FUNCTIONALISATION OF THE CARBOHYDRATE MOIETIES OF PYRIMIDINE NUCLEOSIDES: SYNTHESIS OF AMINO AND SULPHUR MODIFIED THYMIDINES AND URIDINES

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

by

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December-1996

DEDICATED TO MY PARENTS

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Functionalisation Of The Carbohydrate Moieties Of Pyrimidine Nucleosides: Synthesis Of Amino And Sulphur Modified Thymidines and Uridines**" submitted by **Mr. SANJIB BERA** 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 acknowledged in the thesis.

Pathak

Date: 31.12.96

National Chemical Laboratory

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(**Dr. T. Pathak**)

Research Guide

DECLARATION

I hereby declare that the thesis entitled "Functionalisation Of The Carbohydrate Moieties Of Pyrimidine Nucleosides: Synthesis Of Amino And Sulphur Modified Thymidines and Uridines" submitted for Ph.D. degree to the University of Poona has not been submitted by me for a degree to any other University.

Date: 31.12.96

Division of Organic Chemistry (Synthesis),
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Sanjib Bera

(SANJIB BERA)

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Sanjib Bera

(SANJIB BERA)

CONTENTS

Abbreviations

Ac	:	Acetyl
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
Ad	:	Adenine
Bn	:	Benzyl
Bz	:	Benzoyl
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	:	Diisopropyl azodicarboxylate
DMF	:	N,N-Dimethyformamide
DMSO	:	Dimethylsulphoxide
DMTr	:	4,4'-Dimethoxytriphenylmethyl
dThd	:	Deoxythymidine
dTMP	:	Deoxythymidine monophosphate
Et	:	Ethyl
EtOAc	:	Ethylacetate
Gua	:	Guanine
HIV	:	Human Immunodeficiency Virus
Me	:	Methyl
mCPBA	:	*m*-Chloroperbenzoic acid
Ms	:	Methanesulphonyl
MMTr	:	4-Monomethoxytriphenylmethyl
MMPP	:	Magnesium monoperoxypthalate
M.P.	:	Melting point
NDP	:	Nucleoside diphosphate
Nu^-	:	Nucleophile
NaOBz	:	Sodiumbenzoate
PPh_3	:	Triphenylphosphine
Py	:	Pyridine
T	:	Thymine
TBDMS	:	*t*-Butyldimethylsilyl
TBAF	:	Tetrabutylammoniumfluoride
TMG	:	Tetramethyl guanidine
T.S.	:	Transition state
Tr	:	Triphenylmethyl
U	:	Uracil

Synopsis of the Thesis

CHAPTER-I

Opening of 2',3'-O-Anhydro-ring of 2',3'-O-Anhydro-lyxouridine by Amines

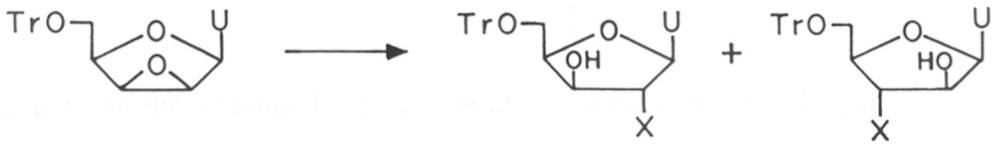
2'-Deoxy-2'-aminothymidine is reported to be a byproduct of 2'-deoxy-2'-azidothymidine (AZT) metabolism. It is, therefore, important to develop methodologies for the synthesis of aminonucleosides. In this context,we decided to develop a general strategy leading to the synthesis of 2'-deoxy-2'-alkylamino- and 3'-deoxy-3'-alkylaminopyrimidine nucleosides. This was achieved by opening the epoxide ring of 1-(5-O-trityl-2,3-O-anhydro-β-D-*lyxo*-furanosyl)-uracil **1** by alkyl- and arylamines under controlled conditions to produce 2'-deoxy-2'-amino-*xylo*- and 3'-deoxy-3'-amino-*ara*-uridine without causing significant, if any, deglycosylation (**Scheme-1**).

Isobutylamine, benzylamine, cyclohexylamine, piperidine, pyrrolidine, morpholine, ethyl *iso*nipecotate, aniline and p-methoxyaniline, all reacted in similar fashion to produce compounds **2a-g** and **3a-i** (**Scheme-1**). N-Methylpiperazine, N-acetylpiperazine, N-methylethanolamine, N,N'-dimethylethylenediamine, diethanolamine, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane also opened the epoxide in varying yields; however, all attempts to separate the isomers failed. The major product (2':3' 1:2.4) obtained from the reaction between **1** and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane was separated as the diacetate derivative **3j**.

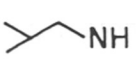
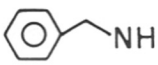
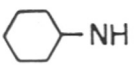
Compounds **2a-f**, **3a-f**, **3h-i** were deprotected using Amberlite IR-120 H^+ in water. Compounds **2g/3g**, were deprotected using 80% acetic acid and the deprotected compounds were collected as their diacetyl derivatives.

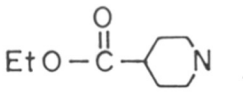
To show the usefullness of products **2** and **3** as versatile intermediates, we synthesised various derivatives from selected compounds. Mesylation of isomeric mixture of compounds **2d/3d** and **2e/3e** followed by reflux in pyridine produced **4d** and **4e** respectively. Compound **4d** on treatment with thiophenol in presence of tetramethylguanidine produced the 2',3'-dideoxy-2',3'-disubstituted derivative **6**. The mixture of isomers **2a/3a** derived from isobutylamine was converted to the epimino derivative **5a** in good yields on treatment with triphenylphosphine and diisopropyl azodicarboxylate (**Scheme-1**).

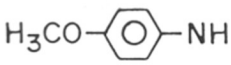
Scheme-1

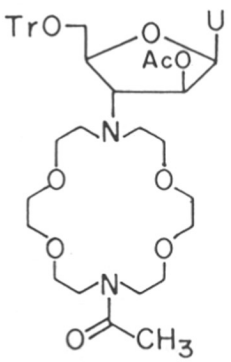


1 **2a-g** **3a-i**

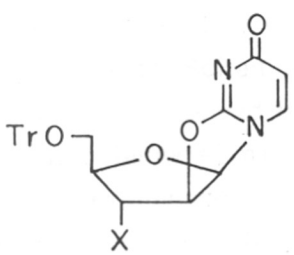
X = **a** :  ; **b** :  ; **c** :  ; **d** :  ;

e : ; **f** : ; **g** :  ; **h** : ;

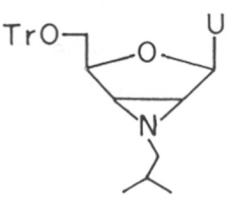
i :  ;



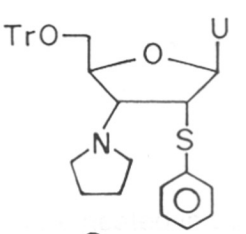
3j



4d : X = **d**
4e : X = **e**



5a



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CHAPTER-II

Studies on the Thermal Degradation and Rearrangement of Sugar Modified Uridine N-Oxides

Tertiary amine N-oxides under pyrolytic conditions undergo two major reactions: a) N-oxides having β-hydrogen atoms undergo an elimination reaction known as Cope elimination with the formation of olefins and hydroxylamines and b) Meisenheimer rearrangement of an alkyl or aryl group from N to O for N-oxides without β-hydrogen to form substituted hydroxylamine. The aminoalcohols obtained from the reactions of secondary amines and uridine epoxide **1** (**Scheme-1**) converted to the corresponding N-oxides by reacting with m-CPBA to N-oxides and their thermal degradations were studied.

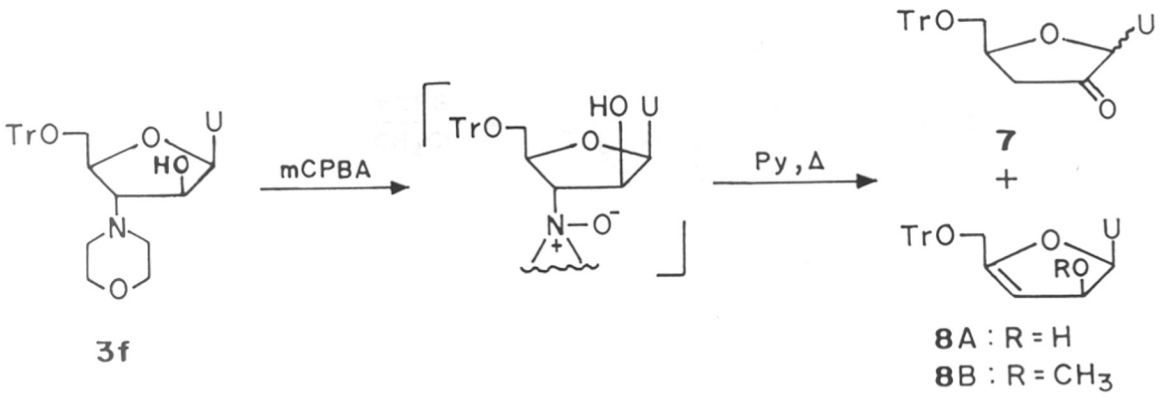
The amine oxide derived from the m-CPBA oxidation aminoalcohol **3f**, when heated in pyridine underwent Cope elimination to produce a mixture of three compounds, namely a mixture of the α- and β- anomer of the 2'-keto uridine **7** (63%) and the 3'-deoxy-3'-ene derivative **8A** (29%). Similarly, a mixture of compounds **10** and **8B** was obtained in a ratio 5:1, when the amine oxide derived from compound **9** was heated in pyridine (**Scheme-2**).

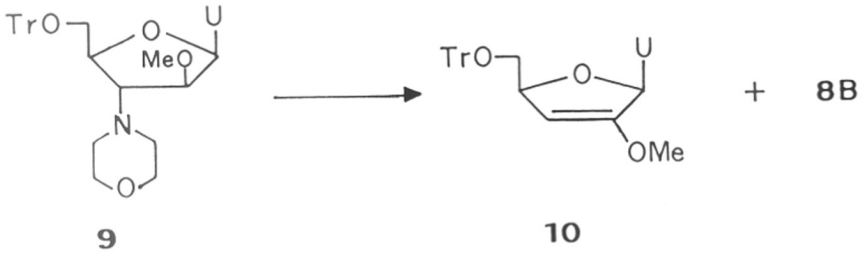
2',3'-Dideoxy-2',3'-(N-alkyl) epimino uridines **5a-c** were treated with m-CPBA in dichloromethane at ambient temperature; the only nucleoside based product that was isolated from all these reactions, was 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl) uracil **11** in 45%, 62% and 52% yields respectively after two steps (**Scheme-2**).

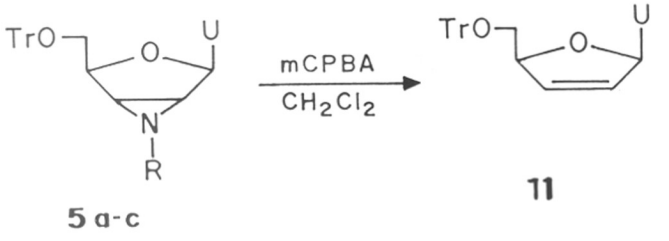
Compounds **12a-c** were oxidised with m-CPBA and the N-oxides were heated in pyridine at elevated temperature. Oxazetidine derivatives **13a-b** were isolated from the reaction mixture in good yields (**Scheme-3**). The same oxazetidine derivatives **13a-b** were obtained when amine oxides derived from compounds **14a-b** were heated in pyridine. The oxazetidine product obtained from the thermal degradation of the N-oxide of **12c** was somewhat unstable. A close examination of the ^{1}H-NMR and HRMS revealed that the product was infact the aminoalcohol **15** (**Scheme-3**).

The regioisomer of **14, 16a-c** were oxidised and the N-oxides were heated in pyridine. The N-oxides underwent rearrangement to produce compounds **17a-c** (**Scheme-4**)

Scheme - 2

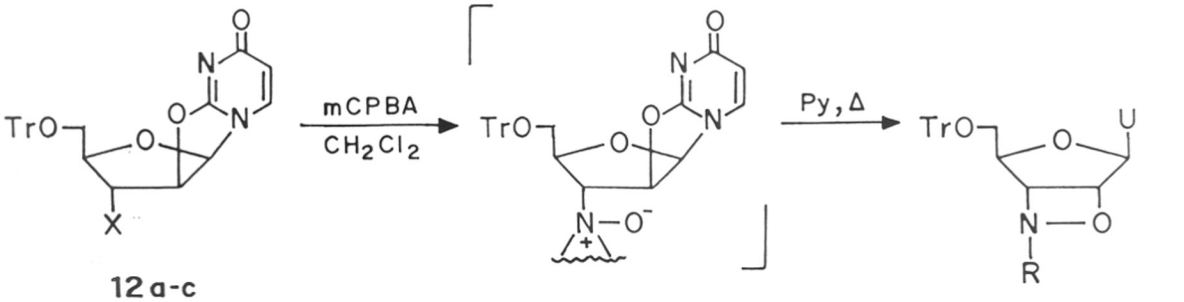






R = a : ; b : ; c :

Scheme-3



12a-c **13a-c**

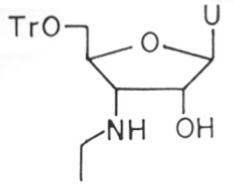
a : N ; **b** : N O ;

c : N

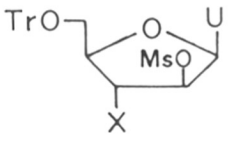
R = **a** :

b :

ii) mCPBA | ii) Py, Δ



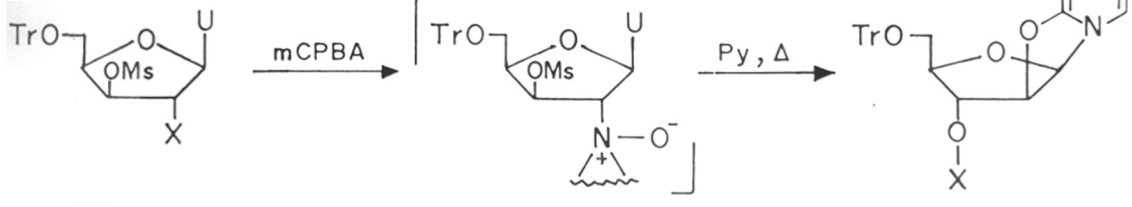
15



14a : N

14b : N O

Scheme-4



16a-c **17a-c**

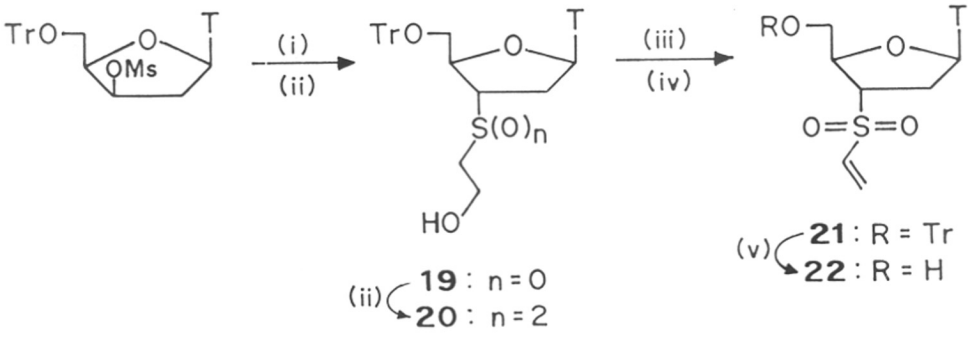
X = **a** : N ; **b** : N O ; **c** : N

CHAPTER-III

Synthesis and Reactivities of 3'-Deoxy-3'-S-(vinylsulphonyl)thymidine

Attempts are currently underway to incorporate electrophilic groups at the 3'-sites of the nucleosides so that these normal compounds can form covalent bonds with biological nucleophiles. We decided to incorporate, at the 3'-site, an electrophilic group such as vinylsulphone, a functionality known for its efficiency for covalent bond formation with a wide variety of nucleophiles. 1-(5-O-Trityl-3-O-mesyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **18** was treated with marcaptoethanol in DMF in the presence of DBU to give compound **19** in 64% yield. Compound **19** was easily oxidised by magnesium monoperoxyphthalate (MMPP) in methanol to the corresponding sulphone **20** in 75% yield. Compound **20** was converted to the mesylated derivative in pyridine at +4°C and the same pyridine solution was heated at 60°C for 0.5h to produce the desired vinylsulphone derivative **21** in 71% overall yield. Compound **21** could be detritylated to the free hydroxy derivative **22** in 85% yield by heating it in 80% aqueous acetic acid solution (**Scheme-5**).

Scheme-5

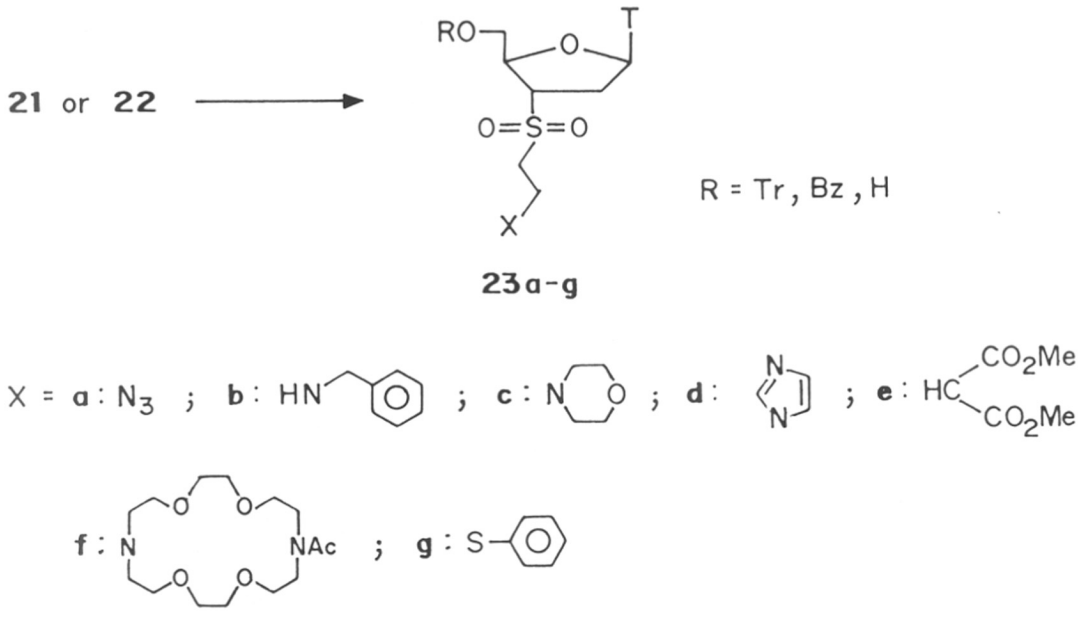


(i) HS⌒OH / DBU / DMF , (ii) MMPP / MeOH / r.t. , (iii) MsCl / Py / +4°C
(iv) 60°C / 0·5h , (v) 80 % HOAc / 100°C

Either the protected vinylsulphone **21** or the deprotected derivative **22** were reacted with various nucleophiles in Michael fashion. Nucleophiles, such as, hydrazoic acid, morpholine, sodium salt of dimethylmalonate, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane and thiophenol reacted smoothly with compound **21** to furnish compounds **23a**, **23c**, **23e**, **23f** and **23g** respectively in excellent to moderate yields (**Scheme-6**). Similarly compound **22** reacted

with benzylamine and imidazole in protic solvent at ambient temperature to produce compounds **23b** and **23d** (after benzoylation in case of **23d**) respectively in high yields. The tritylated derivatives were deprotected with 80% acetic acid and isolated as their benzoylated derivatives. The diaza crown ether product was, however, characterised as 5'-O-trityl-N-acetyl derivative **23f**.

Scheme-6



Part of this work has been published: Tetrahedron **1995**, 51, 7857.

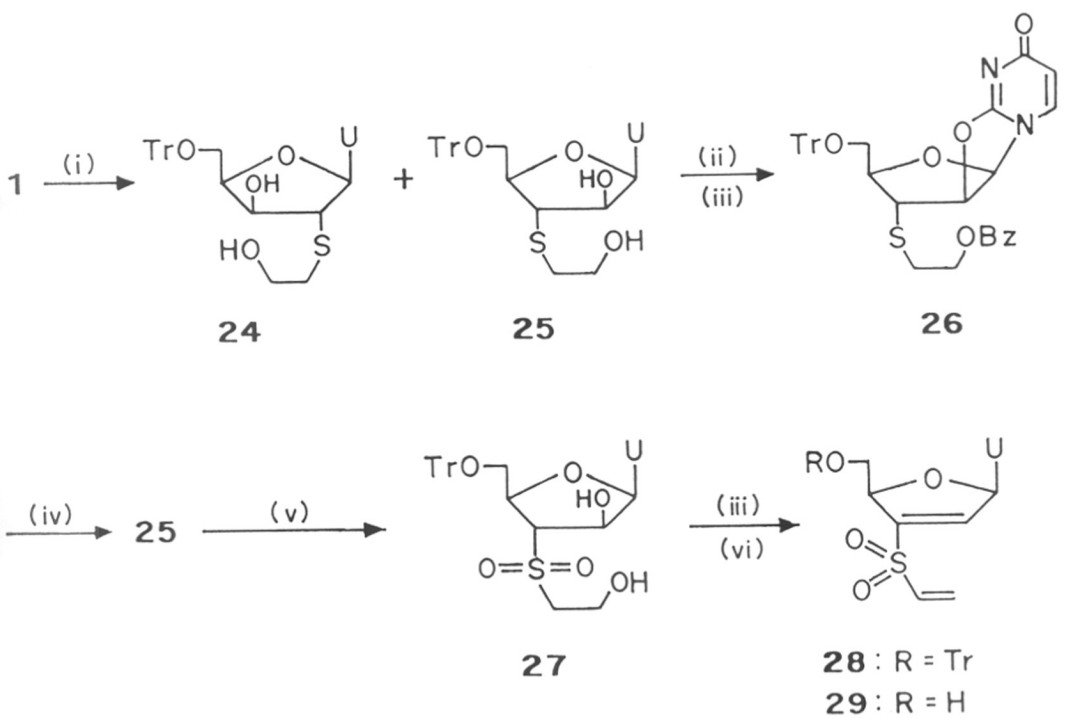
CHAPTER-IV

Synthesis and Reactivities of Sugar Modified Bisvinylsulphonyluridine

In continuation of our interest in the area of nucleosides modified with reactive functionalities, we decided to study the behavior of a sugar modified nucleoside carrying a *bis*vinylsulfone moiety, which was expected to generate bicyclic nucleosides when reacted with appropriate nucleophiles. 5'-O-Trityl-2',3'-O-anhydro-*lyxo*uridine **1** was reacted with mercaptoethanol in presence of TMG to generate a mixture of 2'-deoxy-2'-S-(2-hydroxyethylthio)-5'-O-trityl-*xylo*uridine **24** and 3'-deoxy-3'-S-(2-hydroxyethylthio)-5'-O-trityl-*ara*uridine **25**. The primary

hydroxyl group of the hydroxyethylthio moieties of **24** and **25** were benzoylated selectively at 0°C. After work-up, 2'(3')-hydroxyl groups of the crude benzoylated products were mesylated at 0°C. The resulting mesylated products were heated at 100°C in pyridine to produce 2,2'-O-anhydro-3'-deoxy-3'-S-(mercaptoethylbenzoate)-5'-O-trityluridine **26** in 50% overall yield in four steps. Compound **26** on treatment with aqueous NaOH produced **25** in 96% yield. Oxidation of **25** gave 3'-deoxy-3'-S-(2-hydroxyethylsulfonyl)-5'-O-trityl-*ara*uridine **27** in 86% yield. Both the hydroxyl groups of **27** were mesylated and the crude product obtained after work-up was heated at 40°C in pyridine to produce the desired divinylsulfonyl uridine **28** in 86% yield (**Scheme-7**). Detritylation of compound **21** with 80% aqueous acetic acid did produce compound **29** in impure form. Therefore, after removing tritanol by triturating the detritylating mixture of **29** with ether, crude **29** was treated directly with nucleophiles. The products were isolated as the corresponding benzoylated derivatives.

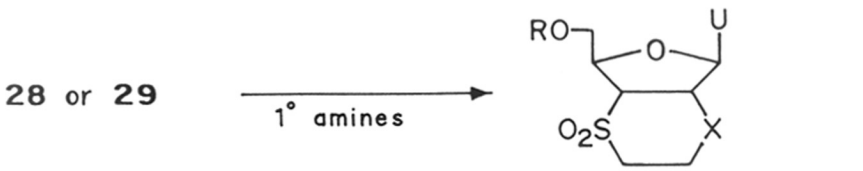
Scheme-7



(i) HS⌒OH , TMG , DMG ; **(ii) (a) Bzcl, Py, 0°C, (b) Mscl, Py, 0°C, (iii) Py, 100°C**
(iv) IN NaOH , EtOH / H_2O (v) MMPP, MeOH (vi) Py , 40 °C

Compounds **28** and **29** were reacted with six primary amines in methanol to produce 2',3'-*cis*fused bicyclic derivatives **30a-e** in high yields in stereoselective fashion (**Scheme-8**).

Scheme-8



30a-e

a : R = Tr , X = N

b : R = Tr , X = N

c : R = Tr , X = N

d : R = Bz , X = N

e : R = Bz , X = N

One equivalent of morpholine reacted selectively with the exocyclic vinylsulfone functionalitity of **28** to produce **31a** in 92% yield. Compound **29** similarly reacted with *p*-anisidine to produce a single product (isolated as its dibenzoyl derivative **31b**). Dimethyl malonate in presence of sodium hydride reacted with **28** to produce **31c** in 86% yield. (**Scheme-9**). Compound 31a

Scheme-9

31a-c

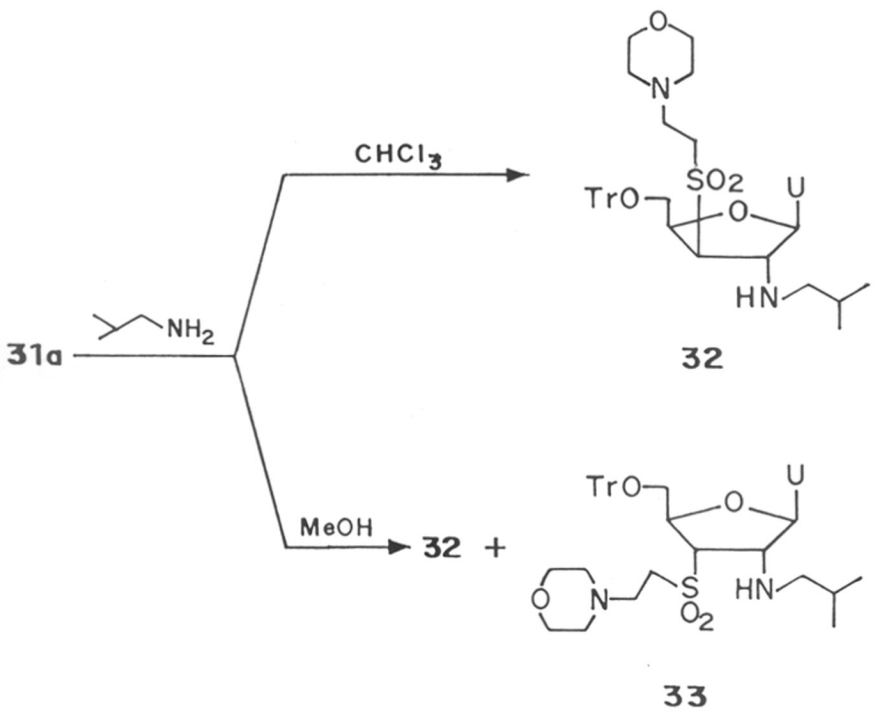
X = **a**: R = Tr ; X = N

b: R = Bz ; X = N

c: R = Tr ; X = CH

on treatment with isobutyl amine in chloroform only one compound **32** was obtained. The same reaction in methanol produced mixture of compounds **32** and **33** (**Scheme-10**).

Scheme - 10



List of Publications

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

Chapter-I Opening of 2',3'-O-Anhydro-ring of 2',3'-O-Anhydro-*lyxo*-uridine by Alkyl and Arylamines. Easy synthesis and preparative Uses of 2'-Deoxy-2'-alkylamino-*xylo*- and 3'-Deoxy-3'-alkylamino-*ara*-uridines.
Sanjib Bera, Tanmaya Pathak and Graham J. Langley, *Tetrahedron*, **1995**, 51, 1459-1470.

Chapter-II Studies on the Thermal Degradation of Sugar-modified Uridine N-Oxides: Olefination, Oxazetidination and Rearrangement.
Sanjib Bera and Tanmaya Pathak. (Communicated).

Chapter-III 3'-Deoxy-3'-(vinylsulphonyl)thymidine-A New Reactive Analogue of AZT: Its Synthesis and Reactivities Towards Various Nucleophiles
Sanjib Bera , Kandasamy Sakthivel, Tanmaya Pathak and Graham J. Langley, *Tetrahedron*, **1995**, 51, 7857-7866.

