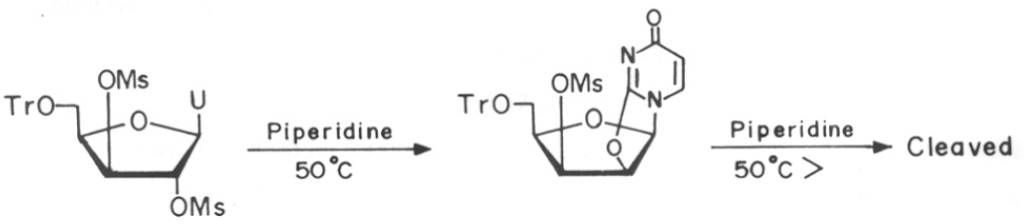
Reactions of 5'-O-trityl-3'-O-mesyl-uridine 17 with secondary amines: Compound **17** was reacted with morpholine, piperidine, pyrrolidine and N-methylpiperazine to furnish mixture of enamines **19a/20a**, **19b/20b**, **19c/20c** and **19d/20d** respectively in good yields (**Scheme-5.8**). Compounds **19a-d** and **20a-d** were similar in all respect to authentic enaminonucleosides reported in previous chapter. These reactions and the product distribution were more or less similar to the reactions between 2',3'-di-O-mesyl-5'-O-trityl-*lyxo*-uridine and secondary amines as reported in the previous chapter; the only difference is that, compound **17** reacted with amines much more slowly (28-30h) than 2',3'-di-O-mesyl-5'-O-trityl-*lyxo*-uridine did (less than 12h with the exception of N-methylpiperazine which took 24h). To illustrate the point that products obtained from these

reactions were indeed the same enamines reported in Chapter-IV, compounds **19a** and **20a** were separated, as representative examples, from the mixture following the same procedure; both compounds were found to be identical (^{1}H-NMR) with the earlier reported isomers.

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21 with secondary amines: 2',3'-Di-O-mesyl-5'-O-trityl-*ara*-uridine **21** was treated with morpholine, piperidine, pyrrolidine and N-methylpiperazine at approximately 80°C. The products obtained were, as expected the enaminonucleosides **19a-d** and **20a-d** (**Scheme-5.9**).

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine 22 with piperidine: 2',3'-Di-O-mesyl-5'-O-trityl-*xylo*-uridine **22**, did not produce any enaminonucleoside at all; the only product that was isolated from the reactions of piperidine at 50°C was 2, 2'-O-anhydro-3'-O-mesyl-5'-O-trityl-*lyxo*-uridine **23** (**Scheme-5.10**). The ^{1}H and ^{13}C NMR was consistent to the structure assigned. It was obvious that 2,2'-O-anhydro ring formation from compound **22** under basic conditions was very facile. The prolonged reaction time or heating at > 50°C caused cleavage of the starting material.

Scheme-5·10



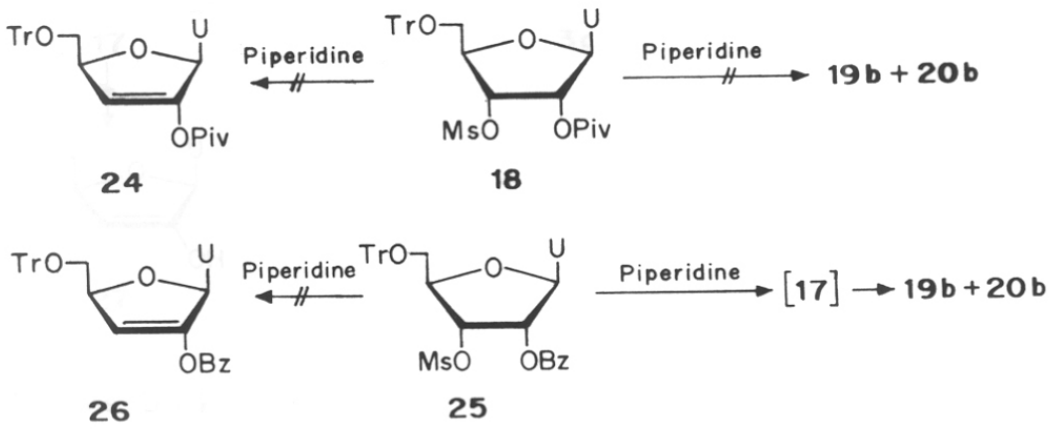
22 **23**

5.3. Discussion

An attempt to react compound **18** with secondary amines failed and the unreacted starting material was recovered. This observation indicated that the formation of 2'-free hydroxyl group was necessary for the enamine formation to take place. This assumption was further