Chapter-IV. Sugar Modified Uridine Bisvinylsulphone: Synthesis of a Bifunctionalised Nucleoside Michael Acceptor and its use in Stereoselective Tandem Cyclisation.
Sanjib Bera, Graham J. Langley and Tanmaya Pathak. (Manuscript in preparation)

CHAPTER-I

Opening of 2',3'-O-Anhydro-ring of 2',3'-O-Anhydro-lyxo-uridine by Amines

1.1. Introduction:

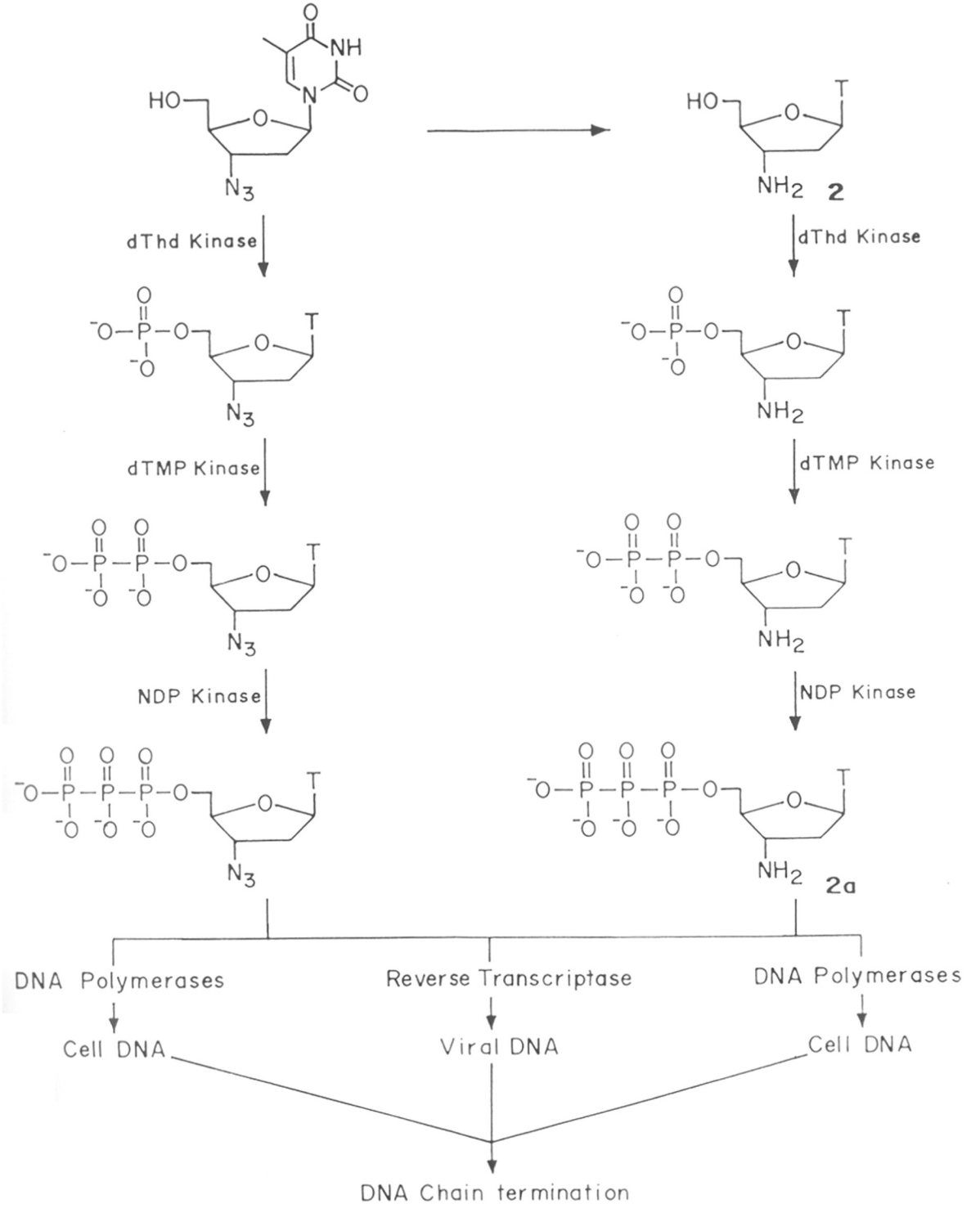
A variety of aminonucleosides were synthesised in the past to study their biological properties[1]. Since the discovery of the anti-HIV (Human Immunodeficiency Virus) activity of 3'-deoxy-3'-azidothymidine[2] **1** (AZT), (**Scheme-1.1**) various modifications have been made at 2' and /or 3'-sites of nucleosides[3-5]. Attempts are currently underway to functionalise 2'- and/or 3'- sites by primary and secondary amines[6-36]. In fact, 3'-amino-3'-deoxythymidine has been found to exhibit wide ranging biological activities[37-40] It was reported more recently that 3'-amino-3'-deoxythymidine **2** was formed from 3'-deoxy-3'-azidothymidine (AZT) in some cells as the reduced product[41] (**Scheme-1.1**). In another report, 3'- amino-3'-deoxythymidine **2** was synthesized 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[37] against HIV-1 (**Scheme-1.1**); the 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 groups containing amino- functionalities[42]. In addition, several 3'-deoxy-3'-alkylamino- **4a-b** and 2'-deoxy-2'-alkylamino- derivatives **5a-c** have been synthesized from compounds **3a** and **3b** respectively (**Scheme-1.2**) and studied against HIV[6]. It was reported[6] two aminonucleosides, compounds **5b** and **5c** have shown weak inhibitory effects against HIV replication. However, a full evaluation of the biological activity of this type of compounds will be possible only when they are easily accessible. 3'-Amino-3'-deoxythymidine **2** was also active against p^{815} mouse leukemia cells. Some naturally occurring nucleoside antibiotics containing aminosugar moieties have also been reported[43-46]. In recent years, various nitrogen containing dephospho-backbone modified dinucleotides were synthesized for developing oligonucleotides with anti-sense properties[47-56]. One example[56] of such compound is demonstrated in **Scheme-1.3**.

1.2. Present Work:

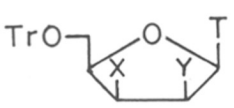
We decided to develop a general strategy leading to the synthesis of 2'-deoxy-2'-alkylamino- and 3'-deoxy-3'-alkylaminopyrimidine nucleosides as AZT contains a pyrimidine base, thymine. This was achieved by opening the epoxide ring of 1-(5-O-trityl-2,3-O-anhydro-β-D-*lyxo*-furanosyl)-uracil **11** by alkyl- and arylamines under controlled conditions to produce

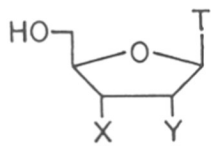
Scheme - 1·1

METABOLIC PATHWAYS OF ZIDOVUDINE (AZT)



Scheme-1·2





3a : X = OMs ; Y = H
3b : X = H ; Y = OMs

4a : X =  ; Y = H

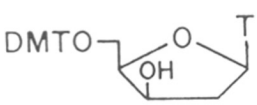
4b : X =  ; Y = H

5a : Y =  ; X = H

5b : Y =  ; X = H

5c : Y =  ; X = H

Scheme-1·3



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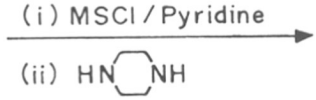

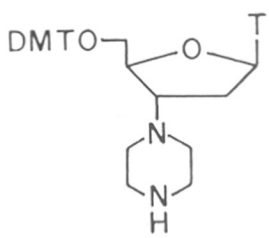

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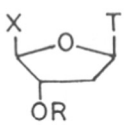
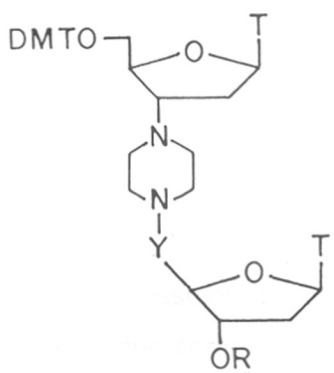


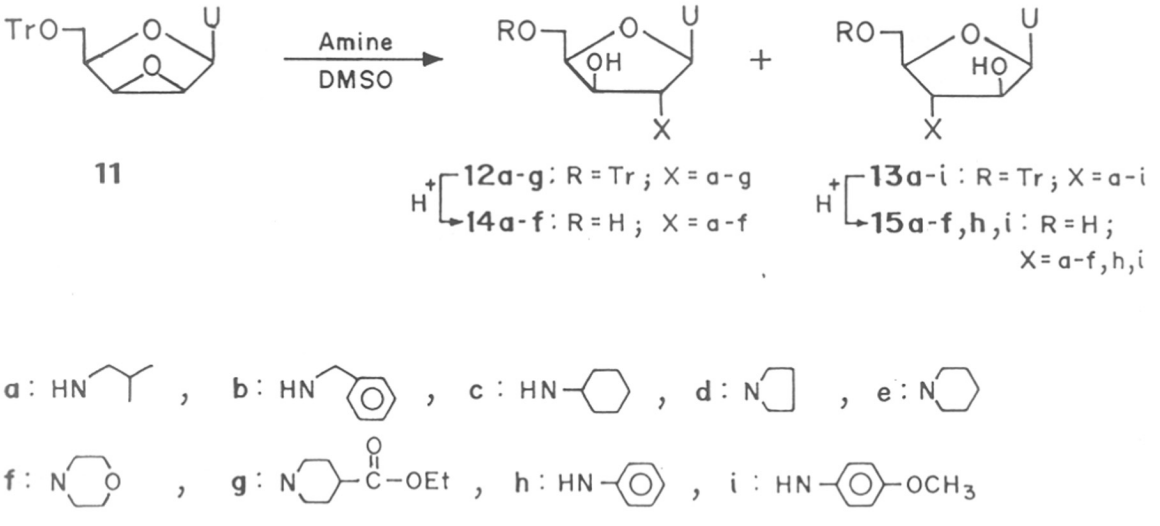
8a : R = TBDMS, Y = CHO
8b : R = H, Y = COOH



9a : R = TBDMS ; Y = CH_2
9b : R = H ; Y = CH_2
10 : R = H ; Y = CO

2'-deoxy-2'-amino-*xylo*- and 3'-deoxy-3'-amino-*ara*-uridine without causing significant, if any, deglycosylation (**Scheme-1.4**).

Scheme- 1·4

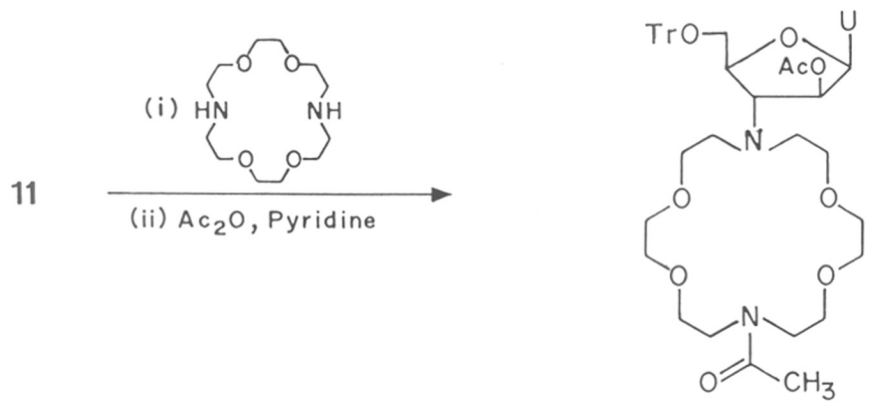


Opening of 1-(5-O-trityl-2,3-O-anhydro-β-D-*lyxo*-furanosyl)-uracil 11 by amines: In general, a solution of compound **11** (1mmol) and amine (5-10mmol) in DMSO (3ml) was heated at 90-95°C. After completion of the reaction (tlc), the reaction mixture was worked up and the compounds were purified by column chromatography. The reaction temperatures varied slightly from amine to amine but the reaction times varied widely (see experimental). In general more basic amines reacted faster than the less basic amines. The aromatic amines were the slowest to react; the reaction mixtures had to be heated for longer times at higher temperatures.

Isobutylamine, benzylamine, cyclohexylamine, piperidine, pyrrolidine, morpholine, ethyl *iso*nipecotate, aniline and p-methoxyaniline, all reacted in similar fashion to produce compounds **12a-g** and **13a-i** (**Scheme-1.4**). Only 3'-deoxy-3'-arylamino compounds could be obtained in pure form from the reaction between aniline or p-methoxyaniline and **11**.

N-Methylpiperazine, N-acetylpiperazine, N-methylethanolamine, N,N'-dimethylethylenediamine, diethanolamine, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane also opened the epoxide in varying yields; however, all attempts to separate the isomers failed. The major product (2':3' 1:2.4) obtained from the reaction between **11** and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane was separated as the diacetate **16** (**Scheme-1.5**); as far as our knowledge goes into literature, **16** is the first reported compound of its kind. It should be noted that in case of isobutylamine, compound **11** was reacted with neat amine to give the desired products in moderate yields. This observation indicated that the use of neat amine had caused deglycosylation (**See discussion**). Nevertheless, use of 7 equivalents of isobutylamine in DMSO (70°C, 20h) produced the mixture of **12a**/**13a** in 80% yield.

Scheme-1.5



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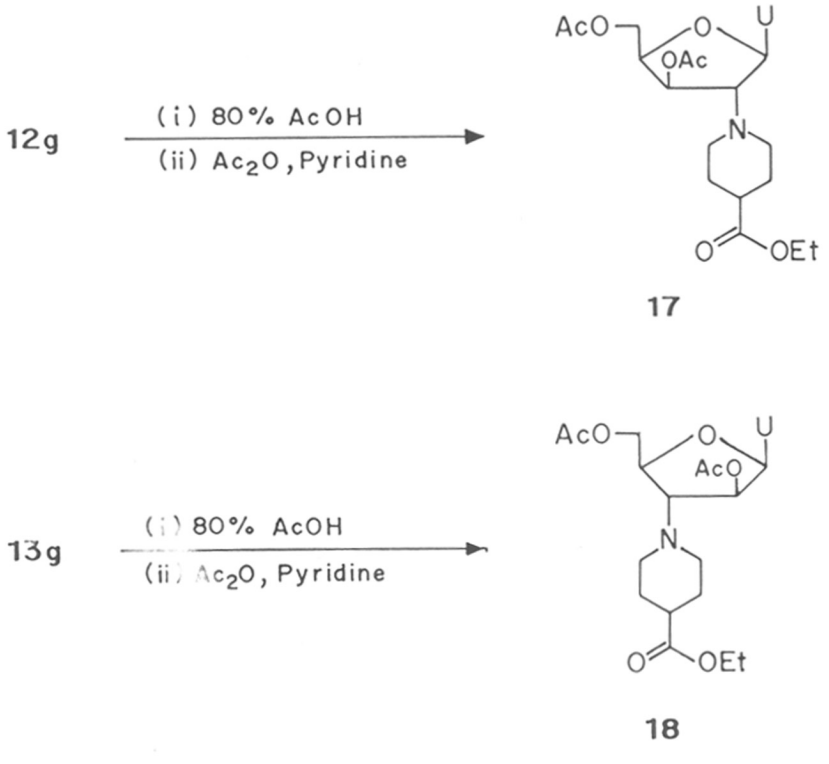
Deprotection of the aminoalcohols: Compounds **12a-f**, **13a-f**, **13h-i** were deprotected using Amberlite IR-120 H^+ in water. The deprotected compounds **14a-f, 15a-f, 15h** and **15i** were eluted out of the column using ammonia solution (**Scheme-1.4**). It was important to neutralise the medium with ammonia as soon as possible to avoid degradation. It was interesting to note that compounds **12a-f** were more stable under acidic conditions than compounds **13a-f**. However, compounds **12g** and **13g** could not be deprotected using the general deprotection

conditions, as elution with ammonia caused partial deprotection of the nipecotyl ester group. Compounds **12g/13g**, were deprotectrd using 80% acetic acid and the deprotected compounds were collected as their diacetyl derivatives **17** and **18** (**Scheme-1.6**). The deprotected compounds **14a-f**, **15a**, **17** and **18** were highly hygroscopic.

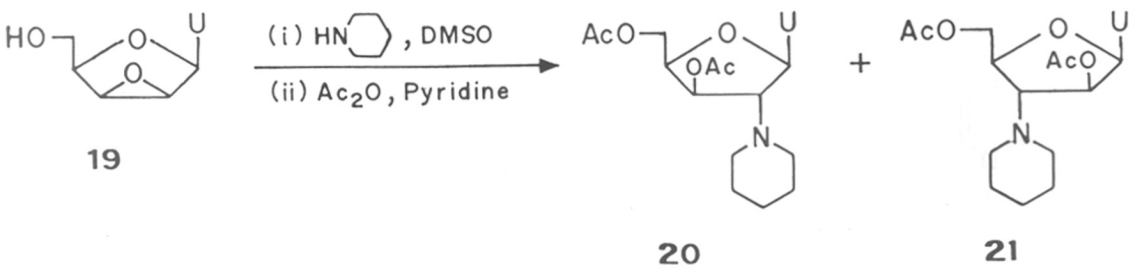
Scheme - 1·6



In order to study the effect of steric bulk of the trityl group on the selectivity of 2' versus 3'-attack of amines, 1-(2,3-O-anhydro-β-D-*lyxo*-furanosyl) uracil **19** was reacted with piperidine in DMSO. The mixture was acetylated to produce a mixture of compounds **21** and **20** in a ratio 3.2:1 (**Scheme-1.7**).

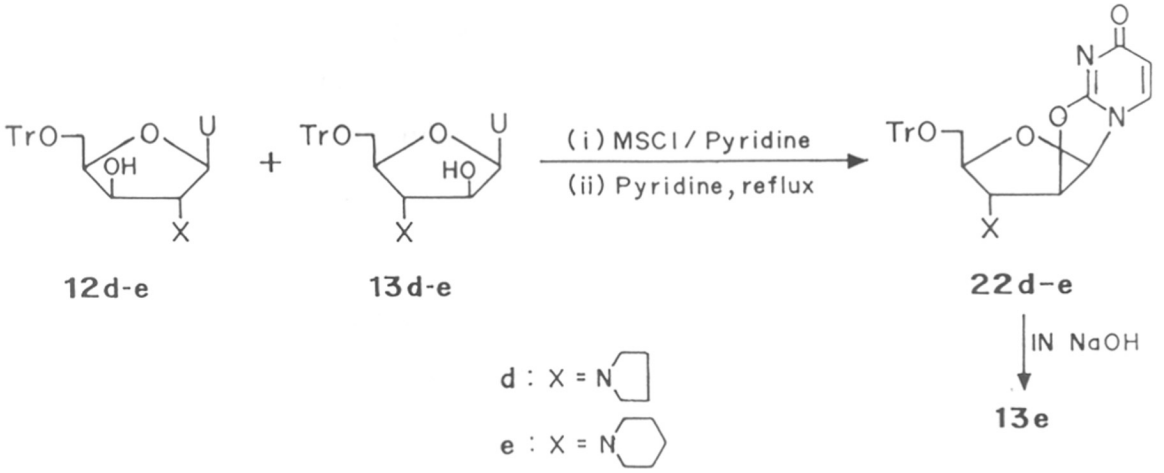
Synthesis of 5'-O-trityl-2,2'-O-anhydro-3'-deoxy-3'-aminouridines 22d-e: A mixture of compounds **12d** and **13d** was mesylated in pyridine at +4°C. The purified mixture was redissolved in pyridine and the solution was heated under reflux for 6 hours to produce the

Scheme - 1·7



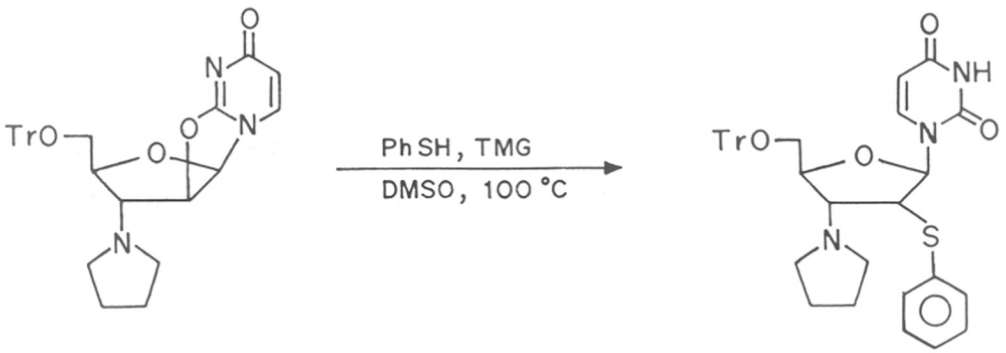
known[8] 3'-deoxy-3'-pyrrolidino-2,2'-O-anhydro-5'-O-trityluridine **22d** (**Scheme-1.8**). Similarly compounds **12e** and **13e** were converted to 3'-deoxy-3'-piperidino-2,2'-O-anhydro-5'-O-trityluridine **22e**. Compound **22e** on treatment with 1N aqueous sodium hydroxide produced 2,2'-O-anhydro ring opened compound which was identical to the major isomer **13e** obtained from the reaction between piperidine and compound **11** (**Scheme-1.8**).

Scheme - 1·8



Synthesis of 1-(5-O-trityl-2,3-dideoxy-2-S-thiophenyl-3-N-pyrrolidino- β-D-*ribo*furanosyl)-uracil 23: Compound **22d** on treatment with thiophenol in presence of tetramethylguanidine produced the 2',3'-dideoxy-2',3'-disubstituted derivative **23** (**Scheme-1.9**).

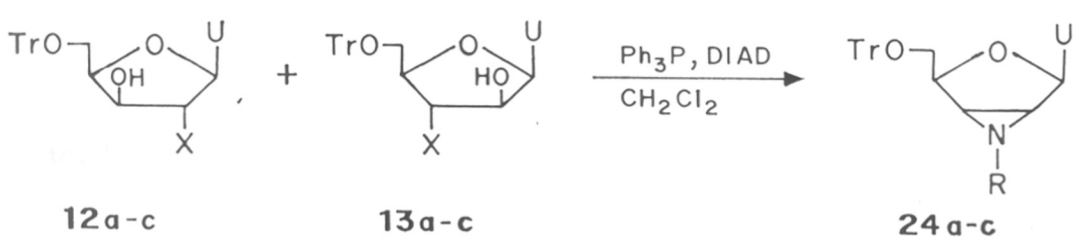
Scheme- 1·9



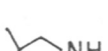
22d **23**

Synthesis of 1-(5-O-trityl-2,3-dideoxy-2,3-epimino-β-D-*ribo*furanosyl)- uracil 24a-c: The compounds derived from primary amines were converted smoothly to the epimino derivatives in good yields. Thus, a mixture of compounds **12a** and **13a** on treatment with triphenyl phosphine and diisopropyl azodicarboxylate produced 1-(5-O-trityl-2,3-dideoxy-2,3-N-isobutylepimino-β-D-ribofuranosyl)- uracil **24a** in 65% yield. Mixture of compounds **12b/13b** and compounds **12c/13c** could also be converted to the corresponding epimino derivatives **24b-c** as was evident from ^{1}H-NMR spectrum of the products; however, the products **24b** and **24c** could not be obtained in pure form as they were always contaminated with triphenyl phosphonium oxide (**Scheme-1.10**).

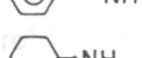
Scheme- 1·10



12a-c **13a-c** **24a-c**

a: X = 

b: X = 

c: X = 

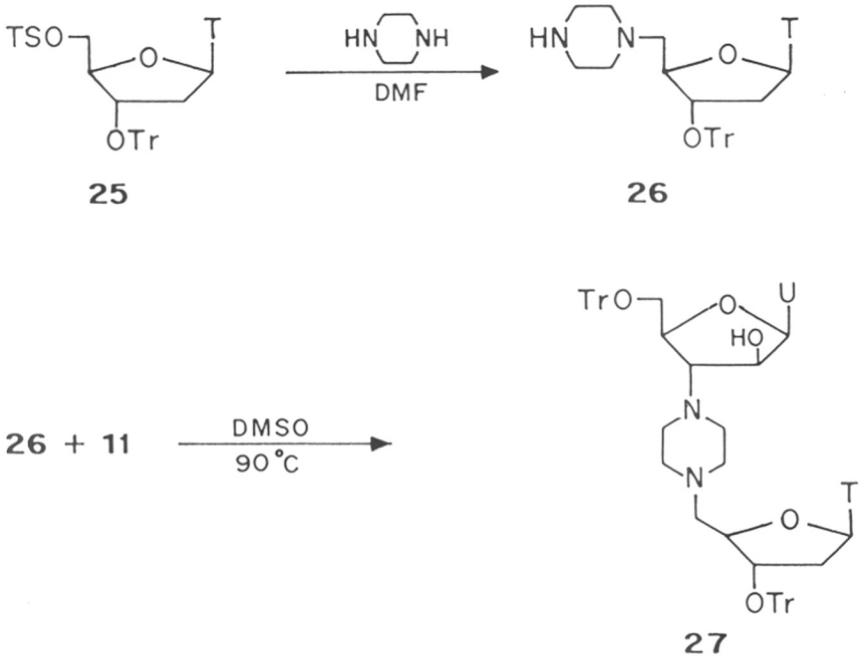
a: X = 

b: X = 

c: X = 

Synthesis of 3'-deoxy-5'-O-trityl-3'-[N-{1-(thymine-1-yl)-1,2,5-trideoxy-3-O-trityl-β-D-erythro-pentofuranos-5-yl}-pipereazino] *ara*uridine 27: We decided to apply the methodology of opening the epoxide with amines to synthesise non phosphate dimer. We therefore, treated compound **11** 5'-deoxy-5'-piperazino-3'-O-trityl thymidine **26** at elevated temperature in DMSO (**Scheme-1.11**). The structure of the only product which was isolated in 29% yield was tentatively assigned as compound **27** on the basis of ^{1}H-NMR (**Fig.-1.1**). However more rigorous data collection is necessary to determine the structure unambiguously.

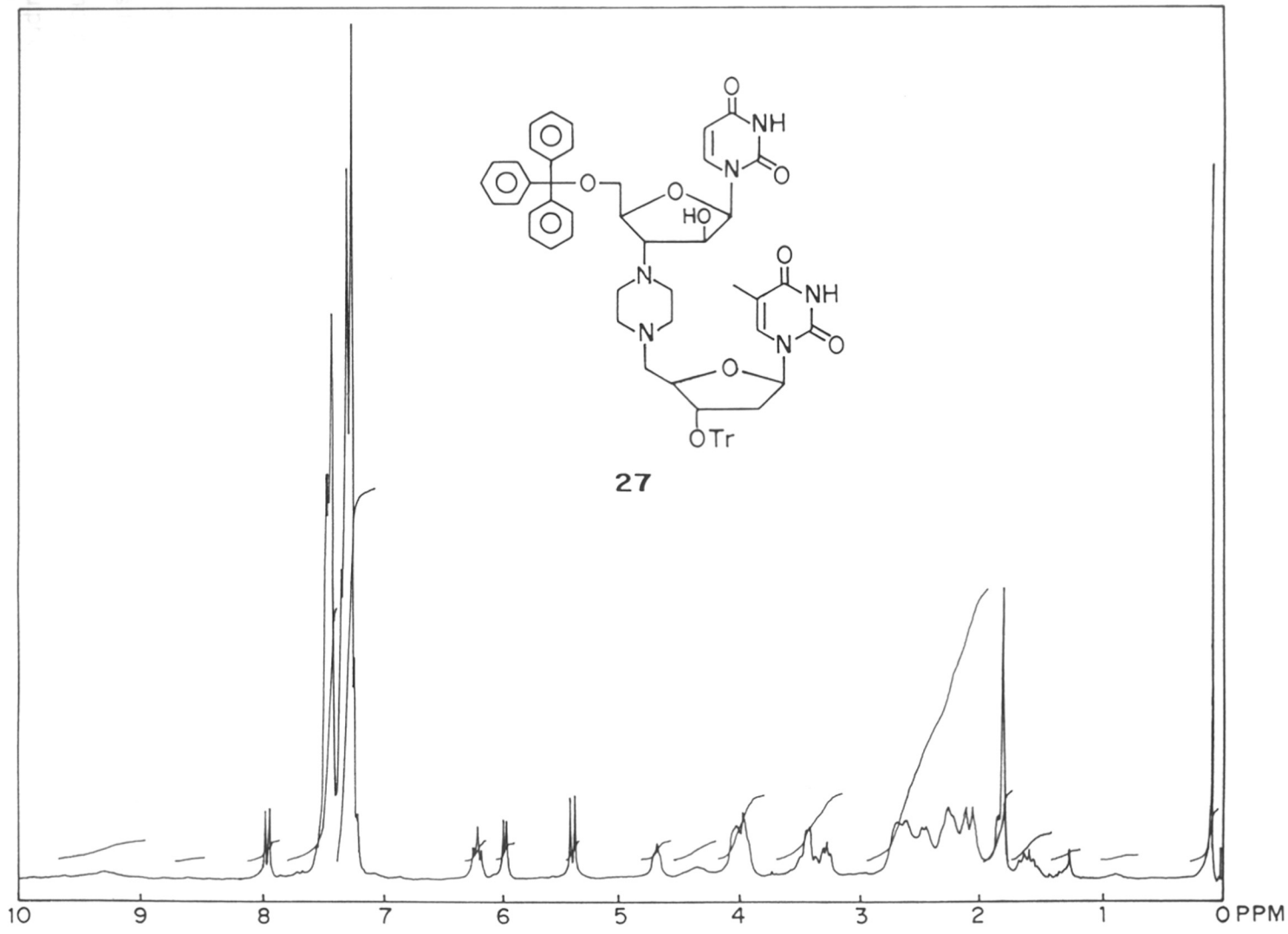
Scheme- 1·11



25 **26** **27**

1.3. Structural Assignment:

The structures of all new compounds were assigned unambiguously by chemical as well as spectroscopic means. That the amines were indeed connected to the 2'- or 3'- carbons was proved by the preparation of compounds **22d**, **22e** and **24a-c**. Although it was well known in the literature[6, 10, 57-61] that the major product of the epoxide ring opening reactions was always the 3'-deoxy-3'-substituted compound, the identity of at least one isomer was established as



27

Figure. 1·1

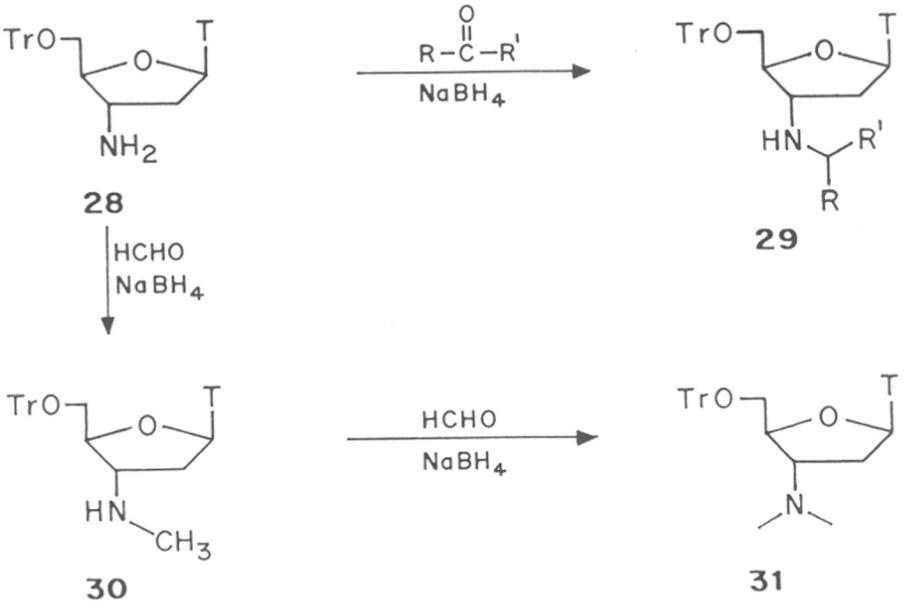
the 3'-deoxy-3'-substituted compound by converting **22e** to the known compound **13e**. However, the preparation of compound **22e** from a mixture of compounds **12e** and **13e** also proved, albeit indirectly, the presence of 2'-deoxy-2'-substituted compound **12e** which was converted to the final product **22e** through a common aziridinium intermediate.

The ^{1}H-NMR of compounds **12a-g** and **13a-i** are consistent with the structures assigned. The H-1' resonances of compounds **12a-c** always appeared more upfield than the resonances of compounds **13a-c**; the coupling constants ($J_{1',2'}$= > 1.4 Hz) of **12a-c** were always much smaller than **13a-c** ($J_{1',2'}$= > 4.6 Hz). The H-2' resonances of compounds **12a-c** were always shielded by almost 1ppm than the H-3' resonances. In case of compounds **13a-c**, as expected, the H-2' resonances were always deshielded than the H-3' resonances. The H-4' resonances of 2'-deoxy-2'-substituted compounds **12a-c** were always deshielded than the same resonances of the 3'-deoxy-3'substituted compounds **13a-c**; this was, most probably due to the presence of more electronegative functionality OH (as opposed to NHR) at C-3' position in compounds **12a-c**. The pattern was more or less similar in case of compounds **12d-g** and **13d-g**. However, in case of H-1' and H-4'-resonances the differences were less pronounced and except for **12d/13d** pair, the $J_{1',2'}$ coupling constant values were very close. The proton signals of compounds **12a/13a**, **12d/13d** and **23** were assigned on the basis of COSY analysis. Further unambiguous proof for these compounds were high resolution mass spectra.

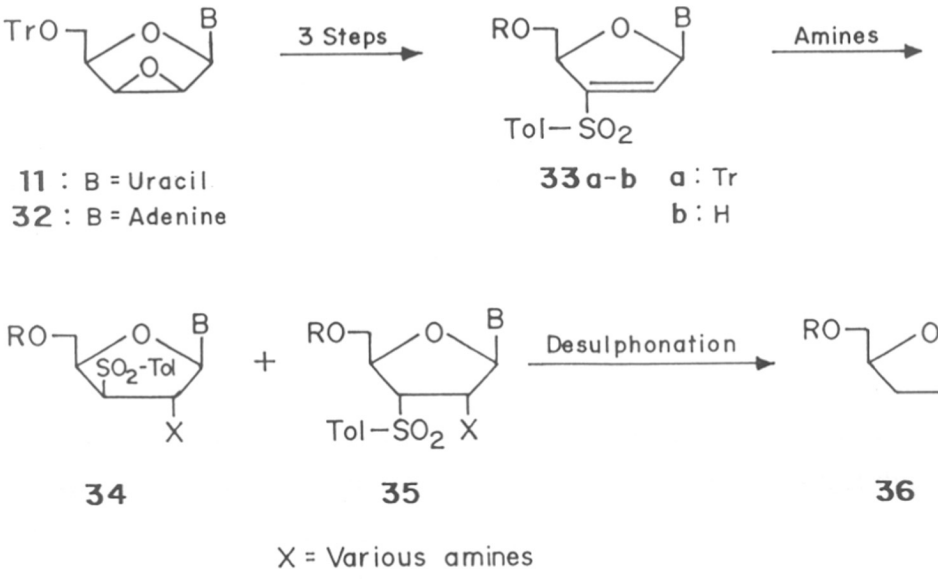
1.4. Discussion:

Alkylamino-substituted nucleosides **29**, **30** and **31** were synthesized earlier by reacting 3'-deoxy-3'-aminonucleosides **28** with an appropriate aldehyde and ketone to give the corresponding Schiff base which was then reduced with sodium borohydride[62,63] (**Scheme-1.12**). Attempted displacement of the 3'-O-mesyl group of 1-(2-deoxy-3-O-methanesulphonyl-β-D-*threo*-pentofuranosyl)thymine **3a** with alkylamines was unsuccessful as the desired products were obtained in very poor yield[6,63](**Scheme-1.2**). Chattopadhyaya and co-workers made use of Michael addition reactions of amines to nucleoside ene-sulphones[7] **33a-b** (**Scheme-1.13**) or ene-selenone[8,9] **37** (**Scheme-1.14**) . However, apart from the facts that the preparation of these starting materials involved multiple steps and in the latter case use of toxic selenium compounds, both the methodologies suffered from certain serious drawbacks: i) the reductive removal of sulfone group after amination caused extensive

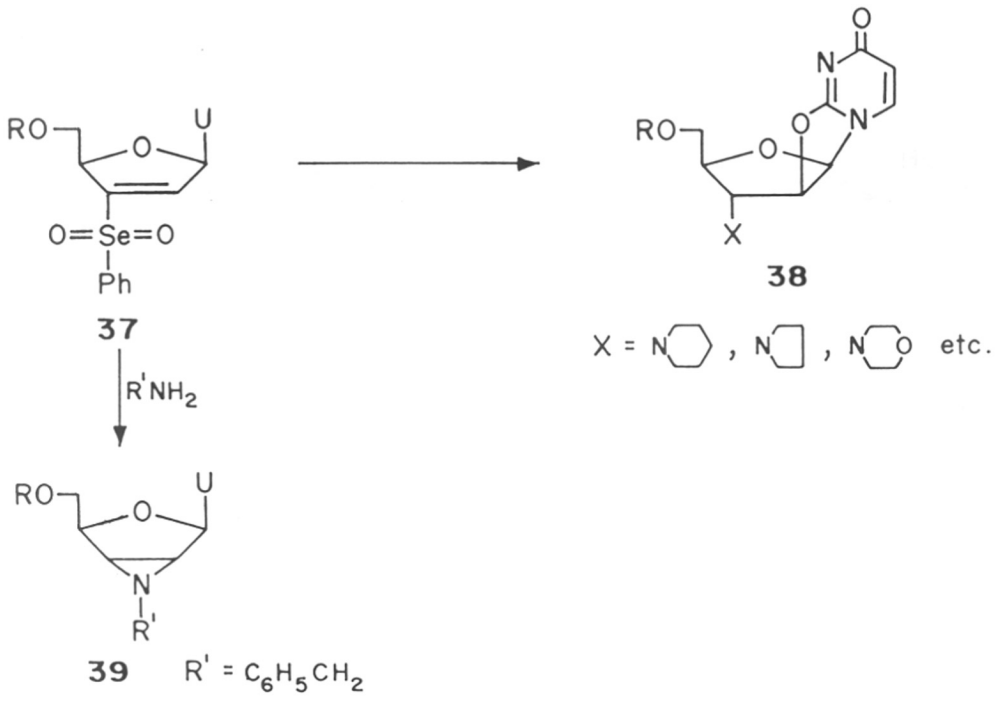
Scheme - 1·12



Scheme - 1·13



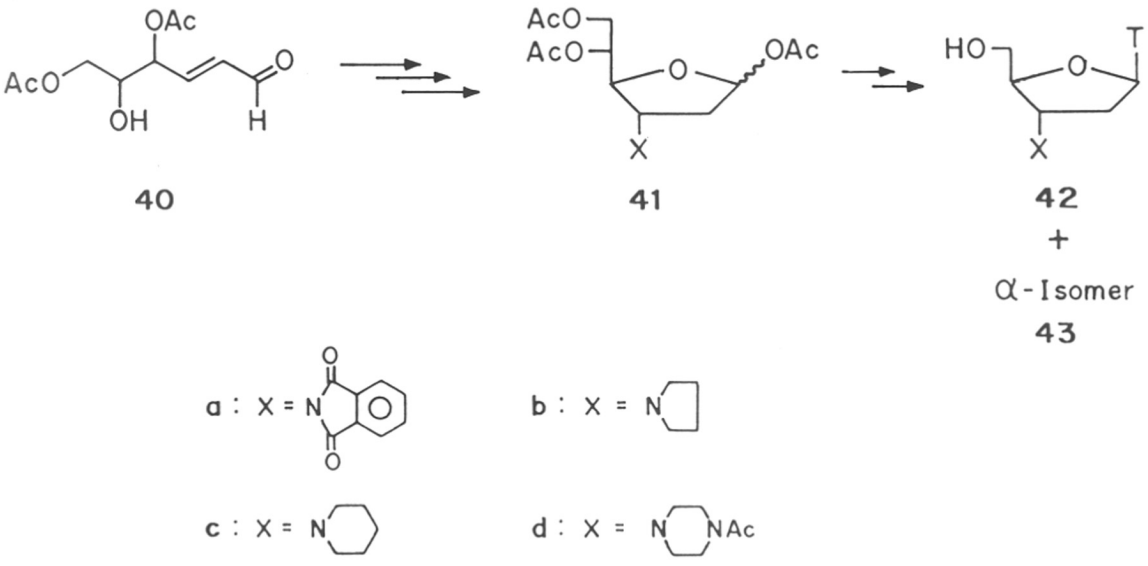
Scheme - 1·14



deglycosylation as was evident from the yield of the products[7] and ii) 2'- and 3'-ene selenones, because of their very special kind of reactivities produced 2,2'-O-anhydro-3'-deoxy-3'-aminouridines **38** or 2',3'-dideoxy-2',3'-epiminouridines [8,9] **39** (depending on the amine used) in uncontrolled fashion. In another development, Wengel and co-workers reacted[22,23] an α,β-unsaturated aldehyde, 4,6-di-O-acetyl-2,3-dideoxy- *aldehydo*-D-erythro-trans-hex-2-enose **40** with amines in Michael fashion; the product was converted to 2',3'-dideoxy-3'-alkylamino-D-ribohexofuranosyl pyrimidines **42** and **43** through multiple steps (**Scheme-1.15**). However, the synthesis was restricted only to piperidine and pyrrolidine derivatives as other amines did not react with the starting α,β-unsaturated aldehyde.

Since, nucleophilic ring opening of 2',3'-O-anhydro nucleoside in general is one of the most efficient ways of functionalising nucleosides[7-9, 1b] and in view of the fact that 3'-amino-3'-deoxy-*ara*-uridine was indeed synthesized[10] by the reactions of 2',3'-O-anhydro-*lyxo*-uridine with ethanolic ammonia, we decided to reinvestigate the reactions between alkyl- and

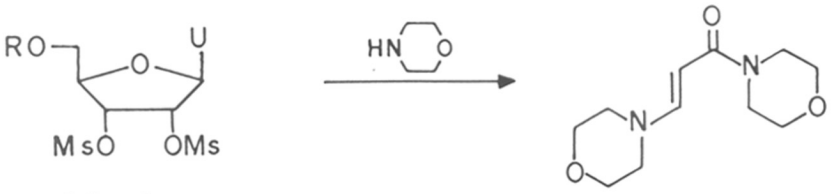
Scheme - 1·15



arylamines and **11** under controlled conditions. Although protected 2',3'-O-*lyxo*anhydro-adenosine reacted with a variety of primary and secondary amines to give isomeric mixtures of 2'-alkylamino and 3'-alkylamino nucleosides, previous attempts to open 2',3'-O-anhydro-lyxo-uridine with pyrrolidine[6] failed as it "led only to cleavage of the glycosidic bond, presumably through the nucleophilic attack at C-6 and/or C-4".

We observed[64] earlier that reaction between 2',3',5'-tri-O-mesyluridine **44b** and neat piperidine at ambient temperature produced an inseparable mixture of compounds. Reaction with morpholine, however, produced 4-(1-oxo-3-(morpholinyl)-2-propenyl)-morpholine **45** after 24h (**Scheme-1.16**). 2',3'-Di-O-mesyl-5'-O-trityluridine 2',3'-di-O-mesyluridine also produced the same compound **45** under identical conditions. This observation led us to believe that in case of pyrimidine nucleoside neat amine should not be used especially if the reaction had be performed at elevated temperature for a relatively longer period. We, therefore, reacted compound **11** with 5-10 eqv of amines in DMSO and found that contrary to the previous

Scheme - 1·16



44a-b

a: R = Ms

b: R = Tr

45

report[6], under the right conditions, alkylamines, both primary and secondary and arylamines, did indeed open the epoxide ring of compound **11** to produce the desired products without causing significant, if any, deglycosylation .

That the presence of the trityl protecting group at the 5'-position did influence the product distribution was evident from the fact that compound **19** on treatment with piperidine produced the corresponding 3'-piperidino- derivative **21** and 2'-substituted derivative **20** in a ratio 3.2:1 (**Scheme-1.7**) (mixture isolated as the diacetates) which is significantly different from the ratio of 3' and 2'isomers, **13e** and **12e** (2.7:1) obtained from the reaction of compound **11** and piperidine.

To show the usefulness of products **12** and **13** as versatile intermediates, we synthesised various derivatives from selected compounds. Mesylation of isomeric mixture of compounds **12d** and **13d** followed by reflux in pyridine produced the known[8] 3'-deoxy-3'-pyrrolidino-2,2'-O-anhydro-5'-O-trityluridine **22d**. Similarly compounds **12e** and **13e** were converted to 3'-deoxy-3'-piperidino-2,2'-O-anhydro-5'-O-trityluridine **22e**. It is obvious that the formation of a reactive aziridinium ion intermediate has led to the conversion to the more stable anhydro derivatives. This method is useful for converting a mixture of *ara*- and *xylo*- isomers to pure *ara*- compound if only 3'-deoxy-3'-substituted compound is required.

1.5. Conclusion:

We have developed a general methodology for the synthesis of a great number and wide

variety of 2'-deoxy-2'-alkylamino-*xylo*- and 3'-deoxy-3'-alkylamino-*ara*-uridines **12a-g** and **13a-i** respectively. We have also demonstrated that these compounds could be converted to various derivatives in controlled fashion.

1.6. Experimental:

Melting points were uncorrected. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merck 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 or solvent chloroform-d as internal standards. All mass spectrometric experiments were carried out on a VG Analytical 70-250-SE normal geometry double focussing mass spectrometer, fitted with an Ion-Techsaddle-field gun. Accurate mass measurements were carried out at 10 000 resolution using mixtures of polyethylene glycols as mass calibrants.

Synthesis of 5'-O-trtyl-2',3'-O-anhydro-*lyxo*uridine 11:

Compound **11** was prepared by the reaction of 5'-O-trityl-2',3'-di-O-mesyl uridine with sodium hydroxide as reported in the literature[10b].

Synthesis of 2',3'-O-anhydro-*lyxo*uridine 19:

Compound **19** was prepared by the reaction of 2',3',5'-tri-O-mesyl uridine with sodium benzoate followed by the treatment with sodium hydroxide as reported in the literature[10a].

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-isobutylamino-*xylo*- uridine 12a and 5'-O-trityl-3'-deoxyxy-3'-N-isobutylamino-*ara*-uridine 13a:

Method-A:

A mixture of compound **11** (1mmol) and neat isobutylamine (4ml)) was heated at 80°C for 10h. The excess amine was removed under reduced pressure. The residue was dissolved

in ethyl acetate (50ml) and the solution was washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on silica gel.

Compound-12a: Yield= 20%.

Compound-13a: Yield=37%.

Method-B: A mixture of compound **11** (1mmol) and isobutylamine (7mmol) in DMSO (4ml) was heated at 70°C for 20h. Excess amines were removed under reduced pressure and worked up as described in **method-A.** The mixture of compounds **12a/13a** was purified over silica gel. (Total yield = 80%).

Compound 12a:

m.p: 101°C

^{1}H-NMR: ($CDCl^3$):δ 7.84 (d, 8.2 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 5.72 (d, 1.4 Hz, 1H) H-1'; 5.59 (d, 8.2 Hz, 1H) H-5; 4.38 (m, 1H) H-4'; 4.11 (d, 1H) H-3'; 3.62 (d, 2H) H-5', H-5''; 3.24 (s, 1H) H-2'; 2.59, 2.43 (m, 2H) isobutyl -CH_2-; 1.71 (m, 1H) isobutyl -CH-; 0.95 (d, 6H) isobutyl (-$CH_3)_2$.

^{13}C-NMR: ($CDCl_3$):δ 164.1, C-4; 150.7, C-2; 143.4, trityl; 141.4, C-6; 128.8, 128.3, 127.6, trityl; 101.5, C-5; 91.4 C-1'; 87.9, trityl; 82.1, C-4'; 76.0/72.3, C-2'/C-3'; 62.5, C-5'; 56.1, isobutyl -CH_2-; 28.6 isobutyl -CH-; 20.7, isobutyl (-$CH_3)_2$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{35}N_3O_5$: 542.2655, found 542.2707.

Compound 13a:

m.p: 99-100°C

^{1}H-NMR: ($CDCl_3$):δ 7.93 (d, 8.0 Hz, 1H) H-6; 7.47-7.22 (m, 15H) trityl; 6.12 (d, 4.7 Hz, 1H)

H-1'; 5.38 (d, 8.0 Hz, 1H) H-5; 4.37 (m, 1H) H-2'; 3.82 (m, 1H) H-4'; 3.50 (m, 2H) H-5', H-5''; 3.30 (t, 1H) H-3'; 2.52, 2.35 (m, 2H) isobutyl -CH_2-; 1.64 (m, 1H) isobutyl -CH-; 0.85 (d, 6H) isobutyl (-CH_3)$_2$.

^{13}C-NMR ($CDCl_3$): δ 165.0, C-4; 151.3, C-2; 143.6, trityl; 142.7, C-6; 128.9, 128.1, 127.5, trityl; 101.1, C-5; 87.5, trityl; 86.1, C-1'; 82.2, C-4'; 75.8/64.5, C-2'/C-3'; 63.7, C-5'; 56.1, isobutyl -CH_2-; 28.6 isobutyl -CH-; 20.7, isobutyl (-CH_3)$_2$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{35}N_3O_5$: 542.2655, found 542.2689.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-benzylamino-*xylo*- uridine 12b and 5'-O-trityl-3'-deoxy-3'-N-benzylamino-*ara*-uridine 13b:

A mixture of compound **11** (1mmol) and benzylamine (5mmol) in DMSO (3ml) was heated at 95°C for 19h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12b:

Yield: 18%

m.p: 105°C

^{1}H-NMR: ($CDCl_3$):δ 7.79 (d, 8.2 Hz, 1H) H-6; 7.69-7.29 (m, 20H) trityl and aromatic; 5.83 (d, 1.4 Hz, 1H) H-1'; 5.56 (d, 8.2 Hz, 1H) H-5; 4.44 (m, 1H) H-4'; 4.15 (m, 1H) H-3'; 3.93 (2xd, 2H) benzyl -CH_2-, 3.64 (m, 2H) H-5', H-5''; 3.35 (s, 1H) H-2'.

^{13}C-NMR: ($CDCl_3$):δ 164.3, C-4; 150.8, C-2; 143.5, trityl; 141.4, C-6; 139.7, 128.8, 128.6, 128.2, 127.4, 127.3, trityl and benzyl; 101.4, C-5; 91.2, C-1'; 87.6, trityl; 82.5, C-4'; 75.6/71.6, C-2'/C-3'; 62.4, C-5'; 52.1, benzyl -CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{35}H_{33}N_3O_5$: 576.2498, found 576.2559.

Compound 13b:

Yield: 62%

m.p: 99°C

^{1}H-NMR: ($CDCl_3$):δ 7.86 (d, 8.1 Hz, 1H) H-6; 7.41-7.20 (m, 20H) trityl and aromatic; 6.11 (d, 4.8 Hz, 1H) H-1'; 5.34 (d, 8.1 Hz, 1H) H-5; 4.37 (t, 1H) H-2'; 3.81 (m, 3H) H-4'and benzyl -CH_2-, 3.43 (m, 3H) H-3', H-5', H-5''.

^{13}C-NMR: ($CDCl_3$):δ 165.0, C-4; 151.3, C-2; 143.6, trityl; 142.7, C-6; 139.8, 128.9, 128.6, 128.4, 128.1, 127.5, 127.3, trityl and benzyl; 101.1, C-5; 87.5, trityl; 86.0, C-1'; 81.8, C-4'; 76.0/63.6, C-2'/C-3'; 63.6, C-5'; 51.9, benzyl -CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{35}H_{33}N_3O_5$: 576.2498, found 576.2510.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-cyclohexylamino-*xylo*-uridine 12c and 5'-O-trityl-3'-deoxy-3'-N-cyclohexyl-amino-*ara*-uridine 13c:

A mixture of compound **11** (1mmol) and cyclohexylamine (5mmol) in DMSO (3ml) was heated at 95°C for 23h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12c:

Yield: 14%

m.p: 91°C

^{1}H-NMR: ($CDCl_3$):δ 7.86 (d, 8.2 Hz, 1H) H-6; 7.50-7.26 (m, 15H) trityl; 5.73 (d, 1.8 Hz, 1H) H-1'; 5.61 (d, 8.2 Hz, 1H) H-5; 4.42 (m, 1H) H-4'; 4.13 (d, 1H) H-3'; 3.63 (d, 2H) H-5', H-5''; 3.48 (bs, 1H) H-2'; 2.62 (m, 1H) cyclohexyl -CH-; 1.77 (m, 4H) and 1.18 (m, 6H) -$(CH_2)_5$-.

^{13}C-NMR: ($CDCl_3$):δ 164.2, C-4; 150.8, C-2; 143.5, trityl; 141.4, C-6; 128.8, 128.2, 127.5, trityl; 101.5, C-5; 91.7, C-1'; 87.8, trityl; 82.0, C-4'; 76.4/68.9, C-2'/C-3'; 62.5, C-5'; 54.7, cyclohexyl -CH-; 34.1, 33.7, 26.1 and 25.2, -$(CH_2)_5$-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{34}H_{37}N_3O_5$: 568.2811, found 568.2849.

Compound 13c:

Yield: 61%

m.p: 114-115°C

^{1}H-NMR: ($CDCl_3$):δ 7.92 (d, 8.1 Hz, 1H) H-6; 7.45-7.17 (m, 15H) trityl; 6.11 (d, 4.7 Hz, 1H) H-1'; 5.37, (d, 8.2 Hz, 1H) H-5; 4.35 (m, 1H) H-2'; 3.81 (m, 1H) H-4'; 3.49 (m, 3H) H-3', H-5', H-5''; 2.48 (m, 1H) cyclohexyl -CH-; 1.81 (m, 4H) and 1.00 (m, 6H) -$(CH_2)_5$-.

^{13}C-NMR: ($CDCl_3$):δ 164.8, C-4; 151.3, C-2; 143.6, trityl; 142.6, C-6; 129.0, 128.2, 127.5, trityl; 101.3, C-5; 87.5, trityl; 85.9, C-1'; 82.3, C-4'; 76.3/61.1, C-2'/C-3'; 63.4, C-5'; 55.0, cyclohexyl -CH-; 33.8, 26.1 and 25.2, -$(CH_2)_5$-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{34}H_{37}N_3O_5$: 568.2811, found 568.2878.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-pyrrolidino-*xylo*- uridine 12d and 5'-O-trityl-3'-deoxy-3'-N-pyrrolidino-*ara*-uridine 13d:

A mixture of compound **11** (1mmol) and pyrrolidine (5mmol) in DMSO (3ml) was heated at 95°C for 5h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water

(3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12d:

Yield: 27%

m.p: 112-113°C

^{1}H-NMR: ($CDCl_3$):δ 7.83 (d, 8.2 Hz, 1H) H-6; 7.49-7.26 (m, 15H) trityl; 6.15 (d, 2.7 Hz, 1H) H-1'; 5.66 (d, 8.2 Hz, 1H) H-5; 4.44 (d, 3.3Hz, 1H) H-3'; 4.31 (m, 1H) H-4'; 3.56 (m, 2H) H-5', H-5''; 2.91 (d, 2.7 Hz, 1H) H-2'; 2.68 (m, 4H) $-CH_2-N-CH_2-$; 1.82 (bs, 4H) $-CH_2-CH_2-$.

^{13}C-NMR: ($CDCl_3$):δ 164.2, C-4; 150.5, C-2; 143.5, trityl; 142.1, C-6; 128.7, 128.2, 127.5, trityl; 102.2, C-5; 88.3, C-1'; 87.7, trityl; 81.1, C-4'; 78.2/74.8, C-2'/C-3'; 62.4, C-5'; 52.6, $-CH_2-N-CH_2-$; 23.4, $-CH_2-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_5$: 540.2498, found 540.2460.

Compound 13d:

Yield: 52%

m.p: 112-113°C

^{1}H-NMR: ($CDCl_3$):δ 7.76 (d, 8.1 Hz, 1H) H-6; 7.5-7.2 (m, 15H) trityl; 6.11 (d, 3.6 Hz, 1H) H-1'; 5.39 (d, 8.1 Hz, 1H) H-5; 4.67 (bs, 1H) H-2'; 4.2 (m, 1H) H-4'; 3.46 (m, 2H) H-5', H-5''; 2.95 (m, 1H) H-3'; 2.58 (m, 4H) $-CH_2-N-CH_2-$; 1.74 (bs, 4H) $-CH_2-CH_2-$.

^{13}C-NMR: ($CDCl_3$):δ 165.5, C-4; 150.9, C-2; 143.9, trityl; 143.4, C-6; 129.0, 128.1, 127.4, trityl; 100.7, C-5; 87.3/86.9, trityl/ C-1'; 80.9, C-4'; 73.3/71.7, C-2'/C-3'; 64.9, C-5'; 52.0, $-CH_2-N-CH_2-$; 23.5 $-CH_2-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_5$: 540.2498, found 540.2436.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-piperidino-*xylo*-uridine 12e and 5'-O-trityl-3'-deoxy-3'-N-piperidino-*ara*-uridine 13e:

A mixture of compound **11** (1mmol) and piperidine (5mmol) in DMSO (3ml) was heated at 90°C for 4h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12e:

Yield: 18%

m.p: 126-127°C

^{1}H-NMR: ($CDCl_3$):δ 7.71 (d, 8.2 Hz, 1H) H-6; 7.49-7.29 (m, 15H) trityl; 6.14 (d, 4.4 Hz, 1H) H-1'; 5.67 (d, 8.2 Hz, 1H) H-5; 4.48 (m, 1H) H-3'; 4.13 (m, 1H) H-4'; 3.51 (m, 2H) H-5', H-5''; 3.05 (m, 1H) H-2'; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.60 and 1.50 (m, 6H) -CH_2-CH_2-CH_2-.