strengthened by the fact that when 2'-O-benzoyl-3'-O-mesyl-5'-O-trityluridine **25** was reacted with piperidine at elevated temperature enaminonucleoside (**19b**/**20b**) formation took place *via* generation of the 2'-free hydroxy derivative **17** as was evident by tlc (**Scheme-5.11**).

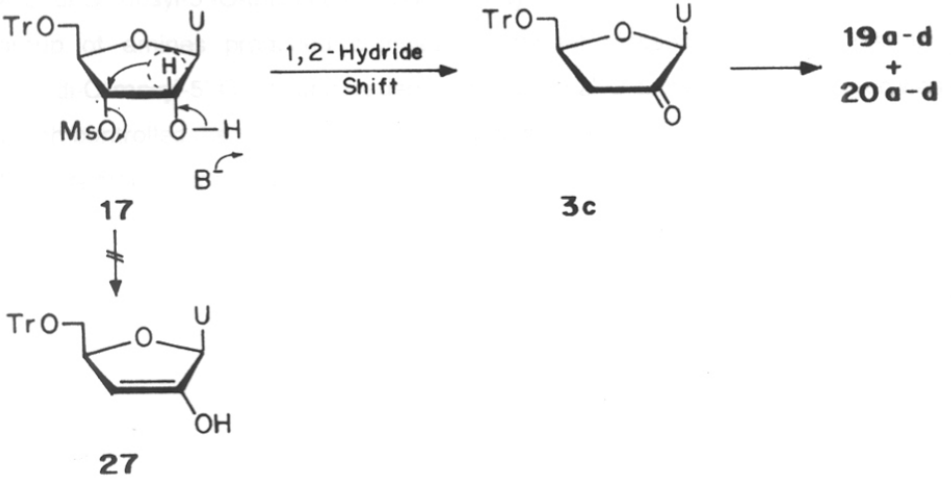
Scheme-5·11



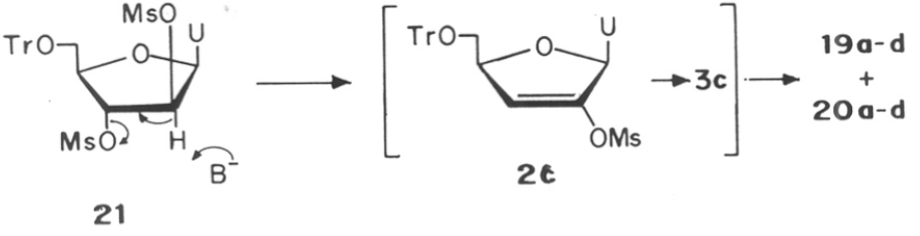
A discussion on the mechanism of formation of compounds **19** and **20** from **17** would be pertinent here. It was obvious that the formation of the 2'-ketouridines **3c** was a prerequisite for the formation of the anomeric mixture of enamines **19** and **20**. The 2'-ketonucleoside **3c** could have formed directly from compound **17** through 1,2-hydride shift or through an enolic intermediate **27**. Although all reports of 1,2-hydride shift[6-16] in case of nucleosides involved metal ions, the present report on the conversion of compound **17** to the 2'-ketouridine **3c** strongly argued in favour of the 1,2-hydride shift mechanism as under no circumstances a *2'-free hydroxy* nucleoside with a leaving group at the 3'-position was ever shown to form an enolic intermediate **27** through elimination (**Scheme-5.12**).

It should also be noted here that although the conversion of any sulphonylated uridine to the 2'-ketouridine could take place either by 1,2-hydride shift or by the elimination of the mesylate, the pathway was controlled by the configurations at the 2'- and 3'-centers of the starting materials. For the formation of the ketouridine **3c** from 2',3'-O-dimesyl-5'-O-trityl-*lyxo*-uridine, both the 1,2-hydride shift and mesylate elimination processes had equal chance to operate (**Scheme-4.9** in Chapter-IV).