^{13}C-NMR: ($CDCl_3$):δ 163.9, C-4; 150.5, C-2; 143.5, trityl; 142.0, C-6; 128.7, 128.2, 127.5, trityl; 102.9, C-5; 87.7, trityl; 85.8, C-1'; 81.1, C-4'; 79.2/72.8, C-2'/C-3'; 62.5, C-5'; 51.9, -CH_2-N-CH_2-; 25.9 and 24.3, -CH_2-CH_2-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{33}H_{35}N_3O_5$: 554.2655, found 554.2643.

Compound 13e:

Yield: 50%

m.p: 118°C

^{1}H-NMR: ($CDCl_3$):δ 7.82 (d, 8.0 Hz, 1H) H-6; 7.54-7.23 (m, 15H) trityl; 6.07 (d, 4.0 Hz, 1H) H-1'; 5.39 (d, 8.0 Hz, 1H) H-5; 4.81 (m, 1H) H-2'; 4.16 (m, 1H) H-4'; 3.45 (m, 2H) H-5', H-5''; 3.07 (m, 1H) H-3'; 2.56 (m, 4H) $-CH_2-N-CH_2-$; 1.56 (m, 6H) $-CH_2-CH_2-CH_2-$.

^{13}C-NMR: ($CDCl_3$):δ 165.4, C-4; 150.4, C-2; 143.6, trityl; 143.3, C-6; 128.7, 127.7, 127.0, trityl; 100.1, C-5; 86.8, trityl and C-1'; 78.4, C-4'; 73.4/70.0, C-2'/C-3'; 65.0, C-5'; 51.3, $-CH_2-N-CH_2-$; 26.0 and 24.3, $-CH_2-CH_2-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{33}H_{35}N_3O_5$: 554.2655, found 554.2561.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-morpholino-*xylo*- uridine 12f and 5'-O-trityl-3'-deoxy-3'-N-morpholino-*ara*-uridine 13f:

A mixture compound **11** (1mmol) and morpholine (5mmol) in DMSO (3ml) was heated at 90°C for 15h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12f:

Yield: 27%

m.p: 100-101°C

^{1}H-NMR: ($CDCl_3$):δ 7.74 (d, 8.1 Hz, 1H) H-6; 7.48-7.26 (m, 15H) trityl; 6.13 (d, 3.9 Hz, 1H) H-1'; 5.68 (d, 8.1 Hz, 1H) H-5; 4.49 (bs, 1H) H-3'; 4.16 (m, 1H) H-4'; 3.75 (m, 4H) $-CH_2-O-CH_2-$, 3.58 (ddd, 2H) H-5', H-5''; 2.95 (m, 1H) H-2'; 2.63 (m, 4H) $-CH_2-N-CH_2-$.

^{13}C-NMR: ($CDCl_3$):δ 164.0, C-4; 150.6, C-2; 143.5, trityl; 141.9, C-6; 128.8, 128.3, 127.6, trityl; 102.8, C-5; 87.9, trityl; 86.7, C-1'; 81.1, C-4'; 78.8/72.4, C-2'/C-3'; 66.9, $-CH_2-O-CH_2-$; 62.4, C-5'; 51.8, $-CH_2-N-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_6$: 556.2448, found 556.2473.

Compound 13f:

Yield: 52%

m.p. 126°C

^{1}H-NMR: ($CDCl_3$):δ 7.84 (d, 8.1 Hz, 1H) H-6; 7.53-7.23 (m ,15H) trityl; 6.06 (d, 4.0 Hz, 1H) H-1'; 5.42 (d, 8.1 Hz, 1H) H-5; 4.82 (bs, 1H) H-2'; 4.15 (m, 1H) H-4'; 3.70 (bs, 4H) -CH_2-O-CH_2-, 3.48 (m, 2H) H-5', H-5''; 3.07 (m, 1H) H-3'; 2.63 (m, 4H) -CH_2-N-CH_2-.

^{13}C-NMR: ($CDCl_3$):δ 165.3, C-4; 150.9, C-2; 143.9, trityl; 143.2, C-6; 128.9, 128.1, 127.4, trityl; 100.8, C-5; 87.4, trityl; 86.5, C-1'; 78.1, C-4'; 72.4/70.9, C-2'/C-3'; 67.2, -CH_2-O-CH_2-; 64.5, C-5'; 51.2, -CH_2-N-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_6$: 556.2448, found 556.2369.

Synthesis of 5'-O-trityl-2'-deoxy-2'-N-(ethyl *iso*nipecotatyl)-*xylo*-uridine 12g and 5'-O-trityl-3'-deoxy-3'-N-(ethyl *iso*nipecotatyl)-*ara*-uridine 13g:

A mixture of compound **11** (1mmol) and ethyl *iso*nipecotate (5mmol) in DMSO (3ml) was heated at 95°C for 7h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Compound 12g:

Yield: 26%

m.p: 105°C

^{1}H-NMR: ($CDCl_3$):δ 7.70 (d, 8.1 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 6.09 (d, 4.2 Hz, 1H) H-1'; 5.65 (d, 8.1 Hz, 1H) H-5; 4.44 (bs, 1H) H-3'; 4.12 (m, 3H) ethyl -CH_2- and H-4'; 3.53 (m, 2H) H-5', H-5''; 3.18 (m, 1H) H-2'; 3.04-1.67 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 1.26 (t, 3H) ethyl CH_3.

^{13}C-NMR ($CDCl_3$): δ 174.9 ethyl CO; 163.9, C-4; 150.4, C-2; 143.5, trityl; 141.8, C-6; 128.7, 128.2, 127.5, trityl; 102.8, C-5; 87.8, trityl; 86.1, C-1'; 81.0, C-4'; 78.6/72.7, C-2'/C-3'; 62.5, C-5'; 60.6, ethyl CH_2; 50.7 and 50.2, -CH_2-N-CH_2-; 40.9, nipecotyl -CH-; 28.2, nipecotyl -CH_2-; 14.3, ethyl -CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{36}H_{39}N_3O_7$: 626.2866, found 626.2812.

Compound 13g:

Yield: 52%

m.p: 105°C

^{1}H-NMR: ($CDCl_3$):δ 7.90 (d, 8.1 Hz, 1H) H-6; 7.50-7.25 (m, 15H) trityl; 6.04 (d, 4.7 Hz, 1H) H-1'; 5.39 (d, 8.1 Hz, 1H) H-5; 4.77 (m, 1H) H-2'; 4.14 (q, 2H) ethyl -CH_2-; 4.05 (m, 1H) H-4'; 3.45 (m, 2H) H-5', H-5''; 3.21 (m, 1H) H-3'; 2.96-1.69 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 1.26 (t, 3H) ethyl CH_3.

^{13}C-NMR: ($CDCl_3$):δ 175.1, ethyl CO; 165.4, C-4; 150.9, C-2; 143.8, trityl; 143.3, C-6; 128.9, 128.1, 127.4, trityl; 100.7, C-5; 87.2, trityl; 86.2, C-1'; 77.9, C-4'; 71.9/70.5, C-2'/C-3'; 64.5, C-5'; 60.5, ethyl -CH_2-; 51.9 and 48.5, -CH_2-N-CH_2-; 41.3, nipecotyl -CH-; 28.9 and 28.6, nipecotyl -CH_2-; 14.4, ethyl -CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{36}H_{39}N_3O_7$: 626.2866, found 626.2793.

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-anilino-*ara*-uridine 13h:

A mixture of compound **11** (1mmol) and aniline (10mmol) in DMSO (2ml) was heated at 95°C

for 42h and then at 110°C for 26h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Yield: 50%

m.p: 121-122°C

^{1}H-NMR ($CDCl_3$): δ 7.83 (d, 8.1 Hz, 1H) H-6; 7.79-7.23 (m, 15H) trityl; 7.15 (m, 2H) and 6.75 (m, 3H), anilino; 6.12 (d, 4.0 Hz, 1H) H-1'; 5.41 (d, 8.1 Hz, 1H) H-5; 4.40 (t, 1H) H-2'; 3.91 (m, 2H) H-3', H-4'; 3.56 (m, 2H) H-5', H-5''.

^{13}C-NMR ($CDCl_3$): δ 165.1, C-4; 151.2, C-2; 146.9, anilino; 143.7, trityl; 142.9, C-6; 129.6, 129.1, 128.3, 127.6, trityl; 118.5, 113.9, anilino; 101.2, C-5; 87.7, trityl; 86.5, C-1'; 82.8, C-4'; 75.7/61.3, C-2'/C-3'; 64.1, C-5'.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{34}H_{31}N_3O_5$: 562.2342, found 562.2320.

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-(*p*-methoxyanilino)-*ara*-uridine 13i:

A mixture of compound **11** (1mmol) and p-methoxyaniline (7mmol) in DMSO (3ml) was heated at 90°C for 29h and then at 110°C for 26h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with water (3x20 ml). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column.

Yield: 74%

m.p: 118-119°C

^{1}H-NMR: ($CDCl_3$):δ 7.80 (d, 8.1 Hz, 1H) H-6; 7.49-7.26 (m, 15H) trityl; 6.72 (m, 4H), anilino; 6.08 (d, 3.8 Hz, 1H) H-1'; 5.37 (d, 8.1 Hz, 1H) H-5; 4.42 (bs, 1H) H-2'; 3.88 (m, 2H) H-3'and

H-4'; 3.74 (s, 3H) OCH_3; 3.56 (m, 2H) H-5', H-5''.

^{13}C-NMR: ($CDCl_3$):δ 165.1, C-4; 152.8, anilino; 151.0, C-2; 143.7, trityl; 142.9, C-6; 140.9, anilino; 129.0, 128.1, 127.5, trityl; 115.4, 115.2, anilino; 101.0, C-5; 87.6, trityl; 86.5, C-1'; 82.8, C-4'; 75.4/62.1, C-2'/C-3'; 64.1, C-5'; 55.9, -OCH_3.

MS (FAB$^+$): $(M)^+$ calc. for $C_{35}H_{33}N_3O_6$: 591.2369, (peak overlaps with mass reference compound, PEG)

General procedure for the deprotection:

Compounds **12a-f**, **13a-f**, **13h-i** (approx. 0.5 mmol each) were dissolved in a mixture of methanol-water (10ml, 4:1v/v). The solution was applied to a column made of Amberlite IR-120 H+ (7cmx2.5cm settled volume) in water. In order to remove tritanol that was generated after deprotection, the column was eluted with methanol. Once all tritanol was eluted (tlc), the column was further eluted either with aqueous ammonia solution (3%; for compounds **12a-d**, **12f**, **13a-b**) or with a mixture of methanol-aqueous ammonia [30% aq. Ammonia (10ml) and methanol (90ml); for compounds **12e**, **13c-f**, **13h-i**]. *Ammonia solution must be added within 15m of loading the compounds on the column.*

2'-Deoxy-2'-N-isobutylamino-*xylo*- uridine 14a

Yield: 73%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.93 (d, 8.1 Hz, 1H) H-6; 5.87 (d, 8.4 Hz, 1H) H-5'; 5.84 (d, 3.2 Hz, 1H) H-1'; 4.33 (m, 2H) H-3', H-4'; 3.91 (m, 2H) H-5', H-5''; 3.33 (m, 1H) H-2'; 2.53 (d, 2H) isobutyl -CH_2-; 1.79 (m, 1H) isobutyl -CH-; 0.88 (d, 6H) isobutyl (-CH_3)$_2$.

^{13}C-NMR (D_2O): δ 166.8, C-4; 152.1, C-2; 142.9, C-6; 102.5, C-5; 90.3, C-1'; 83.8, C-4'; 74.5/71.6, C-2'/C-3'; 60.5, C-5'; 55.7, isobutyl -CH_2-; 27.7, isobutyl -CH-; 20.5, isobutyl (-CH_3)$_2$.

3'-Deoxy-3'-N-isobutylamino-*ara*-uridine 15a:

Yield: 64%

m.p: hygroscopic

^{1}H-NMR: ($D_2$0):δ 7.85 (d, 8.0 Hz, 1H) H-6; 6.12 (d, 4.8 Hz, 1H) H-1'; 5.85 (d, 8.1 Hz, 1H) H-5; 4.42 (m, 1H) H-2'; 3.89 (m, 1H) H-4', H-5', H-5" ; 3.12 (m, 1H) H-3'; 2.53 (m, 2H) isobutyl -CH_2-; 1.77 (m, 1H) isobutyl -CH-; 0.90 (d, 6H) isobutyl (-CH_3)$_2$.

^{13}C-NMR: ($CDCl_3$):δ 167.3, C-4; 152.7, C-2; 144.9, C-6; 102.3, C-5; 87.4, C-1'; 84.1, C-4'; 76.0/66.4, C-2'/C-3'; 63.3, C-5'; 56.9, isobutyl -CH_2-; 29.1, isobutyl -CH-; 22.1, 21.95, isobutyl (-CH_3)$_2$.

2'-Deoxy-2'-N-benzylamino-*xylo*- uridine 14b:

Yield: 75%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.76 (d, 8.1 Hz, 1H) H-6; 7.33 (m, 5H), aromatic; 5.83 (d, 3.5 Hz, 1H) H-1'; 5.74 (d, 8.1 Hz, 1H) H-5; 4.30 (m, 2H) H-3', H-4'; 3.88 (m, 4H) benzyl -CH_2-, H-5', H-5''; 3.30 (m, 1H) H-2'.

^{13}C-NMR (D_2O+DMSO-d_6): δ 166.6, C-4; 151.9, C-2; 142.8, C-6; 138.9, 129.6, 129.2, 128.4, aromatic; 102.6, C-5; 90.1, C-1'; 83.7, C-4'; 74.9/70.2, C-2'/C-3'; 60.6, C-5'; 51.6, benzyl -CH_2-.

3'-Deoxy-3'-N-benzylamino-*ara*-uridine 15b:

Yield: 65%

m.p: 182-183°C

^{1}H-NMR: (D_2O+DMSO-d_6):δ 7.91 (d, 8.1 Hz, 1H) H-6; 7.46 (m, 5H) aromatic; 6.20 (d, 4.6 Hz, 1H) H-1'; 5.78 (d, 8.1 Hz, 1H) H-5; 4.50 (t, 1H) H-2'; 4.00 (m, 5H) H-4', H-5', H-5''and benzyl -CH_2-; 3.27 (m, 1H) H-3'.

^{13}C-NMR: (D_2O+DMSO-d_6):δ 166.3, C-4; 152.1, C-2; 144.6, C-6; 140.8, 130.0, 129.9, 128.7, aromatic; 101.6, C-5; 87.2, C-1'; 84.3, C-4'; 75.6/65.8, C-2'/C-3'; 63.1, C-5'; 52.3, benzyl -CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{16}H_{19}N_3O_5$: 334.1403, found 334.1429.

2'-Deoxy-2'-N-cyclohexylamino-*xylo*-uridine 14c:

Yield: 79%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.94 (d, 8.1 Hz, 1H) H-6; 5.87 (m, 2H) H-1', H-5; 4.32 (m, 2H) H-4', H-3'; 3.93 (d, 2H) H-5', H-5''; 3.59 (d, 1H) H-2'; 2.73 (m, 1H) cyclohexyl -CH-; 1.70 and 1.18 (m, 10H) -$(CH_2)_5$-.

^{13}C-NMR: (D_2O):δ 166.9, C-4; 152.2, C-2; 142.9, C-6; 102.8, C-5; 90.3, C-1'; 83.7, C-4'; 74.9/67.9, C-2'/C-3'; 60.6, C-5'; 55.5, cyclohexyl -CH-; 32.8, 32.4, 26.1 and 25.4, -$(CH_2)_5$-.

3'-Deoxy-3'-N-cyclohexyl-amino-*ara*-uridine 15c:

Yield: 66%

m.p: 191-193°C

^{1}H-NMR: (D_2O+DMSO-d_6):δ 7.70 (d, 8.1 Hz, 1H) H-6; 5.92 (d, 4.7 Hz, 1H) H-1'; 5.63, (d, 8.1 Hz, 1H) H-5; 4.12 (m, 1H) H-2'; 3.65 (m, 3H) H-4', H-5', H-5''; 3.11 (m, 1H) H-3'; 2.49 (m, 1H) cyclohexyl -CH-; 1.60 (m, 4H) and 0.96 (m, 6H) -$(CH_2)_5$-.

^{13}C-NMR (D_2O+DMSO-d_6): δ 166.2, C-4; 152.1, C-2; 144.5, C-6; 101.6, C-5; 86.8, C-1'; 84.3, C-4'; 76.3/62.7, C-2'/C-3'; 62.7, C-5'; 55.6, cyclohexyl -CH-; 34.4, 33.6, 27.1 and 26.2, -$(CH_2)_5$-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{15}H_{23}N_3O_5$: 326.1716, found 326.1731.

2'-Deoxy-2'-N-pyrrolidino-*xylo*- uridine 14d:

Yield: 80%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.91 (d, 8.1 Hz, 1H) H-6; 6.06 (d, 4.1 Hz, 1H) H-1'; 5.91 (d, 8.1 Hz, 1H) H-5; 4.53 (m, 1H) H-3'; 4.23 (m, 1H) H-4'; 3.90 (m, 2H) H-5', H-5''; 3.06 (m, 1H) H-2'; 2.70 (m, 4H) -CH_2-N-CH_2-; 1.80 (bs, 4H) -CH_2-CH_2-.

^{13}C-NMR: (D_2O):δ 166.9, C-4; 152.1, C-2; 143.2, C-6; 103.4, C-5; 88.0, C-1'; 82.9, C-4'; 77.8/73.9, C-2'/C-3'; 60.6, C-5'; 52.9, -CH_2-N-CH_2-; 23.3, -CH_2-CH_2-.

3'-Deoxy-3'-N-pyrrolidino-*ara*-uridine 15d:

Yield: 73%

m.p: 218-220°C

^{1}H-NMR: (D_2O+DMSO-d_6):δ 7.70 (d, 8.1 Hz, 1H) H-6; 5.88 (d, 4.5 Hz, 1H) H-1'; 5.64 (d, 8.1 Hz, 1H) H-5; 4.39 (m, 1H) H-2'; 3.91 (m, 1H) H-4'; 3.63 (m, 2H) H-5', H-5''; 2.74 (m, 1H) H-3'; 2.53 (m, 4H) -CH_2-N-CH_2-; 1.67 (m, 4H) -CH_2-CH_2-.

^{13}C-NMR: (D_2O+DMSO-d_6):δ 165.3, C-4; 151.7, C-2; 144.2, C-6; 101.1, C-5; 86.5, C-1'; 82.5, C-4'; 7??.8/72.0, C-2'/C-3'; 63.1, C-5'; 52.8, -CH_2-N-CH_2-; 23.9 -CH_2-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{13}H_{19}N_3O_5$: 298.1403, found 298.1377.

2'-Deoxy-2'-N-piperidino-*xylo*-uridine 14e:

Yield: 77%

m.p: hygroscopic

^{1}H-NMR: (D_2O+DMSO-d_6):δ 7.87 (d, 8.2 Hz, 1H) H-6; 6.12 (d, 5.4 Hz, 1H) H-1'; 5.93 (d, 8.2 Hz, 1H) H-5; 4.57 (m, 1H) H-3'; 4.14 (m, 1H) H-4'; 3.87 (m, 2H) H-5', H-5''; 3.11 (m, 1H) H-2'; 2.58 (m, 4H) -CH_2-N-CH_2-; 1.52 (m, 6H) -CH_2-CH_2-CH_2-.

^{13}C-NMR: (D_2O+DMSO-d_6):δ 165.5, C-4; 151.8, C-2; 143.3, C-6; 103.9, C-5; 85.9, C-1'; 83.6, C-4'; 79.9/72.4, C-2'/C-3'; 61.1, C-5'; 52.8, -CH_2-N-CH_2-; 26.4 and 25.0, -CH_2-CH_2-CH_2-.

3'-Deoxy-3'-N-piperidino-*ara*-uridine 15e:

Yield: 71%

m.p: 213-214°C

^{1}H-NMR: (D_2O+DMSO-d_6):δ 7.94 (d, 8.2 Hz, 1H) H-6; 6.05 (d, 4.3 Hz, 1H) H-1'; 5.90 (d, 8.2 Hz, 1H) H-5; 4.63 (m, 1H) H-2'; 4.22 (m, 1H) H-4'; 3.89 (m, 2H) H-5', H-5''; 2.98 (m, 1H) H-3'; 2.70 (m, 4H) -CH_2-N-CH_2-; 1.66 (m, 6H) -CH_2-CH_2-CH_2-.

^{13}C-NMR: (D_2O+DMSO-d_6):δ 165.6, C-4; 151.8, C-2; 144.3, C-6; 101.2, C-5; 87.1, C-1'; 80.4, C-4'; 73.9/71.3, C-2'/C-3'; 63.7, C-5'; 52.4, -CH_2-N-CH_2-; 26.6 and 25.1, -CH_2-CH_2-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{14}H_{21}N_3O_5$: 312.1559, found 312.1540.

2'-Deoxy-2'-N-morpholino-*xylo*- uridine 14f:

Yield: 83%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.90 (d, 8.2 Hz, 1H) H-6; 6.13 (d, 5.2 Hz, 1H) H-1'; 5.95 (d, 8.2 Hz, 1H) H-5; 4.62 (m, 1H) H-3'; 4.18 (m, 1H) H-4'; 3.89 (m, 2H) H-5', H-5''; 3.77 (m, 4H) -CH_2-O-CH_2-; 3.14 (m, 1H) H-2'; 2.76 (m, 4H) -CH_2-N-CH_2-.

^{13}C-NMR: (D_2O):δ 166.5, C-4; 151.9, C-2; 143.0, C-6; 103.7, C-5; 87.5, C-1'; 82.7, C-4'; 78.3/71.6, C-2'/C-3'; 66.7, -CH_2-O-CH_2-; 60.6, C-5'; 51.4, -CH_2-N-CH_2-.

3'-Deoxy-3'-N-morpholino-*ara*-uridine 15f:

Yield: 75%

m.p: 126°C

^{1}H-NMR: (DMSO-d6+D_2O):δ 7.69 (d, 8.1 Hz, 1H) H-6; 5.82 (d, 4.9 Hz, 1H) H-1'; 5.57 (d, 8.1 Hz, 1H) H-5; 4.33 (t, 1H) H-2'; 3.87 (m, 1H) H-4'; 3.55 (m, 6H) -CH_2-O-CH_2-, H-5', H-5''; 2.77 (m, 1H) H-3'; 2.49 (m, 4H) -CH_2-N-CH_2-.

^{13}C-NMR: (DMSO-d6+D_2O):δ 165.0, C-4; 151.5, C-2; 143.9, C-6; 101.0, C-5; 86.1, C-1'; 79.6, C-4'; 72.6/70.9, C-2'/C-3'; 67.4, -CH_2-O-CH_2-; 62.9, C-5'; 51.7, -CH_2-N-CH_2-.

MS (FAB^+): $(M+H)^+$ calc. for $C_{13}H_{19}N_3O_6$: 314.1352, found 314.1341.

3'-Deoxy-3'-N-anilino-*ara*-uridine 15h:

Yield: 53%

m.p. >230°C

^{1}H-NMR: (DMSO-d6+D_2O):δ 7.73 (d, 8.1 Hz, 1H) H-6; 7.08 (t, 2H) and 6.59 (m, 3H), anilino; 5.97 (d, 4.2 Hz, 1H) H-1'; 5.59 (d, 8.1 Hz, 1H) H-5; 4.01 (m, 1H) H-2'; 3.85 (m, 1H) H-4'; 3.64 (m, 3H) H-3', H-5', H-5''.

^{13}C-NMR: (DMSO-d6+D_2O):δ 164.7, C-4; 151.3, C-2; 148.4, anilino; 143.5, C-6; 130.0, 117.7,

113.6, anilino; 100.9, C-5; 86.3, C-1'; 83.7, C-4'; 74.7/61.1, C-2'/C-3'; 62.3, C-5'.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{15}H_{17}N_3O_5$: 320.1246, found 320.1277.

3'-Deoxy-3'-N-(*p*-methoxyanilino)-*ara*-uridine 15i:

Yield: 64%

m.p. >230°C

^{1}H-NMR: (DMSO-d6+D_2O):δ 7.70 (d, 8.1 Hz, 1H) H-6; 6.67 (m, 4H), anilino; 5.99 (d, 4.0 Hz, 1H) H-1'; 5.58 (d, 8.1 Hz, 1H) H-5; 3.99 (bs, 1H) H-2'; 3.85 (m, 1H) H-4'; 3.63 (bs, 6H) OCH_3, H-3', H-5', H-5''.

^{13}C-NMR: (DMSO-d6+D_2O):δ 164.5, C-4; 152.2, anilino; 151.2, C-2; 143.5, anilino; 142.5, C-6; 115.6, 114.8, anilino; 100.8, C-5; 86.4, C-1'; 83.9, C-4'; 74.6/61.9, C-2'/C-3'; 62.4, C-5'; 56.3, -OCH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{16}H_{19}N_3O_6$: 350.1352, found 350.1359.

Synthesis of 5'-O-trityl-2'-O-acetyl-3'-deoxy-3'-N-(N-acetyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecanyl)-*ara*- uridine 16:

A mixture of compound **11** (0.5mmol) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (1.5mmol) in DMSO (2ml) was heated at 120°C for 12h. The reaction mixture was diluted with ethyl acetate (30ml) and washed with water (3x10 ml). The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on basic alumina column. The mixture of products was dissolved in pyridine (10ml) and acetic anhydride (3mmol) was added dropwise at room temperature. After 24h pyridine was removed under reduced pressure by coevaporation with toluene. The solid residue was dissolved in ethyl acetate (25ml) and the organic layer was washed with

saturated aqueous sodium bicarbonate followed by water (3x10ml each). The ethyl acetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified on silica gel.

Yield: 28%

m.p: 95°C

^{1}H-NMR: ($CDCl_3$):δ 7.78 (d, 8.1 Hz, 1H) H-6; 7.47-7.27 (m, 15H) trityl; 6.21 (d, 5.5 Hz, 1H) H-1'; 5.62 (m, 1H) H-2'; 5.43 (d, 8.1 Hz, 1H) H-5; 3.96 (m, 1H) H-4'; 3.74-3.40 and 2.87 (m, 27H) H-3', H-5', H-5'' and diazacyclooctadecanyl; 2.11 (s, 3H) ester -CH_3; 2.0 (s, 3H) amide -CH_3.

^{13}C-NMR ($CDCl_3$): δ 171.0, ester CO; 169.1, amide CO; 163.5, C-4; 150.1, C-2; 143.5, trityl; 141.3, C-6; 128.8, 128.1, 127.5, trityl; 101.3, C-5; 87.2, trityl; 83.7, C-1'; 78.5, C-4'; 72.6, C-2'; 71.3, 71.2, 71.0, 70.7, 70.4, 69.8, diazacyclooctadecanyl; 68.2, C-3'; 62.5, C-5'; 52.3, 49.9, 47.0, diazacyclooctadecanyl; 21.7, ester -CH_3; 20.7, amide -CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{42}H_{52}N_4O_{10}$: 815.3867, found 815.3795.

3', 5'-Di-O-acetyl-2'-deoxy-2'-N-(ethyl *iso*nipecotatyl)-*xylo*-uridine 17:

A solution of compound **12g** (0.56 mmol) in aqueous acetic acid (80%, 10 ml) was heated at 100oC for 0.5h. Acetic acid was removed under reduced pressure and coevaporated twice with ethanol. The solid residue was triturated with ether to remove tritanol. The compound thus obtained was dissolved in dry pyridine (15 ml) and acetic anhydride (3mmol) was added dropwise at ambient temperature. The solution was stirred at room temperature overnight. After adding ice-cold water to the reaction mixture, pyridine was removed under reduced pressure and coevaporated twice with toluene. The oily material was partitioned between ethyl acetate and saturated sodium hydrogencarbonate solution. The organic layer was separated, dried over sodium sulphate and evaporated to dryness. The residue was purified by column chromatography on silica gel.

Yield: 60%

m.p: hygroscopic

^{1}H-NMR: ($CDCl_3$):δ 7.47 (d, 8.2 Hz, 1H) H-6; 6.19 (d, 4.6 Hz, 1H) H-1'; 5.80 (d, 8.2 Hz, 1H) H-5; 5.55 (m, 1H) H-3'; 4.35 (t, 1H) H-4'; 4.28 (d, 1H) and 4.11 (m, 3H) ethyl -CH_2-, H-5', H-5''; 3.02-1.82 (m, 10H) H-2, -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 1.23 (t, 3H) ethyl CH_3.

^{13}C-NMR: ($CDCl_3$):δ 174.7 ethyl CO; 170.5, 169.4 2xacetyl CO; 163.5, C-4; 150.3, C-2; 139.8, C-6; 103.3, C-5; 85.2, C-1'; 78.1, C-4'; 76.4/72.7, C-2'/C-3'; 61.5/60.4, C-5'/ethyl CH_2; 50.7 and 50.2, -CH_2-N-CH_2-; 40.6, nipecotyl -CH-; 28.0, nipecotyl -CH_2-; 20.8, 2xacetyl -CH_3; 14.2, ethyl -CH_3.