Scheme-5·12



Scheme-5·13



The formation of enamines **19** and **20** from *ara*-derivative **21** could be attributed to β-elimination reaction only (**Scheme-5.13**). The possibility of 1,2-hydride shift was ruled out in this case by the fact that 1,2 hydride shift could take place only from the same side of the ring.

5.4. Conclusion

We have shown for the first time that a *ribo*nucleoside, such as uridine, as its 5'-O-trityl-3'-O-mesyluridine **17**, on reaction with secondary amines produced enaminonucleosides **19** and **20**. The reaction proceeded through the formation of

2'-ketouridine **3c** *in situ* which was evident from the formation of both the α- and β- anomers of the enaminonucleosides. More interestingly, two *ribo*nucleoside derivatives, 2',3'-di-O-mesyl-5'-O-trityluridine and 5'-O-trityl-3'-O-mesyluridine on reaction with the same group of amines produced completely different classes of compounds; in case of 2',3'-di-O-mesyl-5'-O-trityluridine derivative[2], the 2,2'-O-anhydro ring formation was first step which controlled the course of reactions and in the present case there was no possibility of the intramolecular ring formation.

5.5. Experimental

Melting points were uncorrected. All amines were purchased from Aldrich, U.S.A. and were used without further purification. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS, solvent chloroform-d or dioxane (in case of D_2O) as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

Synthesis of 2'-O-pivaloyl-3'-O-mesyl-5'-O-trityluridine 18:

5'-O-Trityluridine (10mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (60ml) and the reaction mixture was cooled to -20°C in a ice-salt bath. Pivaloyl chloride (13mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was stirred at same temperature. After 3 hours, methanesulphonyl chloride (30 mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 8 hours. The reaction mixture was then poured in to the aqueous saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column to furnish compound **18**.

Yield : 80%

M.P : 110°C

^{1}H-NMR : ($CDCl_3$): δ 9.25 (bs, 1H) NH; 7.64 (d, 8 Hz, 1H) H-6; 7.46-7.25 (m, 15H) trityl; 6.16 (d, 5.6 Hz, 1H) H-1'; 5.55 (t, 1H)/5.43-5.36 (m, 2H) H-5/H-2'/H-3'; 4.39 (m, 1H) H-4'; 3.6 (d, 2H) H-5', H-5''; 3.0 (s, 3H) mesyl CH_3; 1.26 (s, 9H) pivaloyl $(CH_3)_3$

^{13}C-NMR : ($CDCl_3$): δ 177.3, pivaloyl CO; 163.4, C-4; 150.5, C-2; 142.9, trityl; 139.9, C-6; 128.7, 128.1, 127.6, trityl; 103.1, C-5; 88.1, trityl; 86.9/82.1/75.9/72.6, C-1'/C-2'/C-3'/C-4'; 62.2, C-5'; 38.9, pivaloyl; 38.2, mesyl CH_3; 27.0, pivaloyl $(CH_3)_3$.

Synthesis 5'-O-trityl-3'-O-mesyluridine 17:

Compound **18** (3mmol) was treated with aqueous methylamine (3ml) at room temperature for 4 hours. After completion of the reaction (tlc), the reaction mixture was poured into water (100ml) and was extracted with ethylacetate. Ethylacetate solution was dried over anhydrous sodium sulphate and evaporated to oily material. The residue thus obtained was purified on silica gel column to produce compound **17**.

Yield : 68%

M.P : 152°C (152°C)[20]

^{1}H-NMR : ($CDCl_3$): δ 10.99 (bs, 1H) NH; 7.81 (d, 8 Hz, 1H) H-6; 7.46-7.2 (m, 15H) trityl; 5.99 (d, 4.4 Hz, 1H) H-1'; 5.41-5.21 (m, 3H) H-5/ 2'-OH/H-3'; 4.76 (m, 1H) H-4'; 4.45 (m, 1H) H-2'; 3.57 (m, 2H) H-5', H-5''; 3.23 (s, 3H) mesyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 163.4, C-4; 152.1, C-2; 143.2, trityl; 140.0, C-6; 128.8, 128.3, 127.7, trityl; 102.9, C-5; 89.4, trityl; 88.1/82.0/77.5/73.6, C-1'/C-2'/C-3'/C-4'; 62.2, C-5'; 38.2, mesyl CH_3.