2', 5'-Di-O-acetyl-3'-deoxy-3'-N-(ethyl *iso*nipecotatyl)-*ara*-uridine 18:

Compound **13g** (0.7 mmol) was deprotected and acetylated as above.

Yield: 77%

m.p: hygroscopic

^{1}H-NMR: ($CDCl_3$):δ 7.48 (d, 8.2 Hz, 1H) H-6; 6.10 (d, 4.6 Hz, 1H) H-1'; 5.72 (d, 8.1 Hz, 1H) H-5; 5.57 (m, 1H) H-2'; 4.34 (m, 2H) and 4.17 (m, 3H), ethyl -CH_2-, H-4', H-5', H-5''; 3.05 (m, 1H) H-3'; 2.90-1.74 (m, 9H) -CH_2-N-CH_2-, -CH_2-CH-CH_2-; 2.12 and 1.99 (2xs, 6H) 2xacetyl -CH_3; 1.24 (t, 3H) ethyl CH_3.

^{13}C-NMR: ($CDCl_3$):δ 174.6, ethyl CO; 170.7, 168.9, 2xacetyl CO; 163.5, C-4; 150.1, C-2; 140.8, C-6; 101.5, C-5; 84.7, C-1'; 76.6, C-4'; 71.6/71.2, C-2'/C-3'; 64.6/60.5, C-5'/ethyl -CH_2-; 51.7 and 48.4, -CH_2-N-CH_2-; 40.7, nipecotyl -CH-; 28.3 and 28.1, nipecotyl -CH_2-; 20.8 and 20.6, 2xacetyl -CH_3; 14.2, ethyl -CH_3.

Synthesis of 3',5'-di-O-acetyl-2'-piperidino-2'-deoxy-*xylo*uridine 20 and **Synthesis of 2',5'-di-O-acetyl-3'-piperidino-3'-deoxy-*ara*uridine 21:**

A mixture compound **19** (1mmol) and piperidine (5mmol) in DMSO was heated at 90°C for 2h. Excess amine was removed under reduced pressure and the mixture of products was purified over silica gel. The column pure material was then dissolved in dry pyridine (15ml) and acetic anhydride (40mmol) was added dropwise and the reaction mixture was stirred at room temperature for 2 days. Excess acetic anhydride was quenched by addition of ice cold water and pyridine was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate (50ml) and water (2x25ml). The ethyl acetate part was dried over sodium sulphate, filtered and the filtrate was evaporated to dryness. The residue was purified over silica gel.

Yield: 64% (For two steps).

Synthesis of 5'-O-trityl-2,2'-O-anhydro-3'-deoxy-3'-N-pyrrolidinouridine 22d:

To a solution of compounds **12d** and **13d** (2mmol) in dry pyridine (10ml), methanesulphonyl chloride (10mmol) in dry pyridine (10ml) was added dropwise at 0°C. The reaction mixture was left at +4°C overnight. Pyridine was removed in vacuo and residual pyridine was removed by coevaporation with toluene. The oily residue was dissolved in dichloromethane (100ml) and washed with saturated aqueous sodium bicarbonate solution (3x25ml). The organic layer was dried over sodium sulphate, filtered and evaporated to dryness. The dark brown residue was dissolved in dry pyridine (20ml) and the solution was heated under reflux for 6h. The reaction mixture was cooled and pyridine was removed by co-evaporation with toluene. The product was purified by column chromatography on silica gel.

Yield: 64%

m.p. 85°C

^{1}H-NMR: ($CDCl_3$):δ 7.44-7.21 (m, 16H) H-6 and trityl; 6.1 (d, 5.9 Hz, 1H) H-1'; 5.98 (d, 7.4 Hz, 1H) H-5; 5.28 (dd, 6.2 Hz and 1.8 Hz, 1H) H-2'; 4.48 (m, 1H) H-4'; 3.35 (m, 1H) H-3'; 3.07 (d, 2H) H-5', H-5''; 2.56 (m, 4H) -CH_2-N-CH_2-; 1.81 (bs, 4H) -CH_2-CH_2-.

^{13}C-NMR: ($CDCl_3$):δ 171.8, C-4; 159.4, C-2; 143.4, trityl; 134.8, C-6; 128.5, 128.1, 127.4, trityl; 110.2, C-5; 90.4, C-1'; 87.1, trityl; 86.1, C-2'; 83.9, C-4'; 70.1, C-3'; 64.0, C-5'; 51.5, $-CH_2-N-CH_2-$; 23.5 $-CH_2-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{32}H_{31}N_3O_4$: 522.2393, found 522.2382.

Synthesis of 5'-O-trityl-2,2'-O-anhydro-3'-deoxy-3'-N-piperidinouridine 22e:

The product was synthesised and purified as described in case of compound **22d**.

Yield: 53%

m.p. 109°C

^{1}H-NMR: ($CDCl_3$): δ 7.43-7.20 (m, 16H) H-6 and trityl; 6.05 (d, 5.9 Hz, 1H) H-1'; 5.94 (d, 7.4 Hz, 1H) H-5; 5.32 (dd, 5.9 Hz, 1H) H-2'; 4.47 (m, 1H) H-4'; 3.37 (m, 1H) H-3'; 3.05 (m, 2H) H-5', H-5''; 2.43 (m, 4H) $-CH_2-N-CH_2-$; 1.60 and 1.44 (m, 4H) $-CH_2-CH_2-CH_2-$.

^{13}C-NMR: ($CDCl_3$): δ 171.9, C-4; 159.5, C-2; 143.4, trityl; 134.8, C-6; 128.6, 128.1, 127.5, trityl; 110.3, C-5; 90.6, C-1'; 87.2, trityl; 84.7, C-2'; 81.8, C-4'; 72.1, C-3'; 64.4, C-5'; 51.2, $-CH_2-N-CH_2-$; 25.7 and 23.8 $-CH_2-CH_2-CH_2-$.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{33}H_{33}N_3O_4$: 536.2549, found 536.2501.

Synthesis of 1-(5-O-trityl-2,3-dideoxy-2-S-thiophenyl-3-N-pyrrolidino-β-D-ribofuranosyl)-uracil 23:

To a solution of thiophenol (10mmol) in DMSO, tetramethylguanidine (12mmol) was added. After 15m at room temperature, compound **22d** (1mmol) was added to the solution. The reaction mixture was heated at 100°C for 30h. The dark brown solution was cooled to room temperature and ethyl acetate (25ml) was added. The organic layer was washed with water (3x10ml), separated and dried over sodium sulphate, filtered and evaporated to dryness. The product was purified by column chromatography on silica gel.

Yield: 27%

m.p. 104°C

^{1}H-NMR: ($CDCl_3$):δ 7.71 (d, 8.2 Hz) H-6; 7.55-7.23 (m, 20H) trityl and thiophenyl; 6.24 (d, 6.2 Hz, 1H) H-1'; 5.02 (d, 8.1 Hz, 1H) H-5; 4.37 (m, 1H) H-4'; 4.11 (t, 1H) H-2'; 3.85 (m, 1H) H-3'; 3.63 (dd, 1H) and 3.39 (dd, 1H) H-5', H-5''; 2.69 (m, 4H) -CH_2-N-CH_2-; 1.80 (bs, 4H) -CH_2-CH_2-.

^{13}C-NMR: ($CDCl_3$):δ 163.1, C-4; 150.2, C-2; 143.2, trityl; 140.1, C-6; 133.7, 133,1, 129.2, thiophenyl; 128.9, 128.2, 127.7, trityl; 102.3, C-5; 90.4, C-1'; 87.9, trityl; 79.5, C-4'; 66.0, C-5'; 63.5/57.0 C-2'/C-3'; 50.9, -CH_2-N-CH_2-; 23.7 -CH_2-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{38}H_{37}N_3O_4S$: 632.2583, found 632.2481.

Synthesis of 1-(5-O-trityl-2,3-dideoxy-2,3-N-*iso*butylepimino-β-D-*ribo*furanosyl)-uracil 24:

A mixture of compounds **12a** and **13a** (1mmol), triphenylphosphine (1.5mmol) and diisobutyl diazodicarboxylate (2mmol) in dichloromethane (10ml) was stirred at room temperature for 8h under nitrogen. Dichloromethane was removed under reduced pressure and the compound was purified by column chromatography on silica gel.

Yield: 65%

m.p. 89-90°C

^{1}H-NMR: ($CDCl_3$):δ 7.63 (d, 8.1 Hz, 1H) H-6; 7.47-7.24 (m, 15H) trityl; 5.9 (s, 1H) H-1'; 5.13 (d, 8.1 Hz, 1H) H-5; 4.34 (t, 1H) H-4'; 3.35 (ddd, 2H) H-5', H-5''; 2.7 (d, 4.7Hz, 1H)/2.58 (d, 4.7Hz, 1H) H-2'/H-3'; 2.22 (m, 2H) -N-CH_2-; 1.9 (m, 1H) amino -CH-; 0.99 (d, 6H) amino $(CH_3)_2$.

^{13}C-NMR: ($CDCl_3$):δ 163.9, C-4; 150.7, C-2; 143.2, trityl; 140.9, C-6; 128.7, 128.1, 127.5, trityl; 101.8, C-5; 87.5, trityl; 86.8, C-1'; 81.9, C-4'; 65.9/64.4, C-5'/-N-CH_2-; 48.8/46.2,

C-2'/C-3'; 29.1, amino -CH-; 20.9, amino -$(CH_3)_2$.

MS (FAB^+): $(M+H)^+$ calc. for $C_{32}H_{33}N_3O_4$: 524.2549, found 524.2499.

Synthesis of 3'-deoxy-5'-O-trityl-3'-[N-{1-(thymine-1-yl)-1,2,5-trideoxy-3-O-trityl-β-D-erythro-pentofuranos-5-yl}-pipereazino] *ara*uridine 27:

To a solution of compound **25** (1mmol) in DMF(2ml) piperazine (5mmol) was added and the reaction mixture was stirred for 2 days. The reaction mixture was diluted with ethyl acetate (70ml) and washed with water. The ethyl acetate part was dried over sodium sulphate and was evaporated to dryness. The solid residue was purified over basic alumina column to produce compound **26** (64%). A mixture of compound **26** and **11a** was dissolved in DMSO (2ml) and heated at 90°C for 16h. The reaction mixture was diluted with ethyl acetate and washed with water. The ethyl acetate part was dried over sodium sulphate and evaporated to dryness. The product was purified over silica gel column. Yield=29%.

^{1}H-NMR: ($CDCl_3$):δ 8.0 (d,1H); 7.60-7.25 (m,31H); 6.25 (t,1H); 6.0 (d,1H); 4.65 (m,1H), 3.98 (m,3H); 3.55-3.25 (m,3H); 2.82-2.05 (m,11H); 1.80 (s,3H), 1.62 (m,1H).

Synthesis of 4-(1-Oxo-3-(morpholinyl)-2-propenyl)-morpholine 45 from 2',3',5'-tri-O-mesyluridine 44a:

2',3',5'-Tri-O- mesyluridine (1mmol) was treated with neat morpholine (3ml) at ambient temperature for 24h. The amine was removed under reduced pressure and the compound was purified by column chromatography on basic alumina.

^{1}H-NMR ($CDCl_3$): δ 7.45 (d, 12.6 Hz, 1H) H-3; 4.99 (d, 12.6 Hz, 1H) H-2; 3.73-3.53 (m, 12H) and 3.19 (t, 4H) morpholine.

^{13}C-NMR ($CDCl_3$): δ 168.1, CO; 151.6, C-3; 84.9, C-2; 66.8 and 66.2, H_2C-O-CH_2; 48.7 and 44.1, H_2C-N-CH_2.

MS (EI): m/z 226 (M^+, 25%); 140 (M^+ - morpholinyl, 100%).

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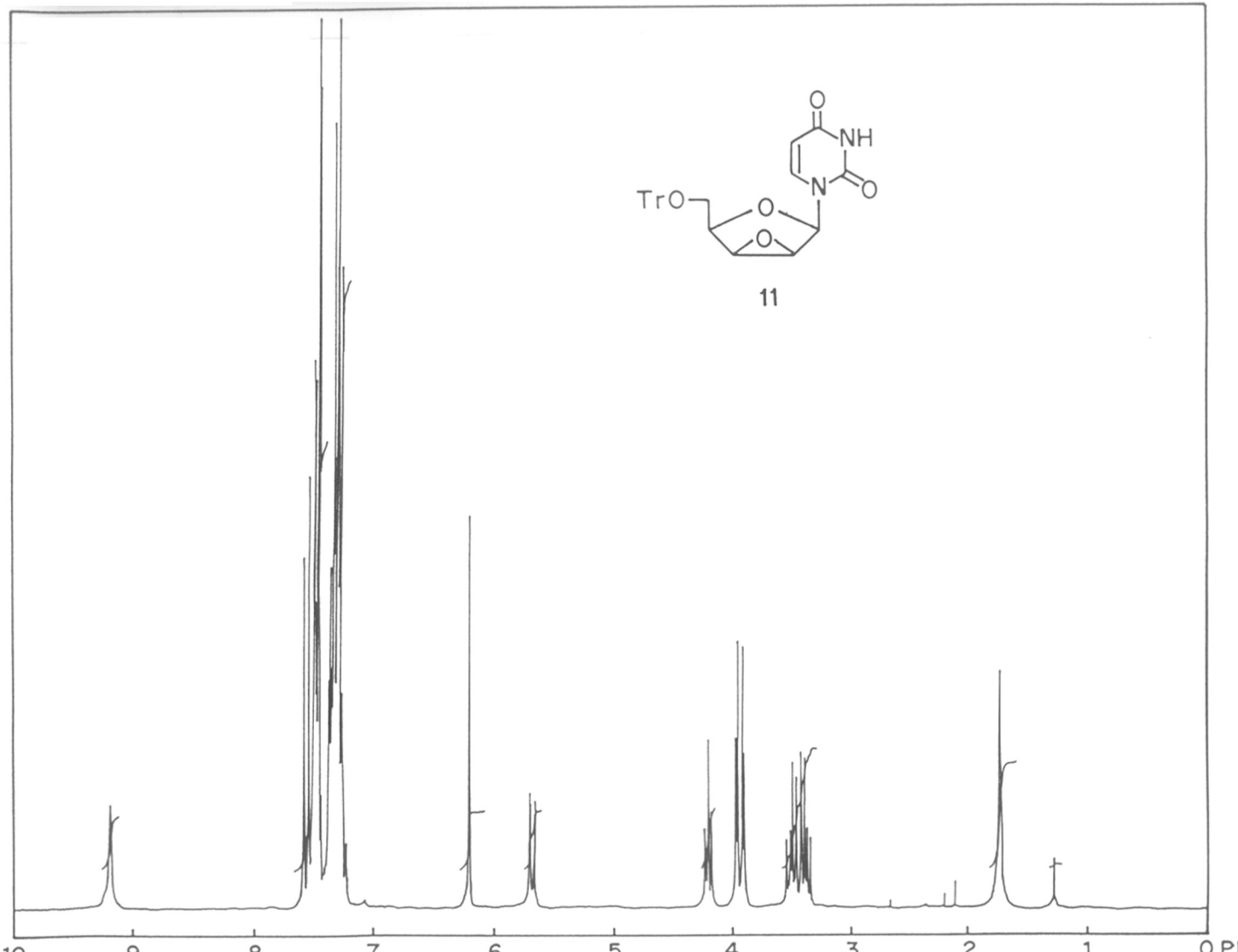
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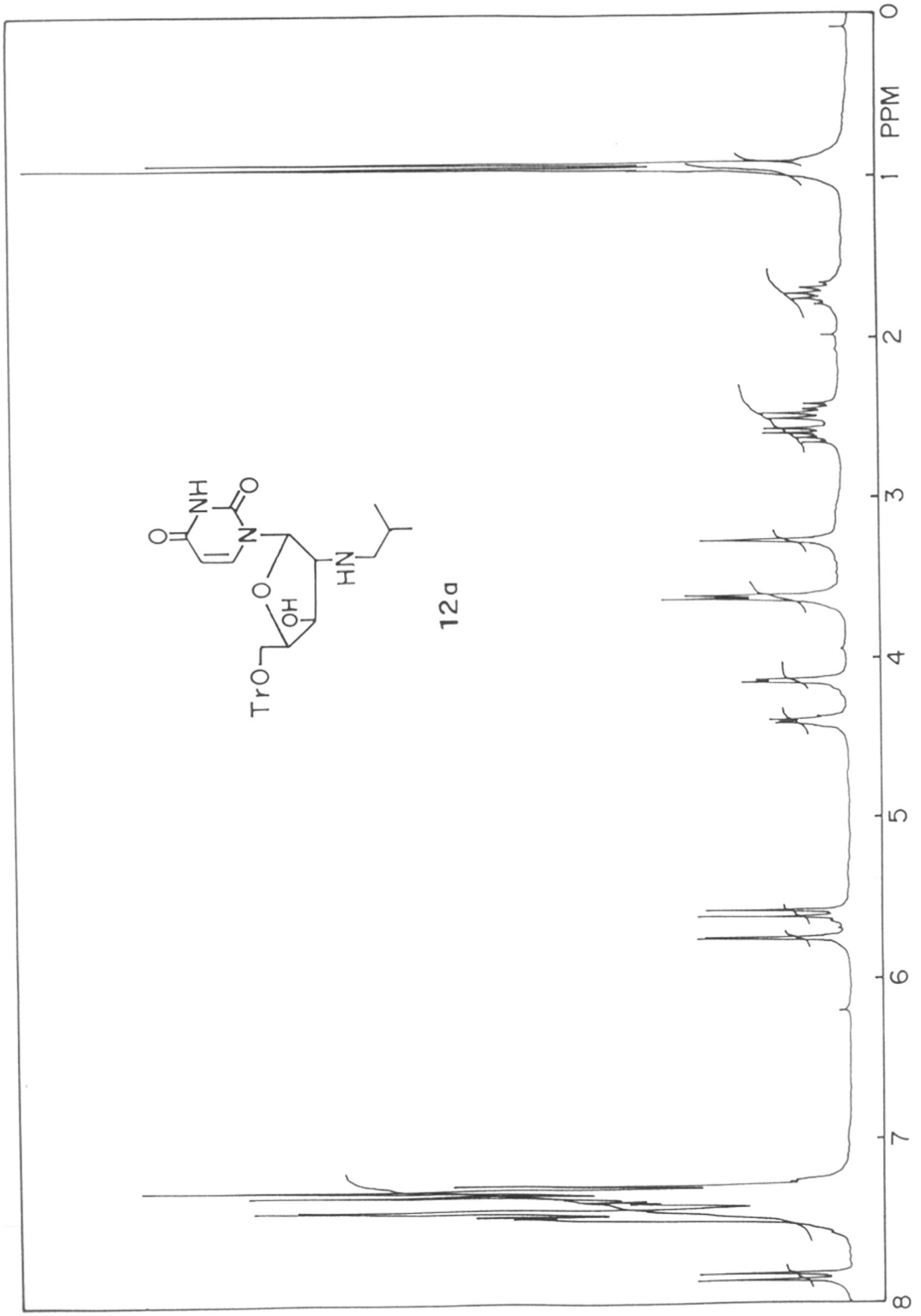

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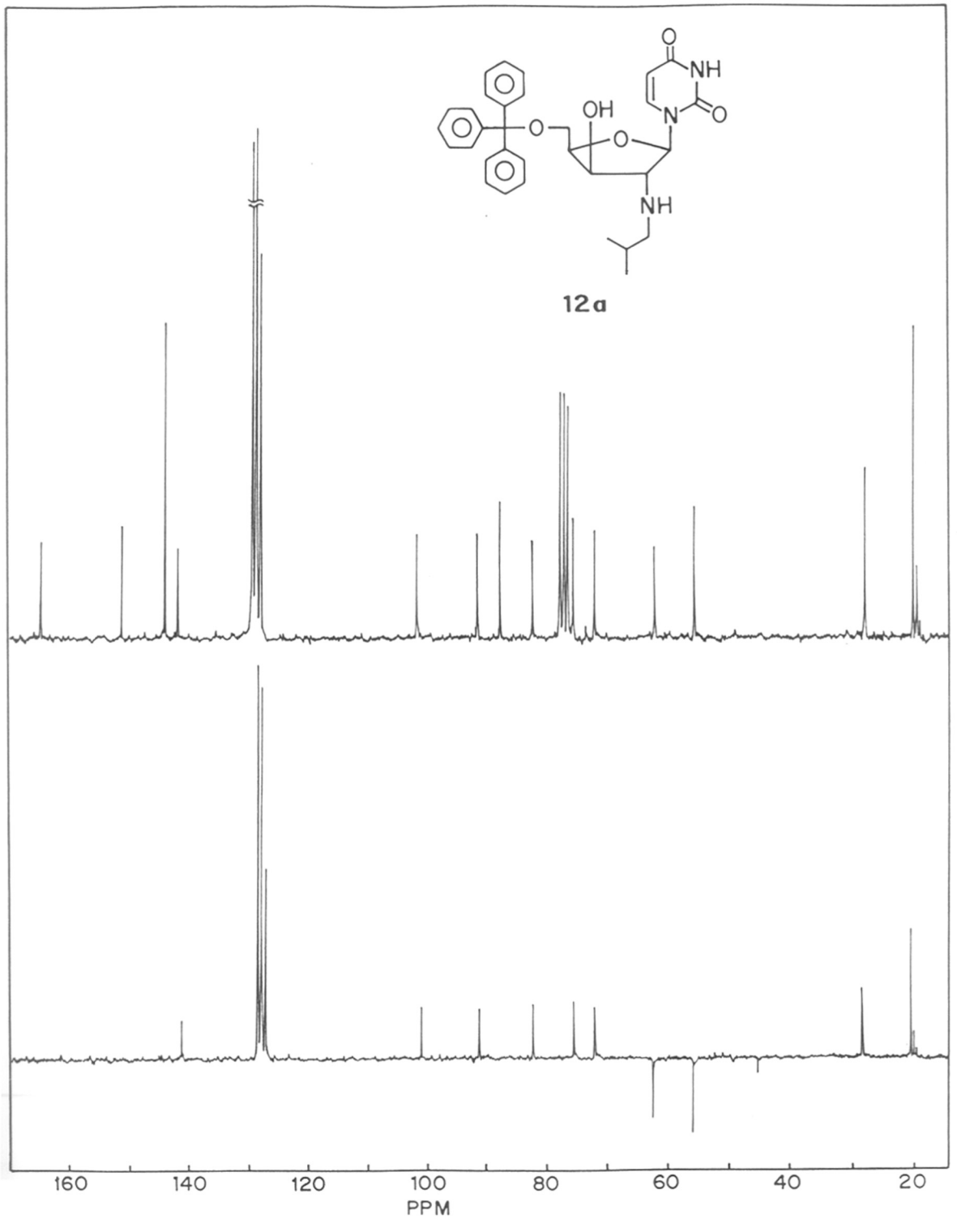

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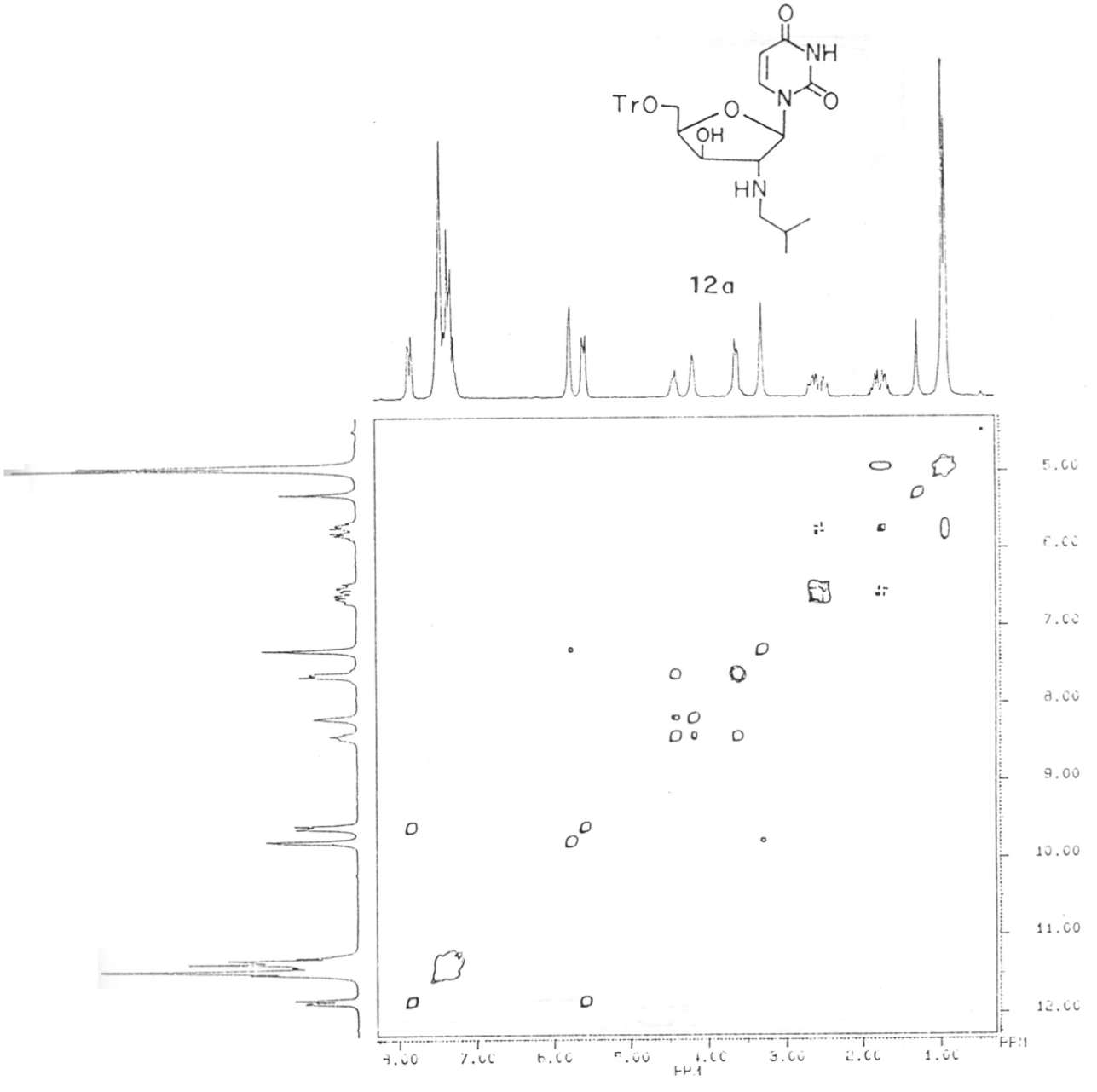
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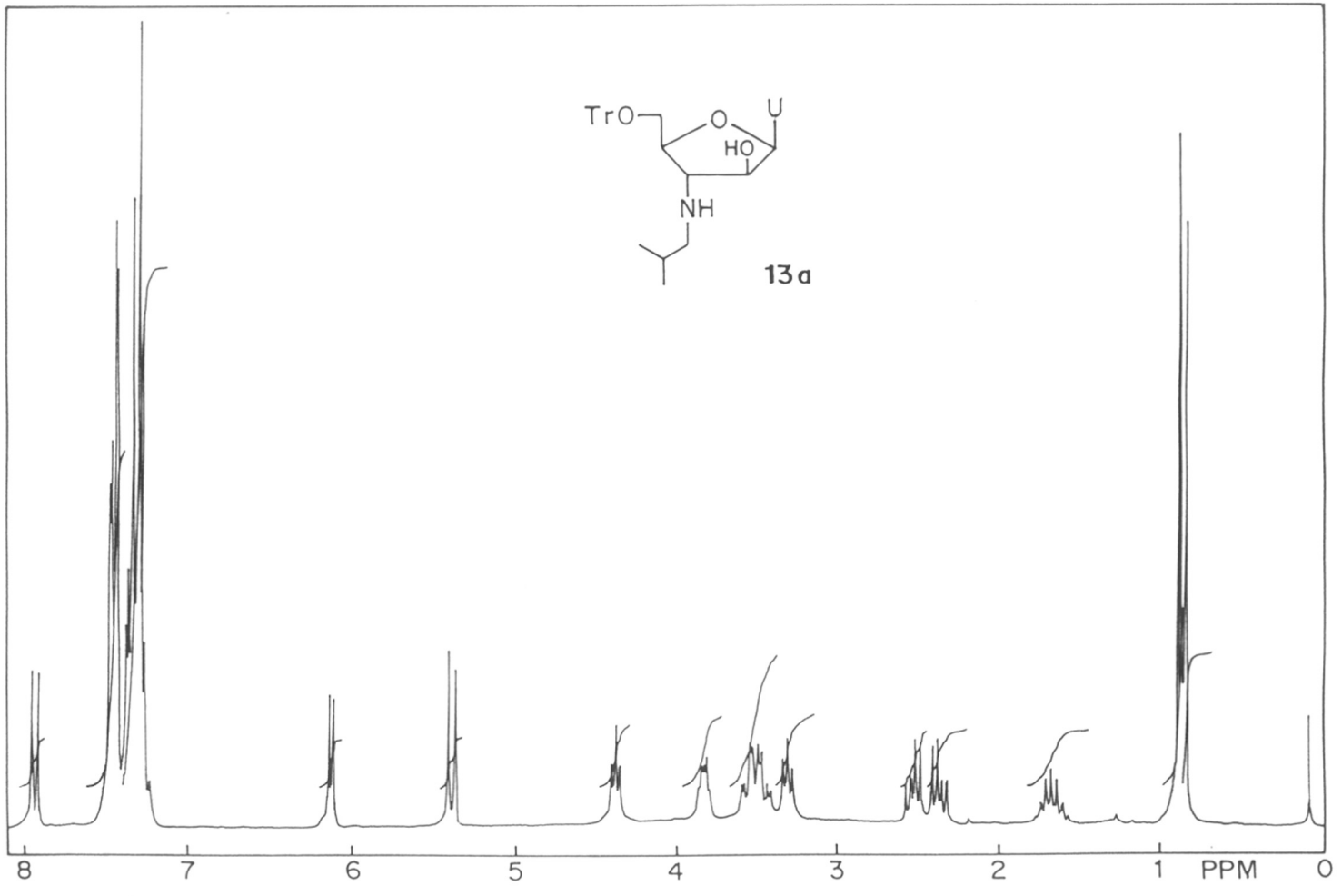
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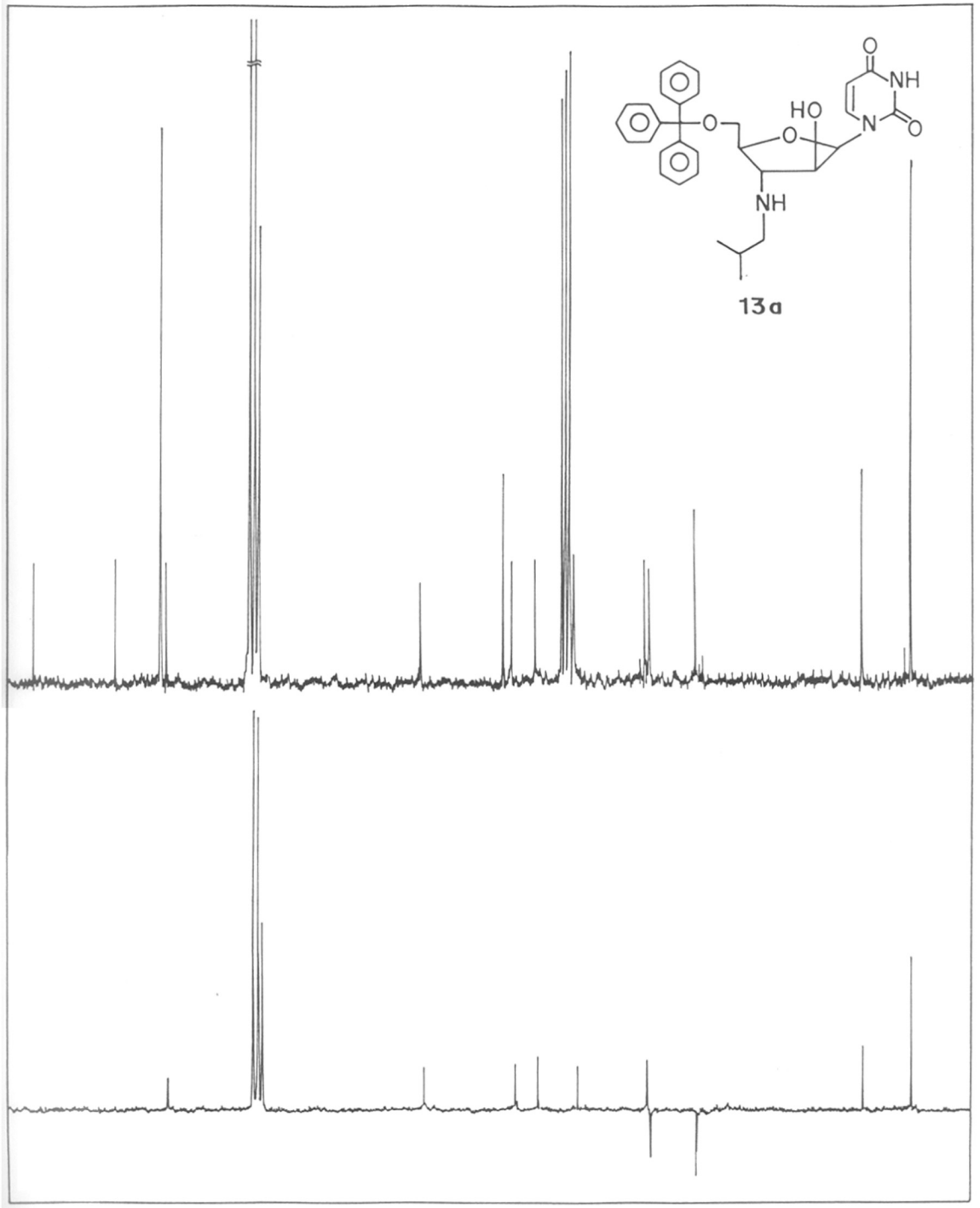

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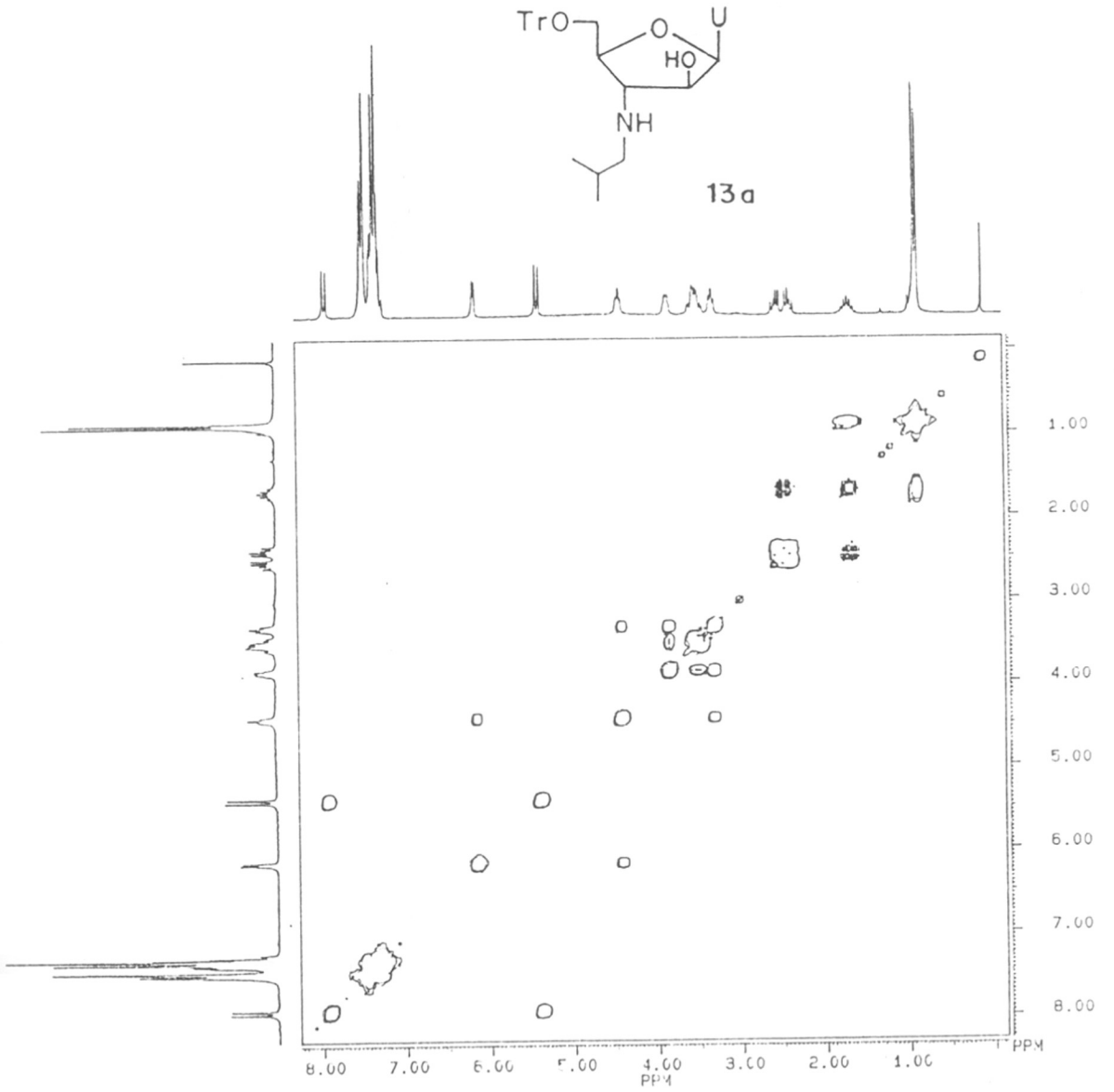
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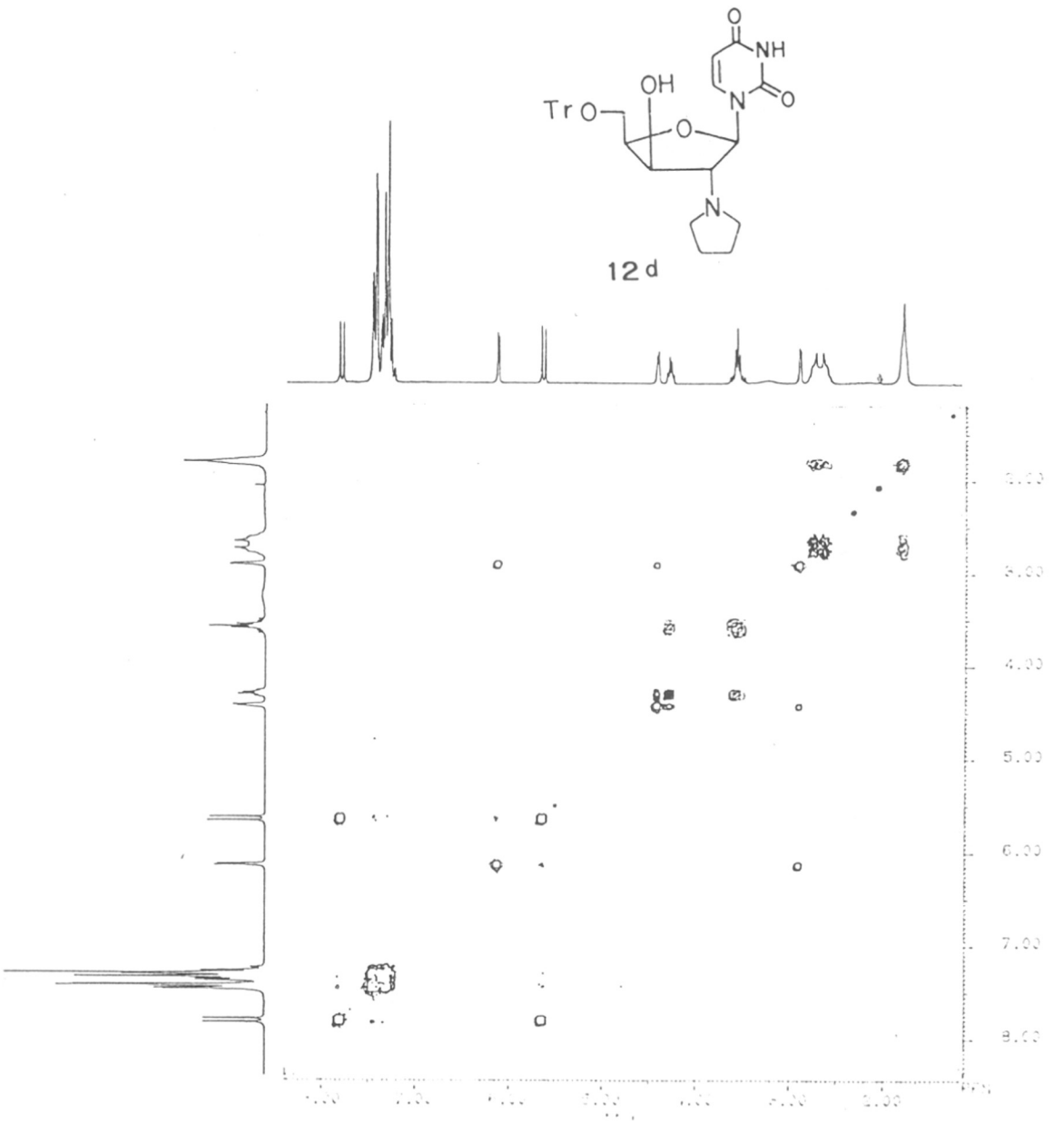
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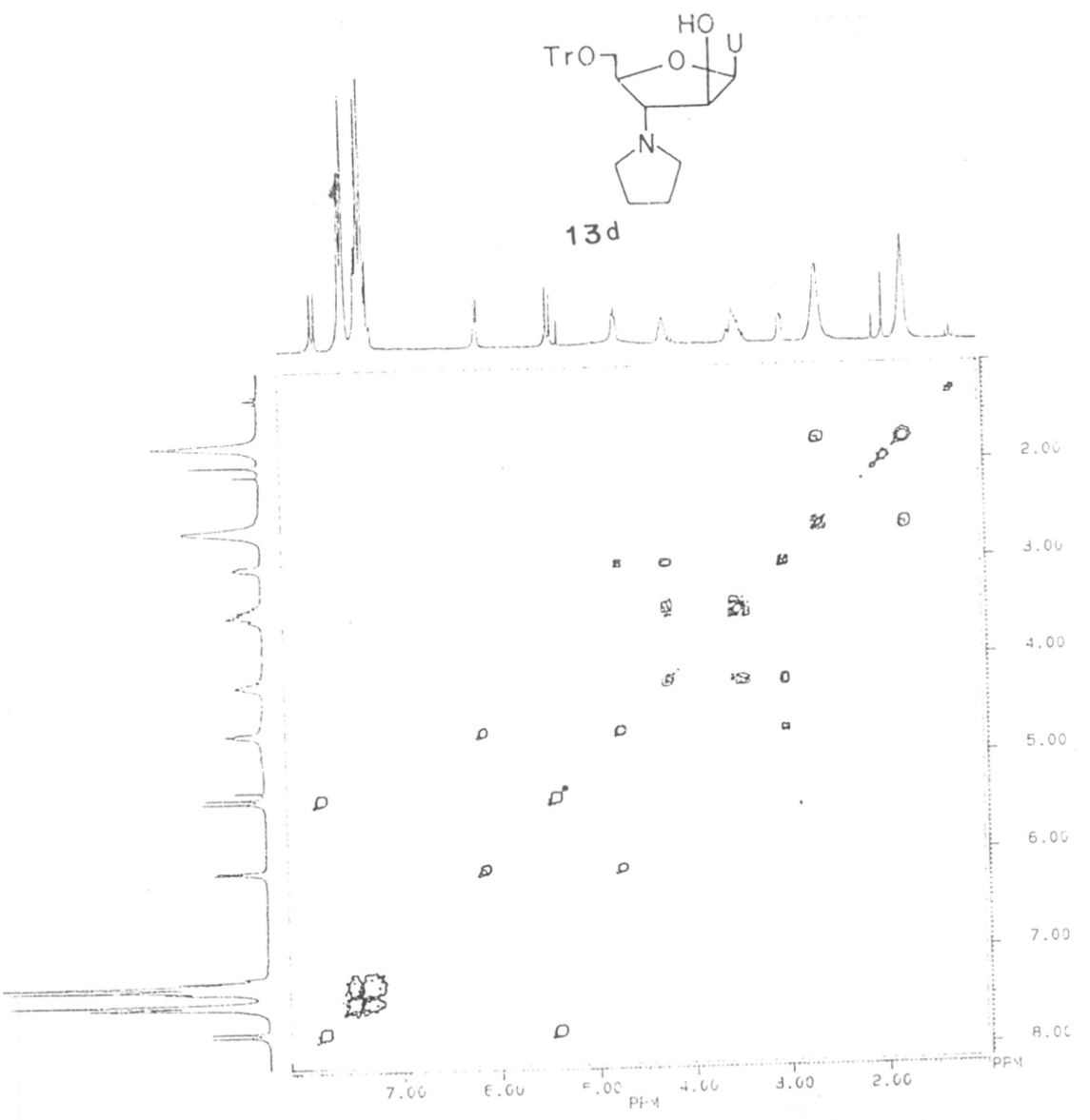
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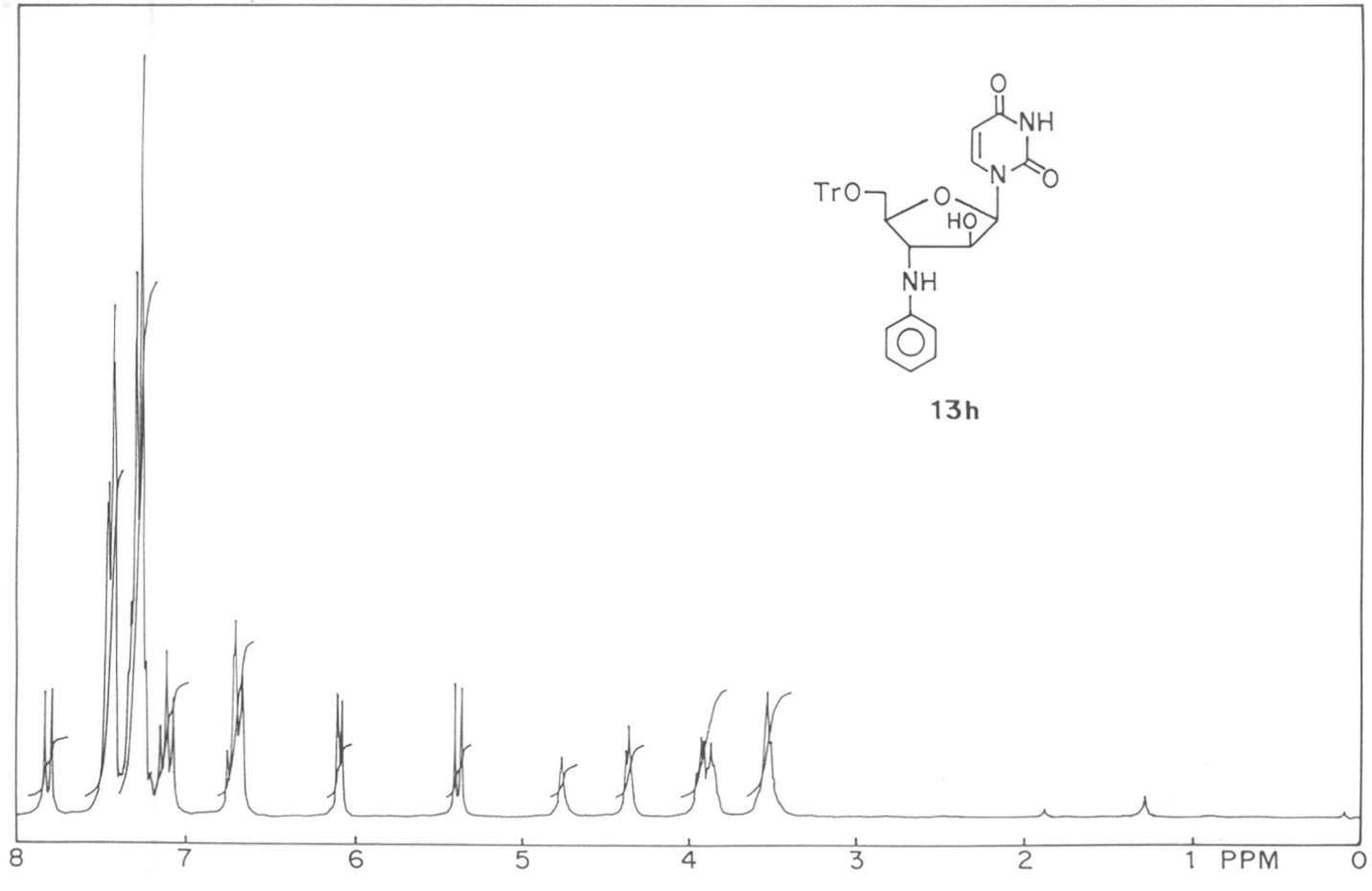

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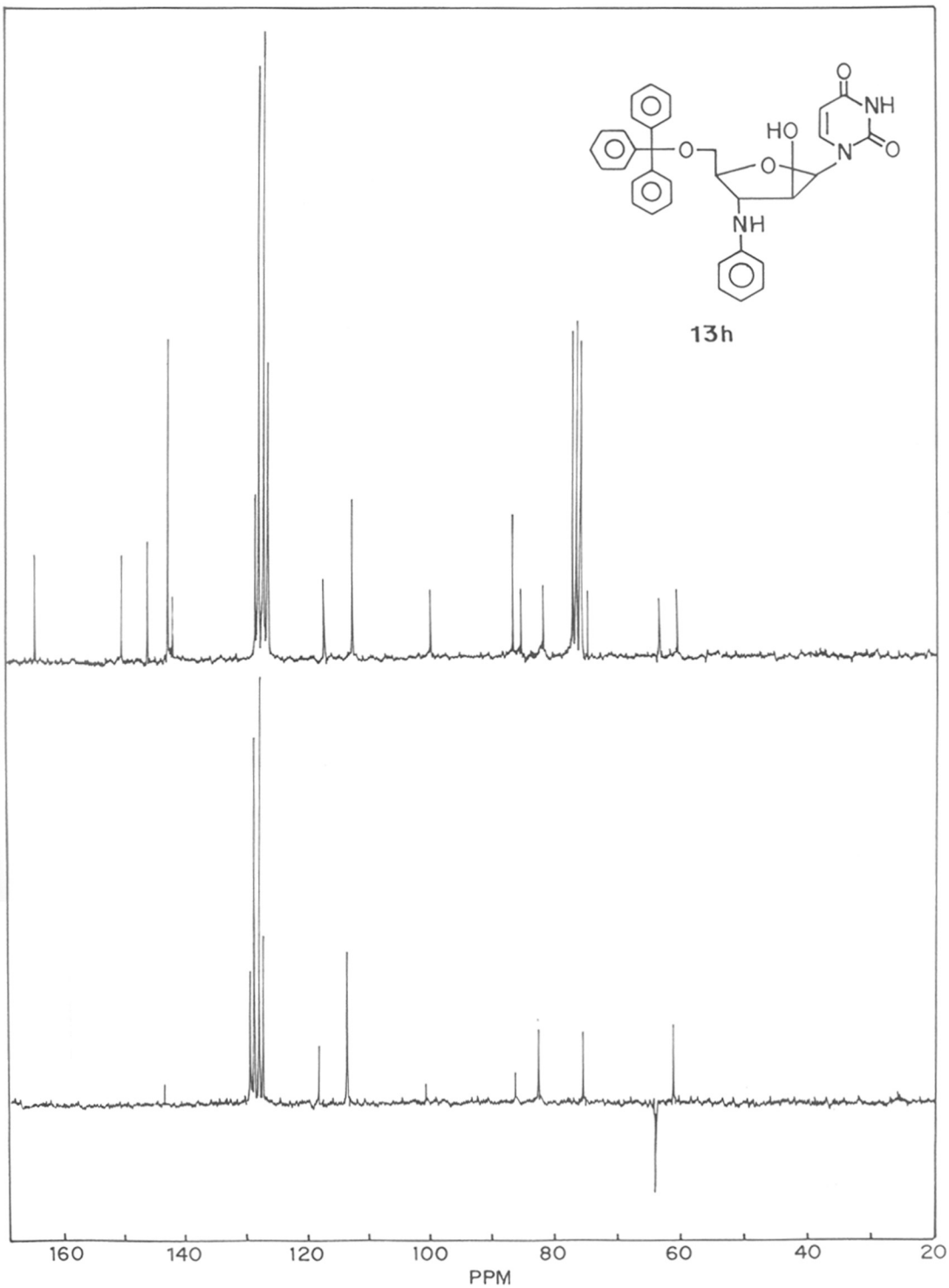