Reactions of 5'-O-trityl-3'-O-mesyluridine 17 with morpholine:

A solution of compound **17** (0. 5mmol) in neat morpholine (2ml) was heated under reflux for 30h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19a** and 1-(2,3-dideoxy- 2-N-morpholino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20a**. Yield: 72%. Compound **20a** was separated from the mixture by crystallisation from methanol.

Reactions of 5'-O-trityl-3'-O-mesyluridine 17 with piperidine:

A solution of compound **17** (0. 5mmol) in neat piperidine (2ml) was heated at 90°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19b** and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20b**. Yield: 65%.

Reactions of 5'-O-trityl-3'-O-mesyluridine 17 with pyrrolidine:

A solution of compound **17** (0. 5mmol) in neat pyrrolidine (2ml) was heated at 80°C for 30h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19c** and 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20c**. Yield: 60%.

Reactions of 5'-O-trityl-3'-O-mesyluridine 17 with N-methylpiperazine:

A solution of compound **17** (0. 5mmol) in neat N-methylpiperazine (2ml) was heated at 100°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford

1-(2,3-dideoxy-2-N-(N-methylpiprazino)-5-O-trityl-α-D-*glycero*-pent-2- enofuranosyl)- uracil **19d** and 1-(2,3-dideoxy-2-N- (N-methylpiprazino)-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20d**. Yield: 65%.

Synthesis of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21:

5'-O-Trityl-*ara*uridine (10mmol) was dried by coevaporation with dry pyridine and redissolved in the same solvent (60ml) and the reaction mixture was cooled to 0°C. Methanesulphonyl chloride (30mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 8 hours. The reaction mixture was then poured into the aqueous saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column.

Yield : 75%

M.P : 178°C (178-180°C)[19]

^{1}H-NMR : ($CDCl_3$): δ 9.6 (bs, 1H) NH; 7.6 (d, 8 Hz, 1H) H-6; 7.48-7.23 (m, 15H) trityl; 6.27 (d, 4 Hz, 1H) H-1'; 5.58 (d, 8 Hz, 1H) H-5; 5.38 (m, 2H) H-2, H-3'; 4.17 (m, 1H) H-4'; 3.59-3.5 (m, 2H) H-5', H-5''; 3.08 (s, 3H)/3.04 (s, 3H), 2'/3' mesyl CH_3.

^{13}C-NMR : ($CDCl_3$): δ 163.4, C-4; 150.5, C-2; 143.2, trityl; 140.5, C-6; 128.8, 128.2, 127.6, trityl; 102.6, C-5; 87.7, trityl; 83.5/80.4/80.2/80.2; C-1'/C-2'/C-3'/C-4'; 61.2, C-5'; 38.6/38.4, 2'/3' mesyl CH_3.

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21 with morpholine:

A solution of compound **21** (1mmol) in neat morpholine (2ml) was heated under reflux for 8h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford

1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19a** and 1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20a**. Yield: 60%

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21 with piperidine:

A solution of compound **21** (1mmol) in neat piperidine (2ml) was heated at 80°C for 6h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19b** and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20b**. Yield: 56%.

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21 with pyrrolidine:

A solution of compound **21** (1mmol) in neat pyrrolidine (2ml) was heated at 70°C for 5h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19c** and 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20c**. Yield: 44%.

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*ara*-uridine 21 with N-methylpiperazine:

A solution of compound **21** (1mmol) in neat N-methylpiperazine (2ml) was heated at 80°C for 8h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-(N-methylpiprazino)-5-O-trityl-α-D-*glycero*-pent-2- enofuranosyl)-uracil **19d** and 1-(2,3-dideoxy-2-N- (N-methylpiprazino)-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)-uracil **20d**. Yield: 53%.

Synthesis of 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine 22

*Xylo*uridine[13] (10mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (60ml). Trityl chloride (13mmol) was added and the solution was kept for overnight at room temperature. The reaction mixture was then heated at 100°C for 3 hours. After completion of the tritylation (tlc), the reaction mixture was cooled to 0°C. Methanesulphonyl chloride (30 mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 8 hours. The reaction mixture was then poured into the aqueous saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column.