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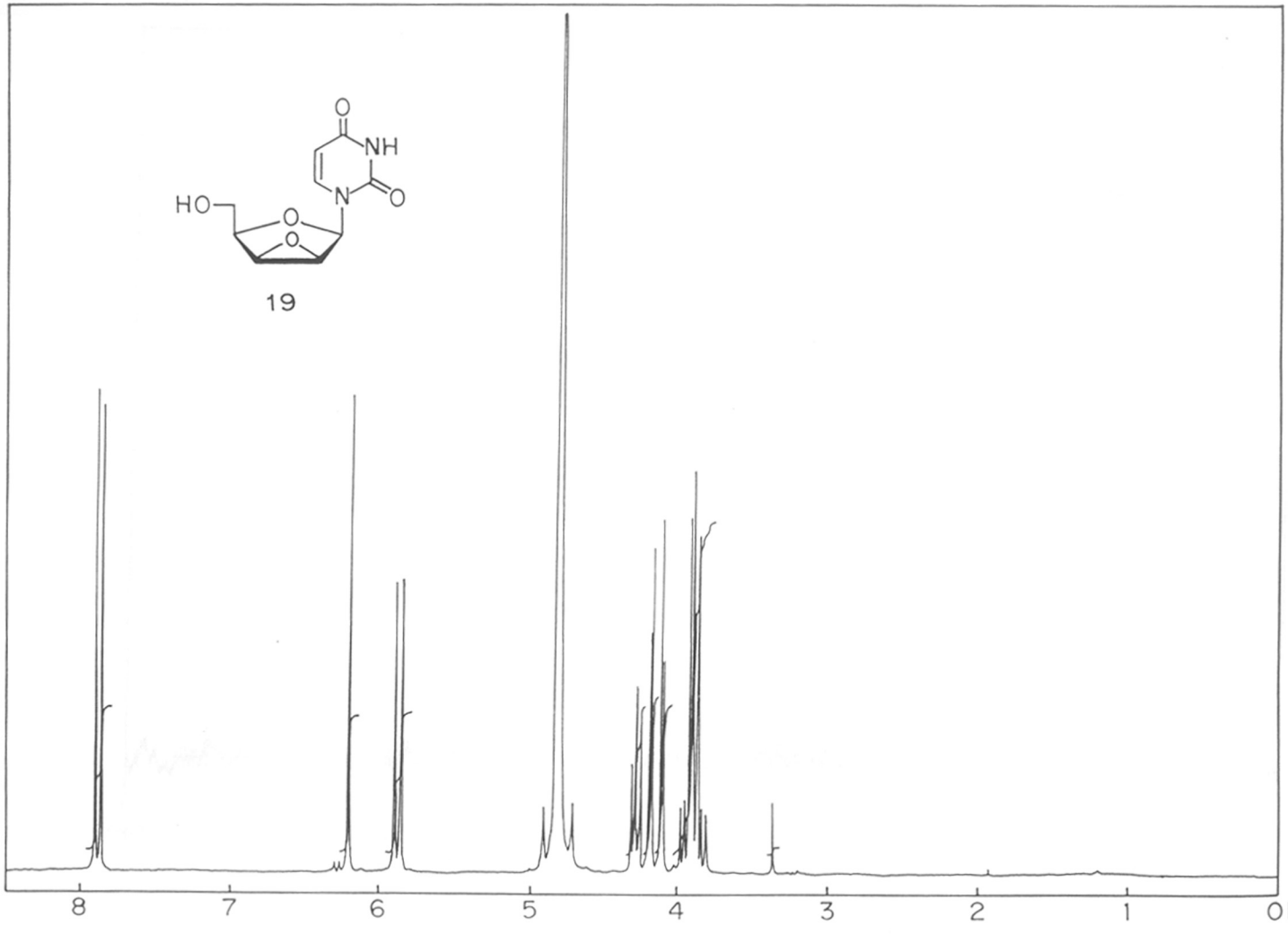
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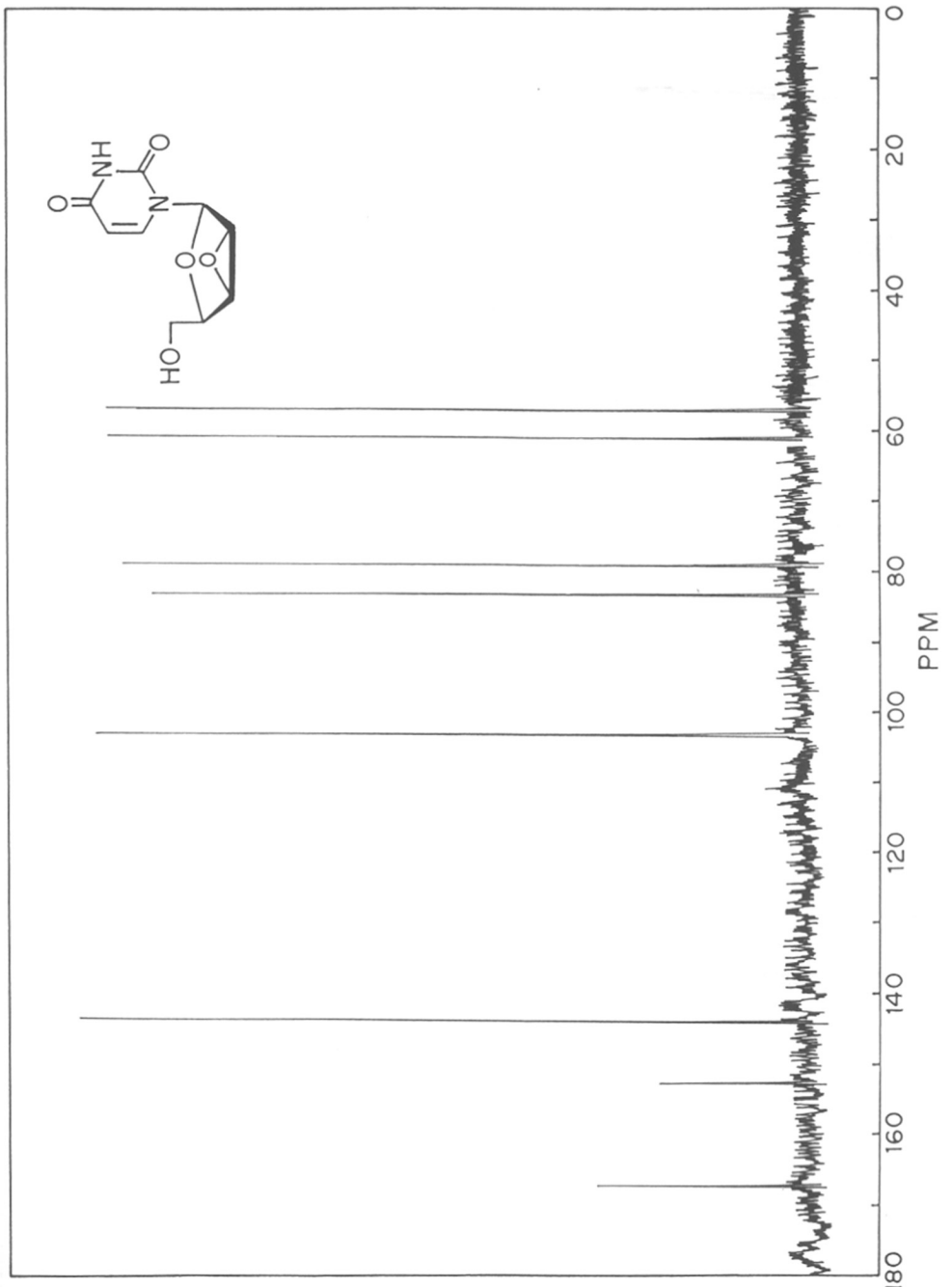
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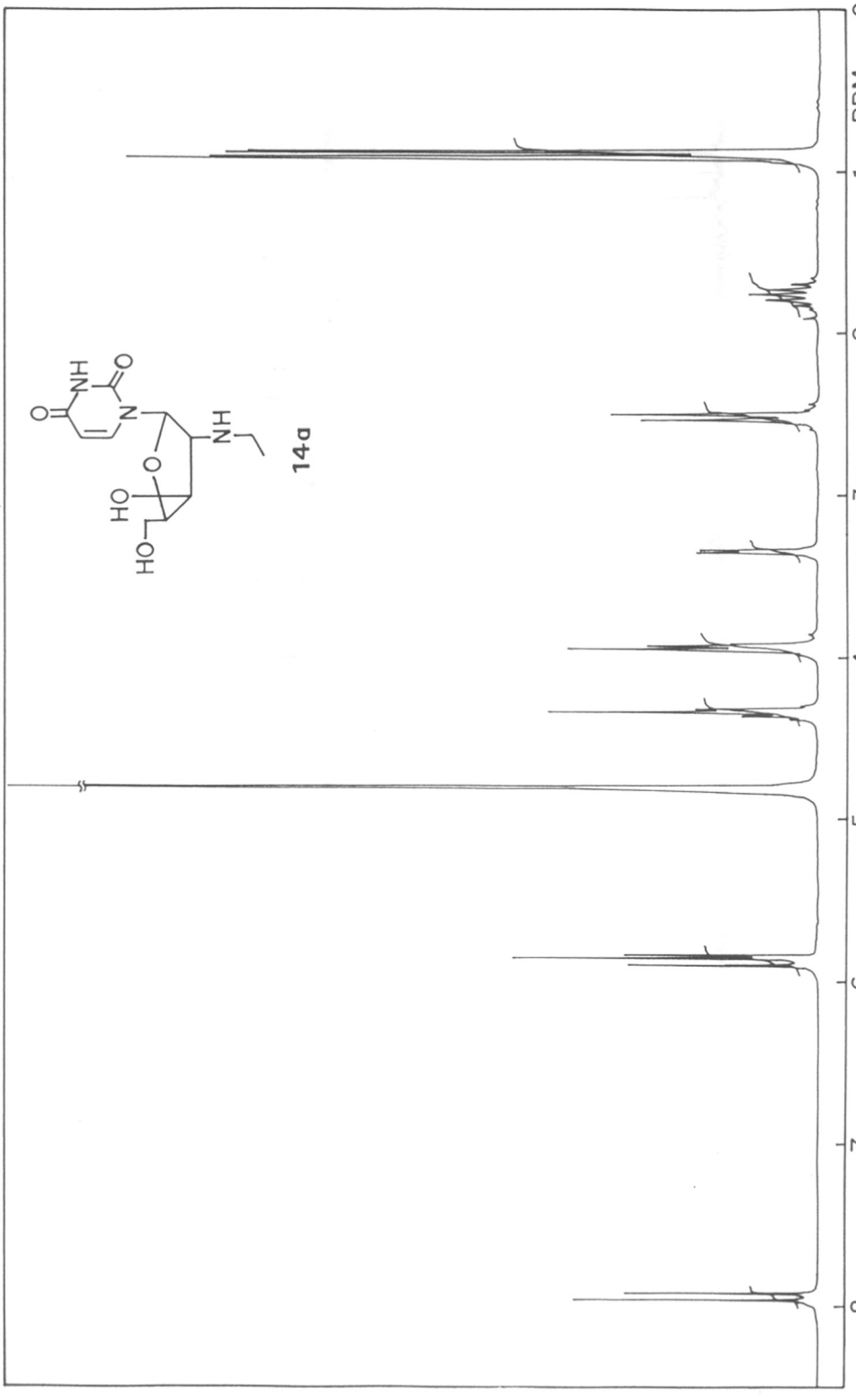
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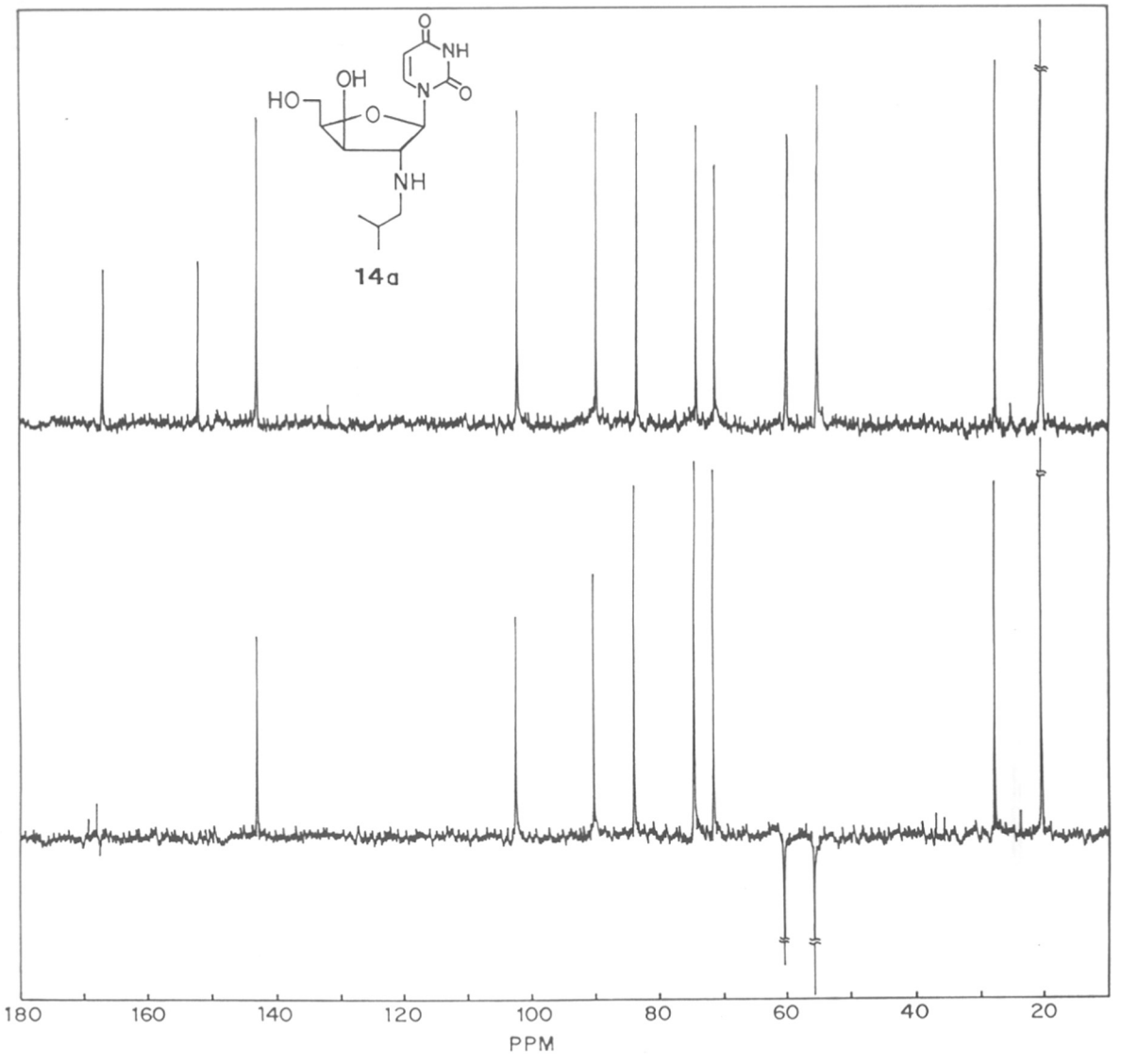
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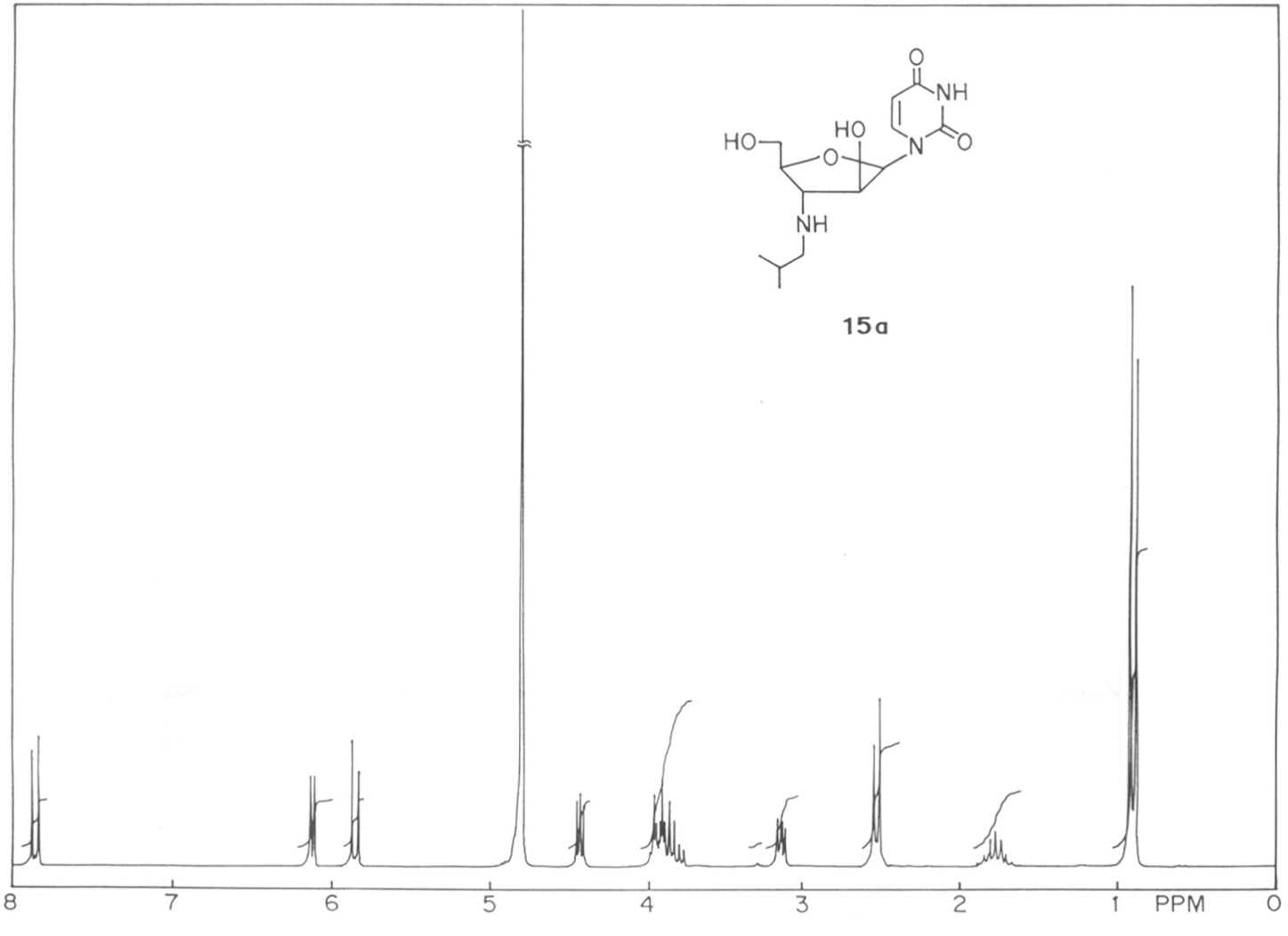
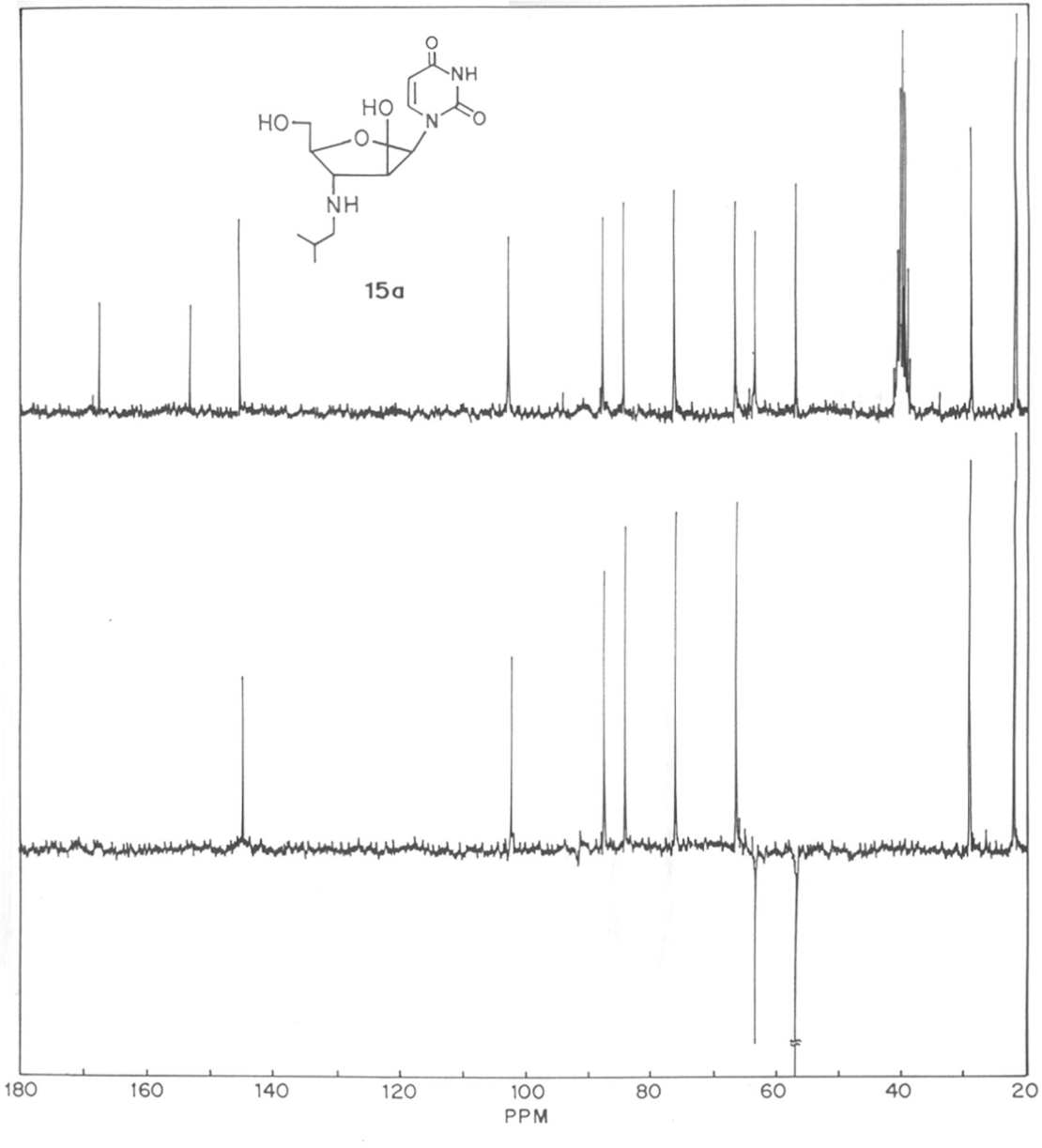


15a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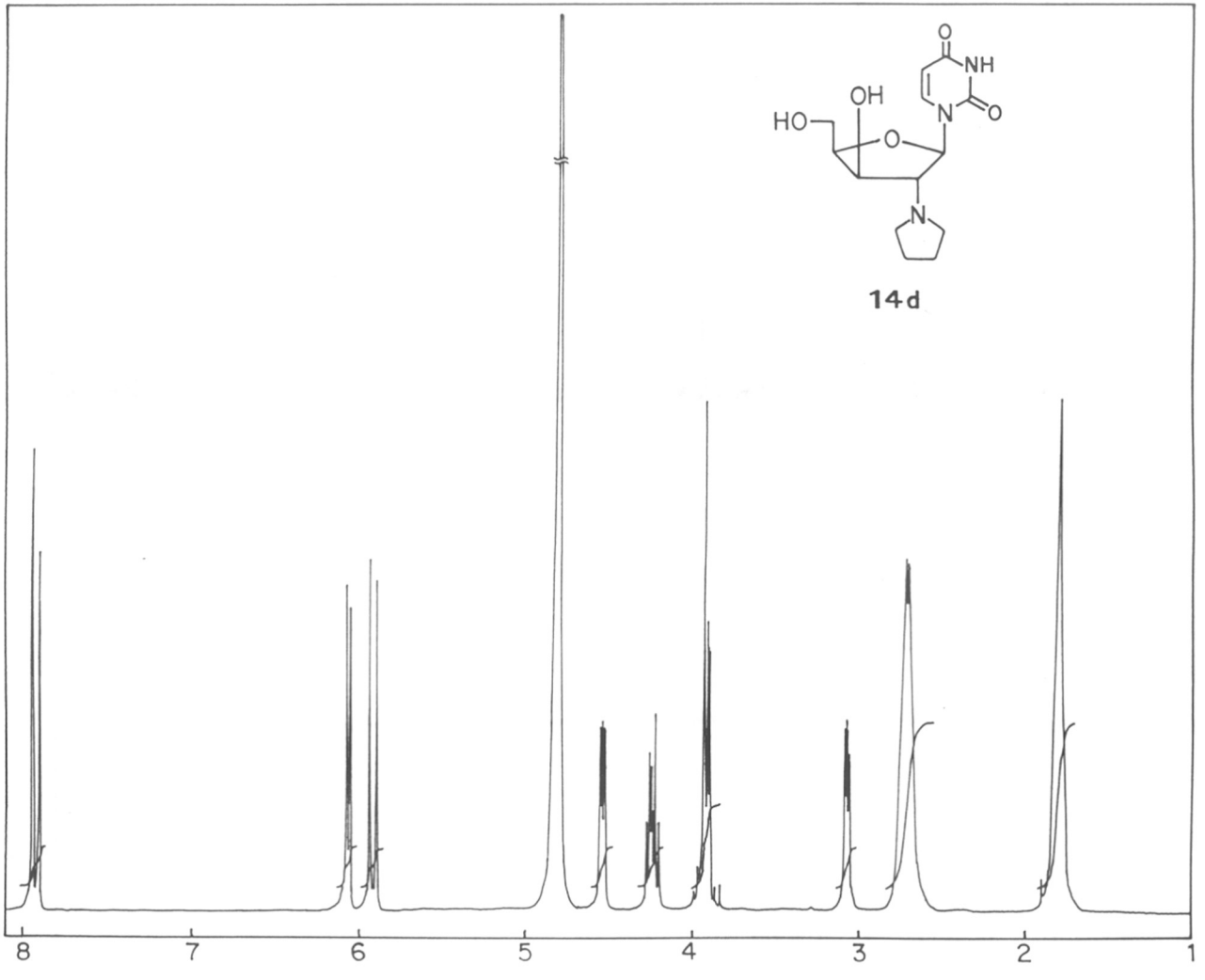
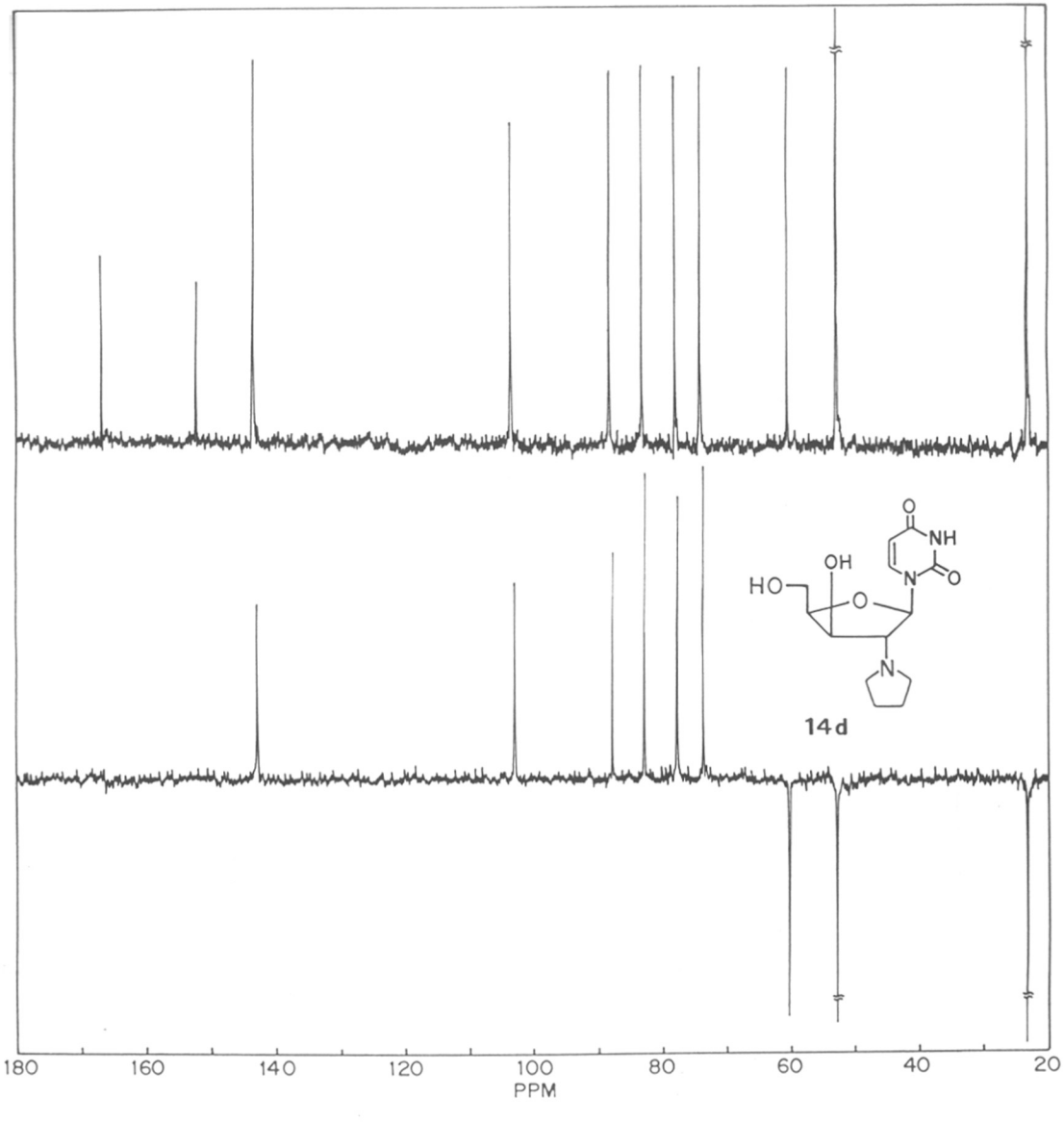
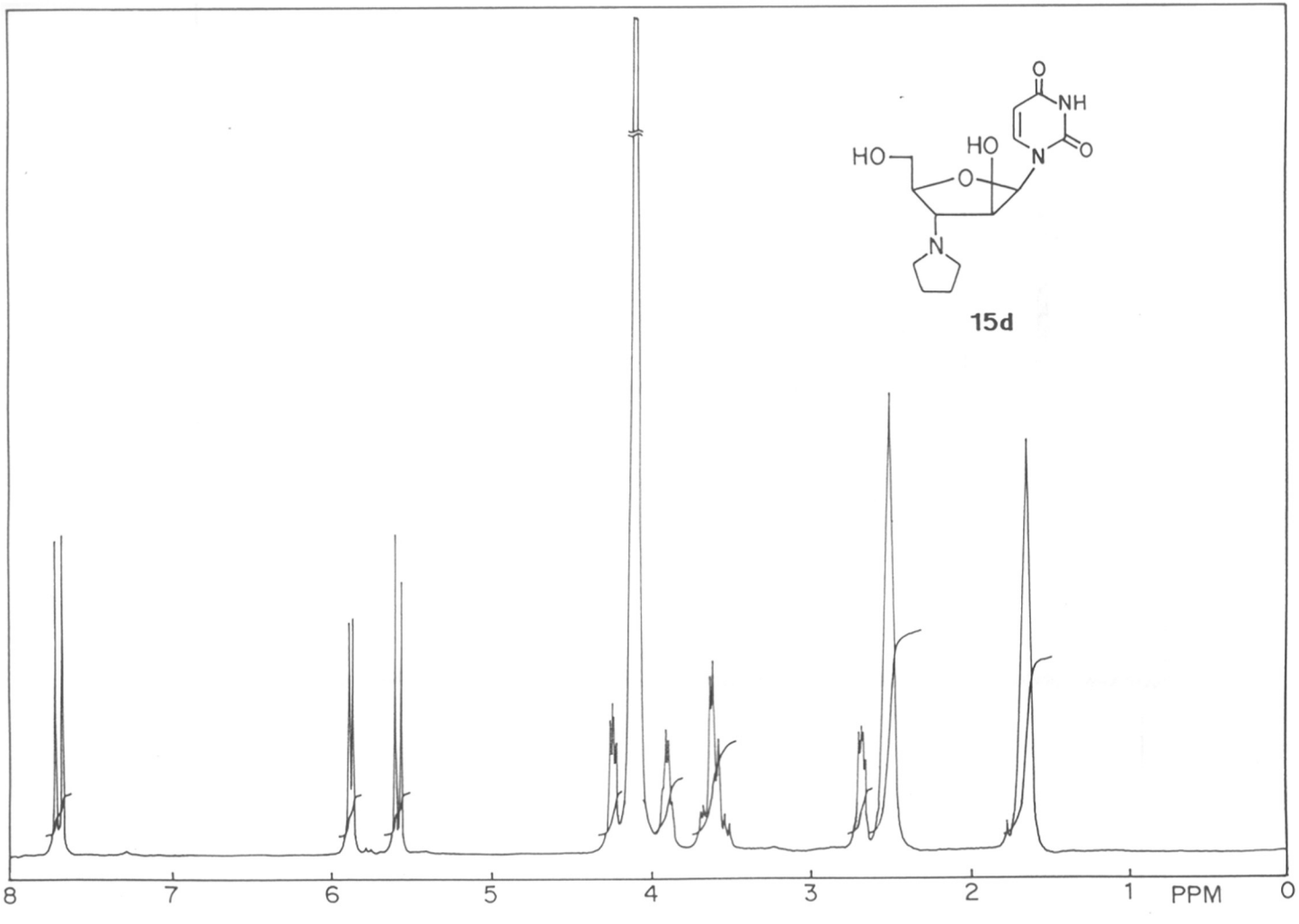
HO
O
NH
N
O
NH
15a
180
160
140
120
100
80
60
40
20
PPM