Yield : 75%

M.P : 139°C (138-141°C)[19]

^{1}H-NMR : ($CDCl_3$): δ 9.6 (bs, 1H) NH; 7.65-7.24 (m, 16H) trityl, H-6; 6.22 (d, 3.8 Hz, 1H) H-1'; 5.7 (d, 8 Hz, 1H) H-5; 5.41 (m, 1H)/5.22 (m, 1H) H-2'/H-3'; 4.8 (m, 1H) H-4'; 3.66-3.42 (m, 2H) H-5', H-5''; 3.27 (s, 3H)/2.93 (s, 3H) 2'/3' mesyl CH_3.

^{13}C-NMR : ($CDCl_3$): δ 163.7, C-4; 150.9, C-2; 143.1, trityl; 138.9, C-6; 128.8, 128.2, 127.6, trityl; 102.6, C-5; 88.5, trityl; 87.9/83.6/80.8/79.7, C-1'/C-2'/C-3'/C-4'; 61.0, C-5'; 38.7/38.2, 2'/3' mesyl CH_3.

Reactions of 2',3'-di-O-mesyl-5'-O-trityl-*xylo*-uridine 22 with piperidine:

A solution of compound **22** (0.5mmol) in neat piperidine (2ml) was heated at 50°C. After 5h, the excess amine was removed under reduced pressure. The oily residue was purified by column chromatography on siliga gel to produce 2, 2'-O-anhydro-3'-O-mesyl-5'-O-trityl-*lyxo*-uridine **23**.

Yield : 70%

M.P : 174°C

^{1}H-NMR : ($CDCl_3$): δ 7.4-7.2 (m, 16H) trityl, H-6; 6.01 (d, 4 Hz, 1H) H-1'; 5.87 (d, 7.4 Hz, 1H) H-5; 5.47 (t, 1H)/5.34 (t, 1H) H-2'/H-3'; 4.33 (m, 1H) H-4'; 3.27-3.13 (m, 2H) H-5', H-5''; 2.92 (s, 3H), mesyl CH_3

^{13}C-NMR : (DMSO-d_6): δ 171.1, C-4; 160.1, C-2; 143.6, trityl; 136.9, C-6; 128.5, 128.3, 127.6, trityl; 109.4, C-5; 88.9, trityl; 86.9/80.2/79.6/76.8; C-1'/C-2'/C-3'/C-4'; 62.4, C-5'; 38.1, mesyl CH_3

Mass : m/z 545 (M^+-1); 304 (M^+-trityl); 215 (M^+-trityl-OCNCO-H_2O).

Synthesis of 2'-O-benzoyl-3'-O-mesyl-5'-O-trityluridine 25:

5'-O-Trityluridine (5mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (25ml). The reaction mixture was cooled to 0°C and benzoyl chloride (6.5mmol) in pyridine (10ml) was added dropwise to it. After completion of the addition, the reaction mixture was stirred at the same temperature for 6 hours. The reaction mixture was then poured into aqueous saturated sodium bicarbonate solution (300ml) and was extracted with ethyl acetate (3x100ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel (230-400 mesh) column to furnish 2'-O-benzoyl-5'-O-trityluridine in 20% yield. 2'-O-Benzoyl-5'-O-trityluridine (1mmol) was dissolved in dry pyridine (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (2.5mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 4 hours. The reaction mixture was then poured into aqueous saturated sodium bicarbonate solution (150ml) and was extracted with ethyl acetate (3x50ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column to furnish compound **25**.

Yield : 86%

M.P : 104°C

^{1}H-NMR : ($CDCl_3$): δ 9.1 (bs, 1H) NH; 8.12 (m, 2H) and 7.75-7.2 (m, 19H) trityl, benzoyl and H-6; 6.42 (d, 5.6 Hz, 1H) H-1'; 5.7 (t, 5.3, 6.2 Hz, 1H)/5.6 (m, 1H) H-2'/H-3'; 5.4 (d, 8 Hz, 1H) H-5; 4.5 (m, 1H) H-4'; 3.65 (m, 2H) H-5', H-5''; 2.95 (s, 3H) mesyl CH_3

^{13}C-NMR : ($CDCl_3$): δ 165.6, benzoyl CO; 163.3, C-4; 150.6, C-2; 142.9, trityl; 139.8, C-6; 134.2, 130.21, benzoyl; 128.9, 128.3, 127.7, trityl; 103.4, C-5; 88.4, trityl; 86.3/82.8/77.8/73.5; C-1'/C-2'/C-3'/C-4'; 62.7, C-5'; 38.4, mesyl CH_3

Mass : m/z 668 (M^+); 590 (M^+-CH_3SO_2); 504 (M^+-$C_6H_5CO_2$-NHCO); 460 (M^+-uracil-CH_3SO_3H); 425 (M^+-$C_{19}H_{15}$); 409 (M^+-$C_{19}H_{15}O$); 315 (M^+-$C_{19}H_{15}O$-CH_3SO_3H); 304 (M^+-$C_{19}H_{15}$-$C_6H_5CO_2$)

Reactions of 2'-O-benzoyl-3'-O-mesyl-5'-O-trityluridine 25 with piperidine:

A solution of compound **25** (0. 5mmol) in neat piperidine (2ml) was heated at 90°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl)- uracil **19b** and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)- uracil **20b**. Yield: 55%.

5.6. References

1. Sakthivel, K.; Bera, S.; Pathak, T. *Tetrahedron*, **1993**, 49, 10387-92.
2. Sakthivel, K.; Suresh, C. G.; Pathak, T. *Tetrahedron*, **1994**, 50, 13251-60.
3. Sasaki, T.; Minamoto, K.; Suzuki, H. *J. Org. Chem.*, **1973**, 38, 598-607.
4. Sasaki, T.; Minamoto, K.; Hattori, K. *J. Org. Chem.*, **1973**, 38, 1283-6.
5. Sasaki, T.; Minamoto, K.; Hattori, K. *Tetrahedron*, **1974**, 30, 2689-94.
6. Kawana, M.; Yamasaki, N.; Nishikawa, M.; Kuzuhara, H. *Chemistry Lett.*, **1987**, 2419-22.
7. Kawana, M.; Yamasaki, N.; Nishikawa, M.; Kuzuhara, H. *Chemistry Lett.*, **1987**, 2419-22.
8. Kawana, M.; Nishikawa, M.; Yamasaki, N.; Kuzuhara, H. *J. Chem. Soc. Perkin Trans I*, **1989**, 1593-6.
9. Kawana, M.; Kuzuhara, H. *J. Chem. Soc. Perkin Trans I*, **1992**, 469-78.
10. Kawana, M.; Takeuchi, K.; Ohba, T.; Kuzuhara, H.; *Bull. Chem. Soc.Jpn.*, **1988**, 61, 2437-42.
11. Kawana, M.; Koresawa, T.; Kuzuhara, H.; *Bull. Chem. Soc.Jpn.*, **1983**, 56, 1095-100.
12. Kawana, M.; Emoto, S.; *Chem. Lett.*, **1977**, 597-8.
13. Kawana, M.; Emoto, S.; *Tetrahedron Lett.*, **1975**, 23, 3395-8.
14. Kawana, M.; Emoto, S.; *Bull. Chem. Soc.Jpn.*, **1980**, 53, 222-9.
15. Hansske, F.; Robins, M. J.; *J. Am. Chem. Soc.*, **1983**, 105, 6736-7.
16. Juntunen, S; Chattopadhyaya, J. *Acta. Chem. Scand.*, **1985**, B39, 149-55.
17. Kawana, M.; Kuzuhara, H. *Tetrahedron Lett.*, **1987**, 28, 4075-8.
18. Yung, N.C.; Fox, J.J. *J. Am. Chem. Soc.*, **1961**, 83, 3060-6.
19. Johnson, R.; Joshi, B.V.; Neidle, S.; Reese, C.B.; Snook, C.F. *Tetrahedron Lett.*, **1992**, 33, 8151-4.
20. Joachim, T.; Rasch, D. *Nucleosides Nucleotides*, **1985**, 4, 487-506.
21. Vial, J.M.; Johansson, N.G.; Vrang, L.; Chattopadhyaya, J. *J. Antivir. Chem. Chemother.*, **1990**, 1, 183-202.
22. Griffin, B.E.; Jarman, M.; Reese, C.B. *Tetrahedron*, **1968**, 24, 639-62.