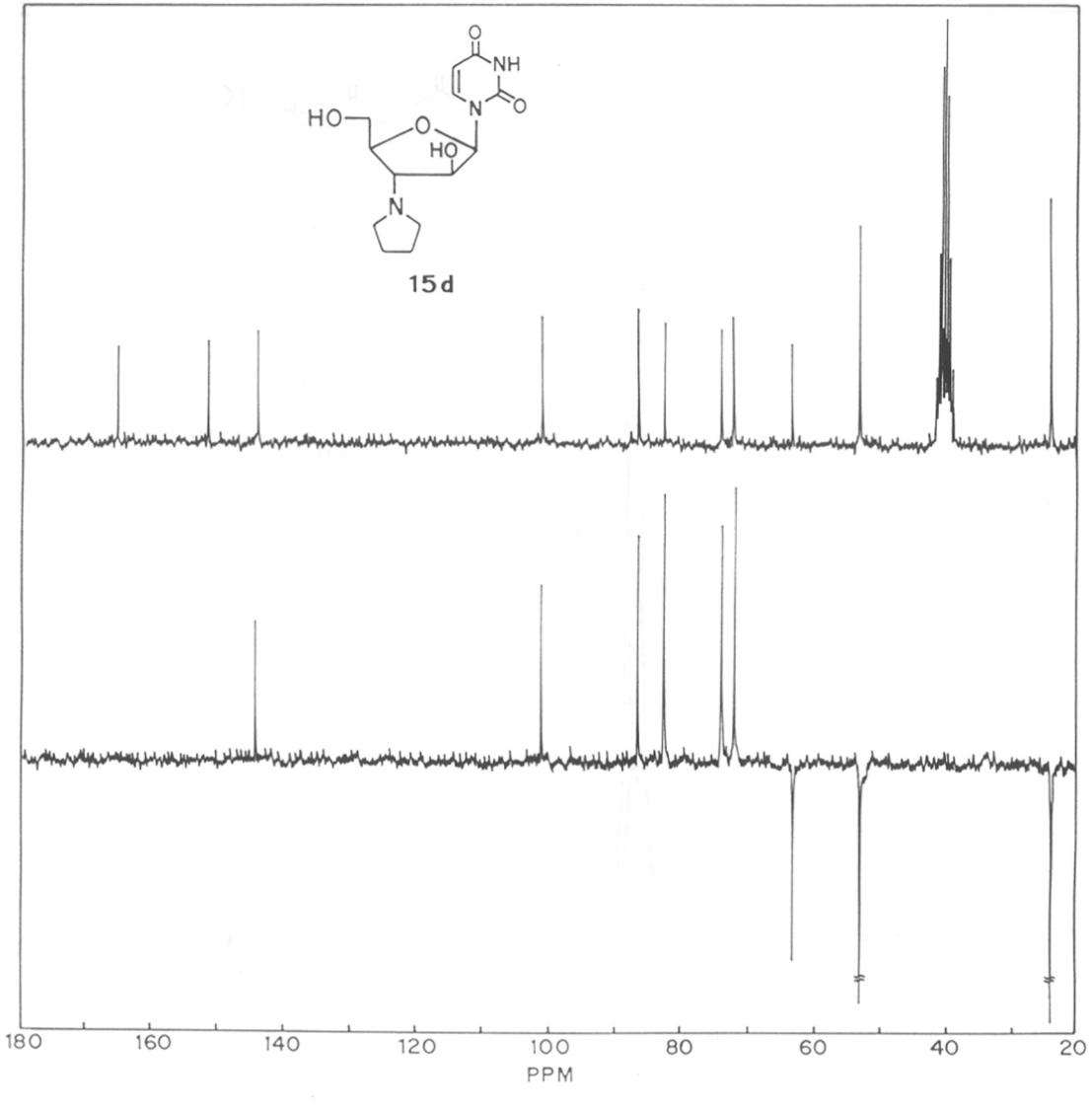
14d

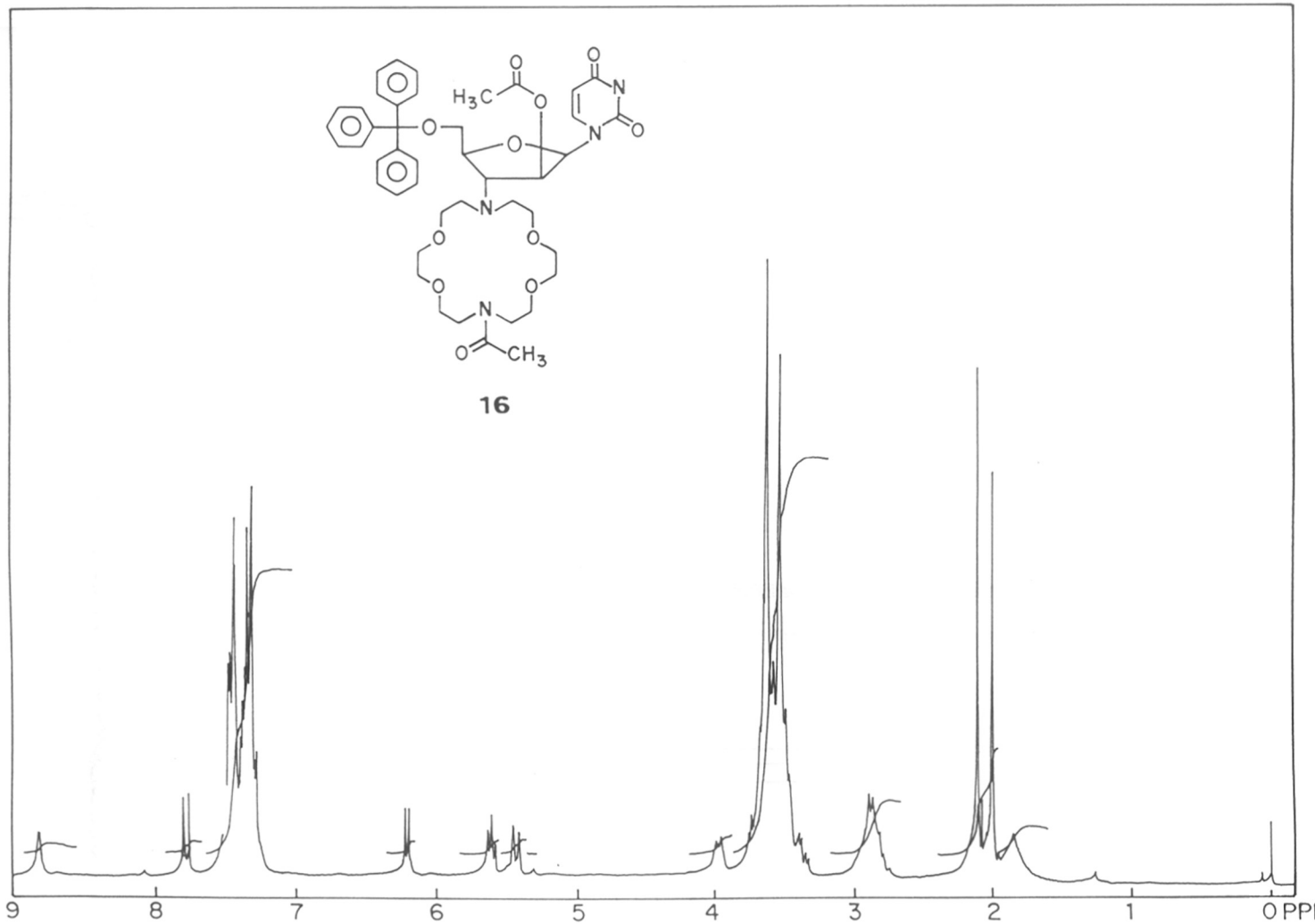


14 d



15d


O
NH
HO
O
N
O
HO
N
15d
180
160
140
120
100
80
60
40
20
PPM



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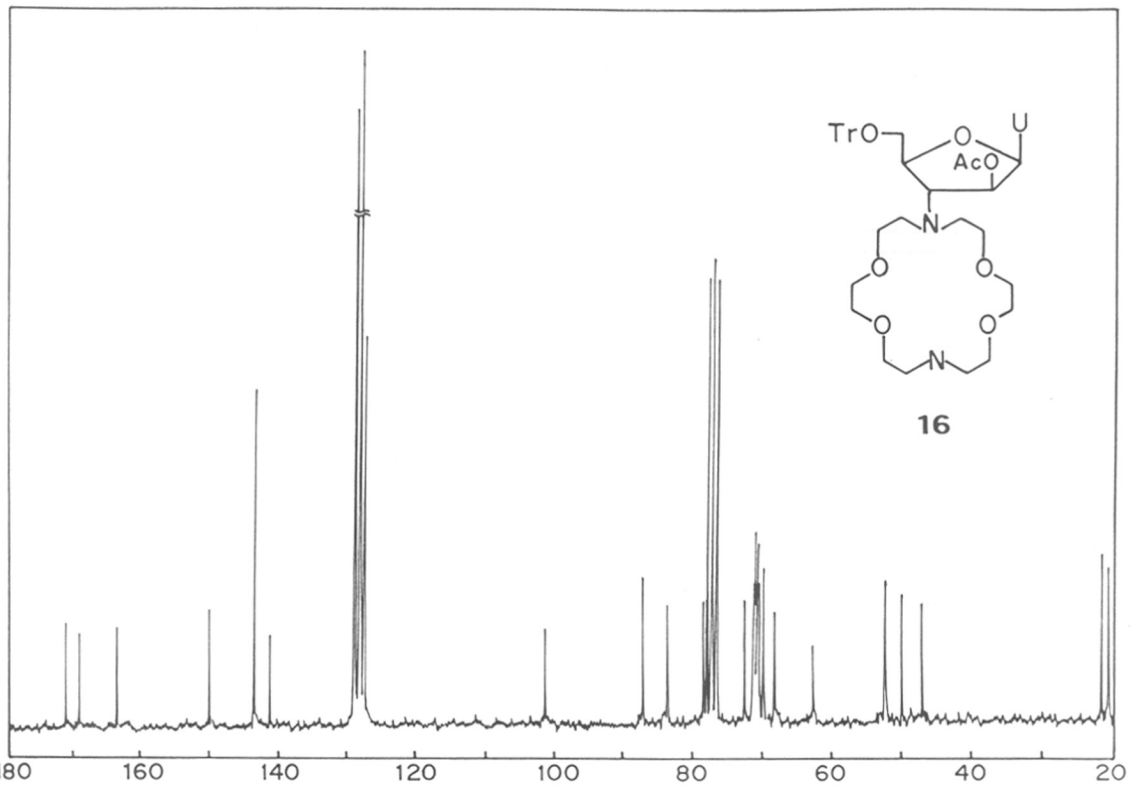
TrO
O
U
AcO
N
O
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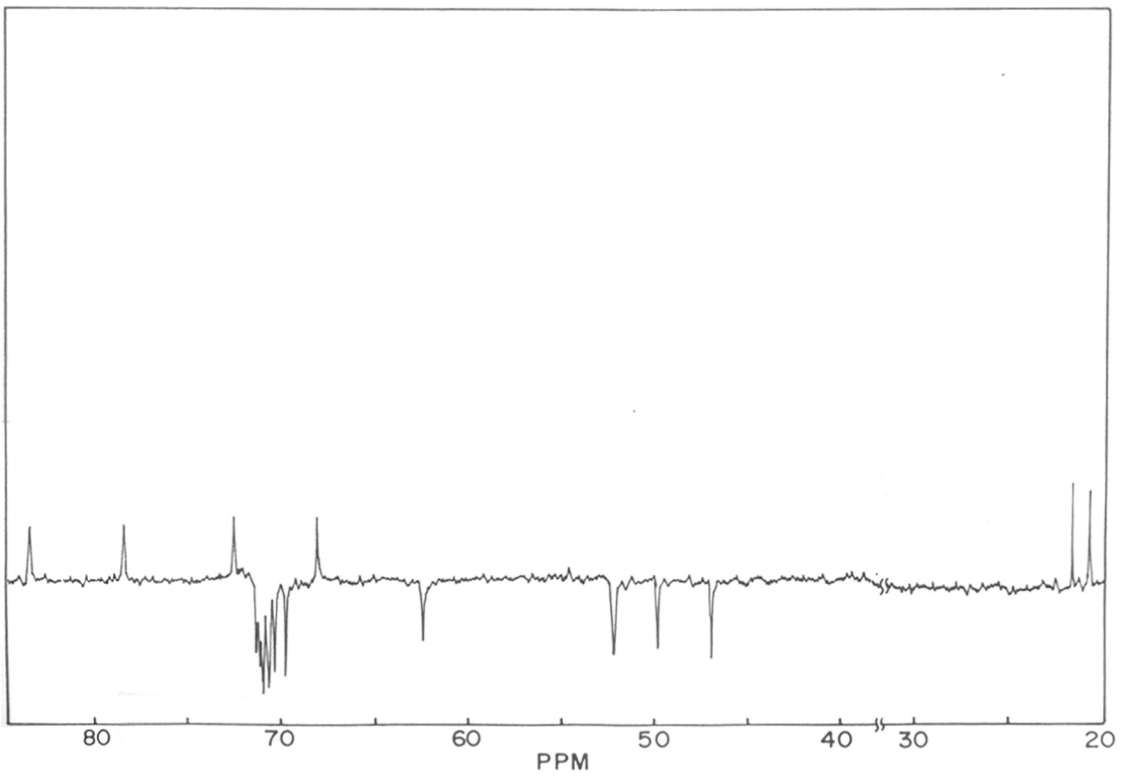
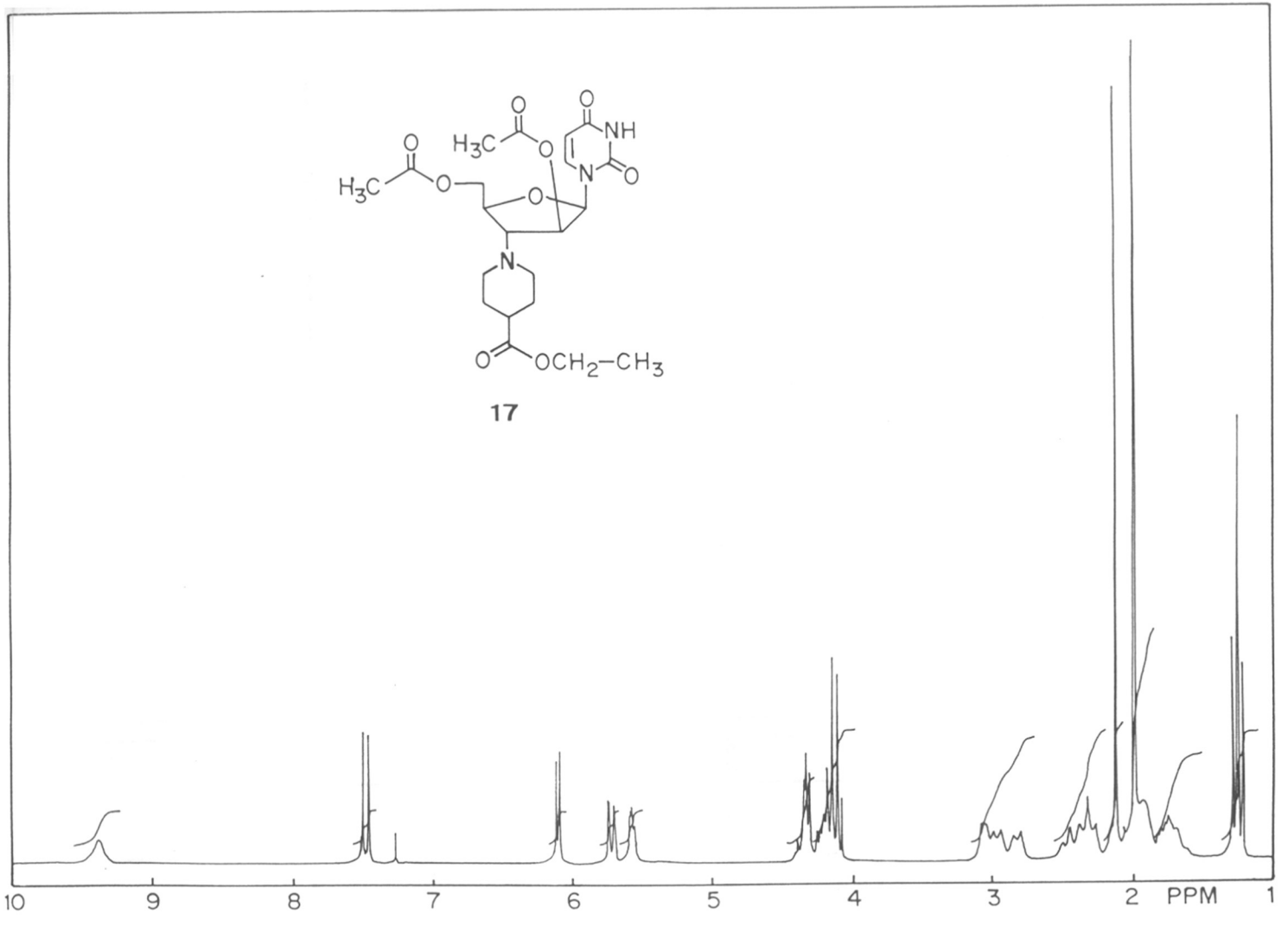
O
O
N
180
160
140
120
100
80
60
40
20

16


80
70
60
50
40
30
20
PPM



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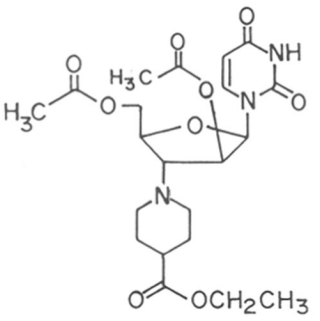

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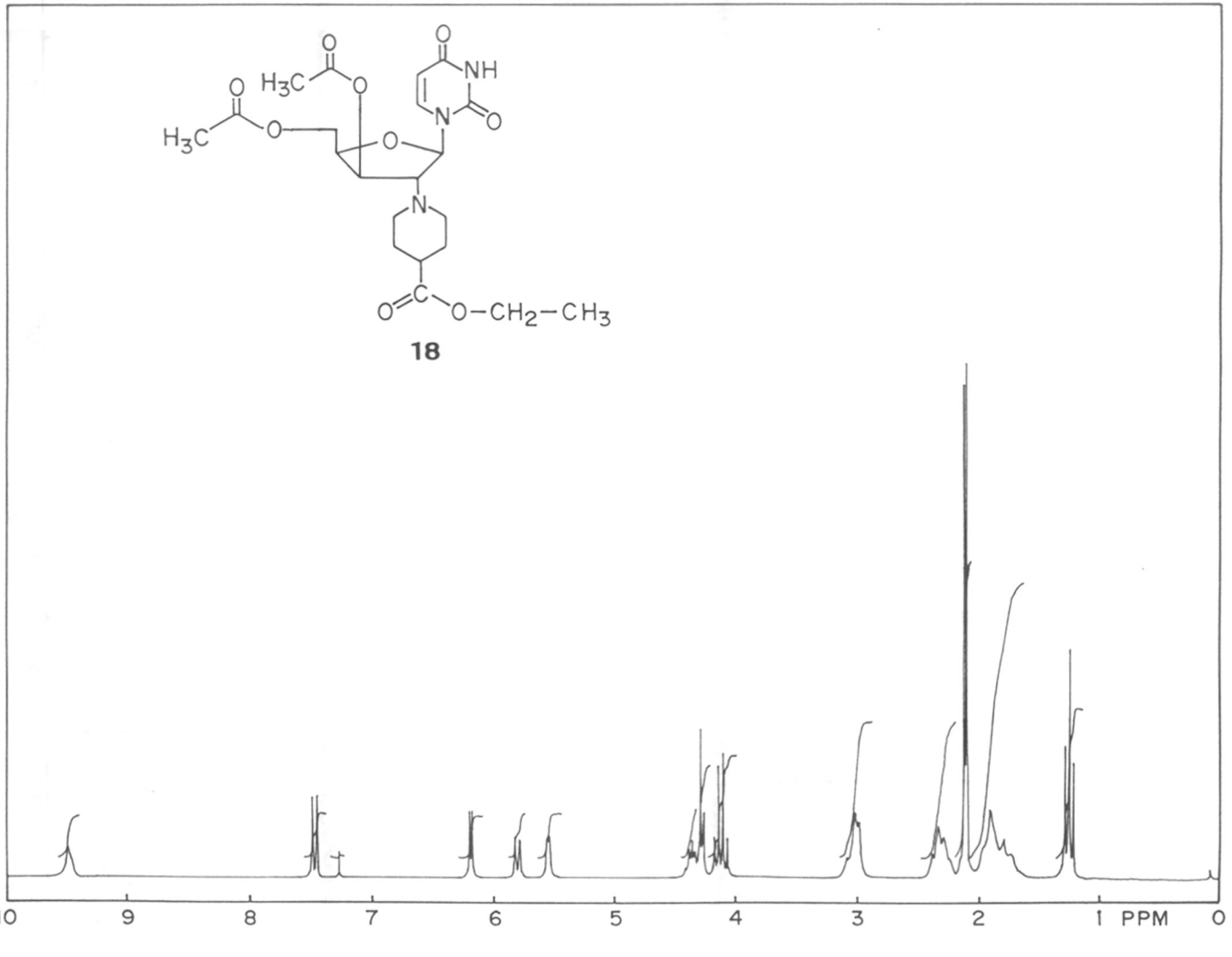

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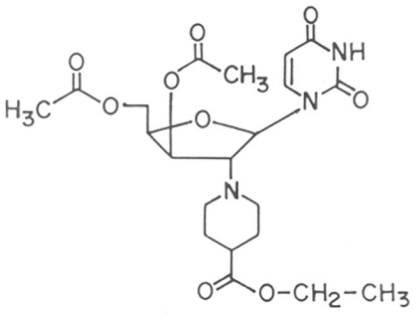

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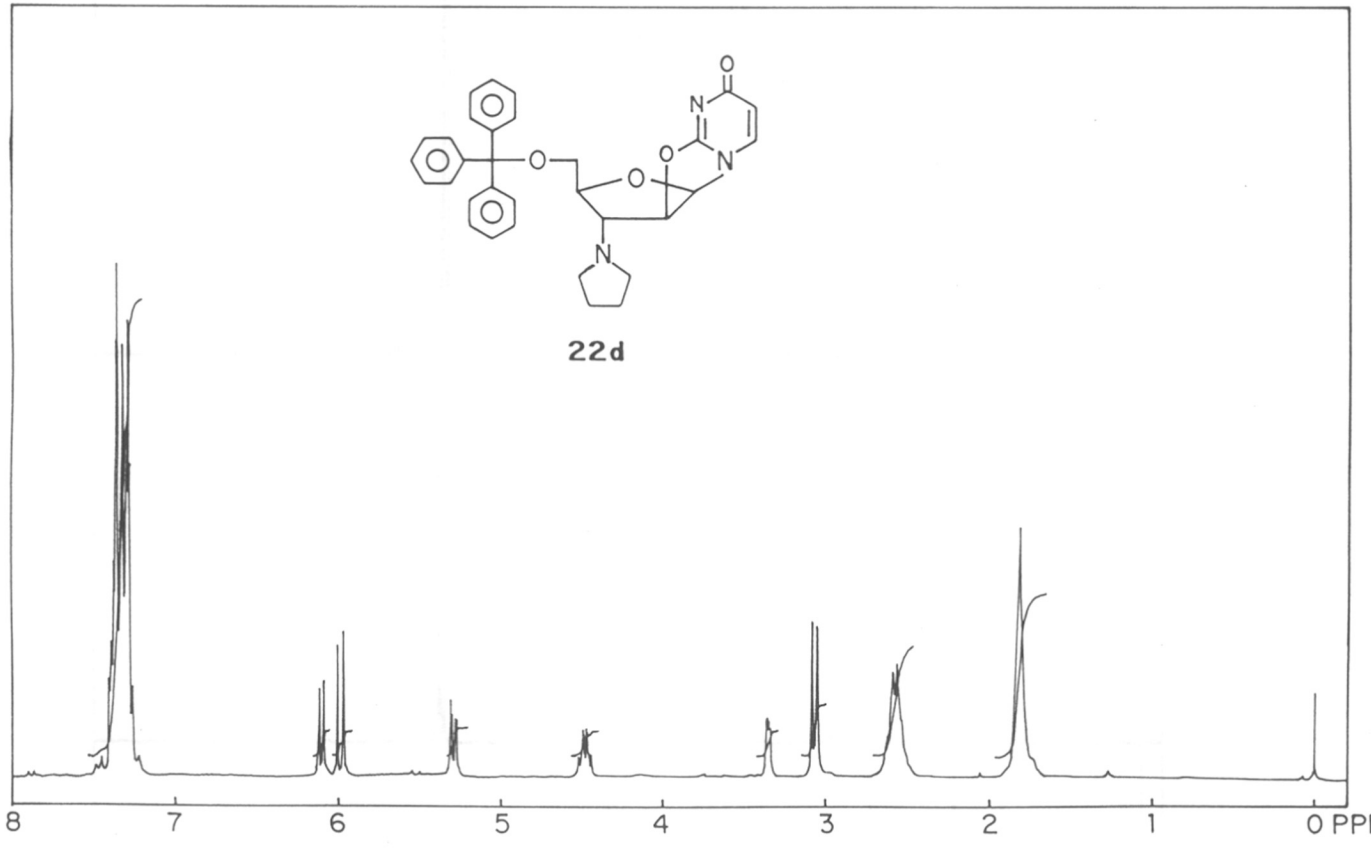
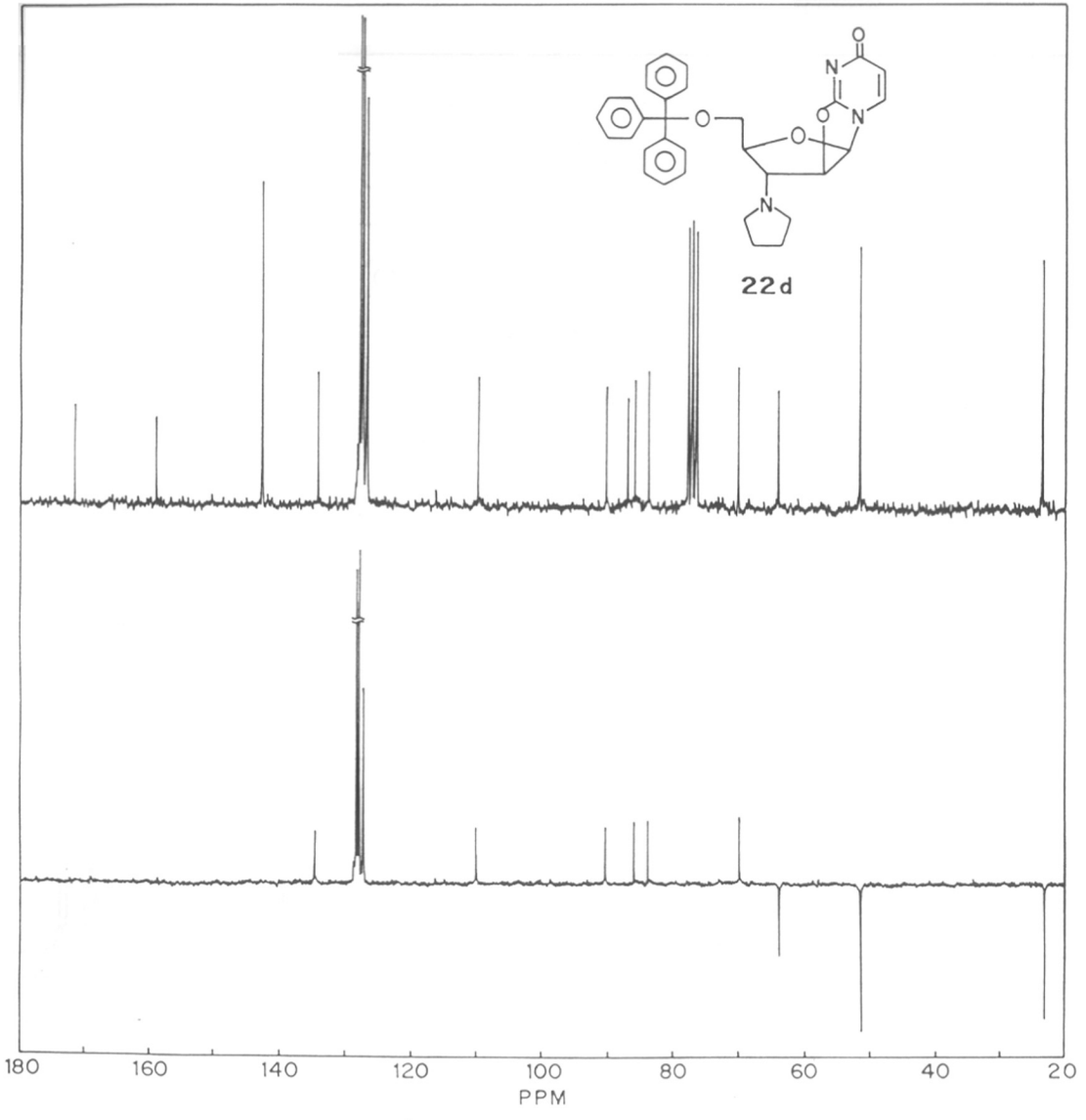
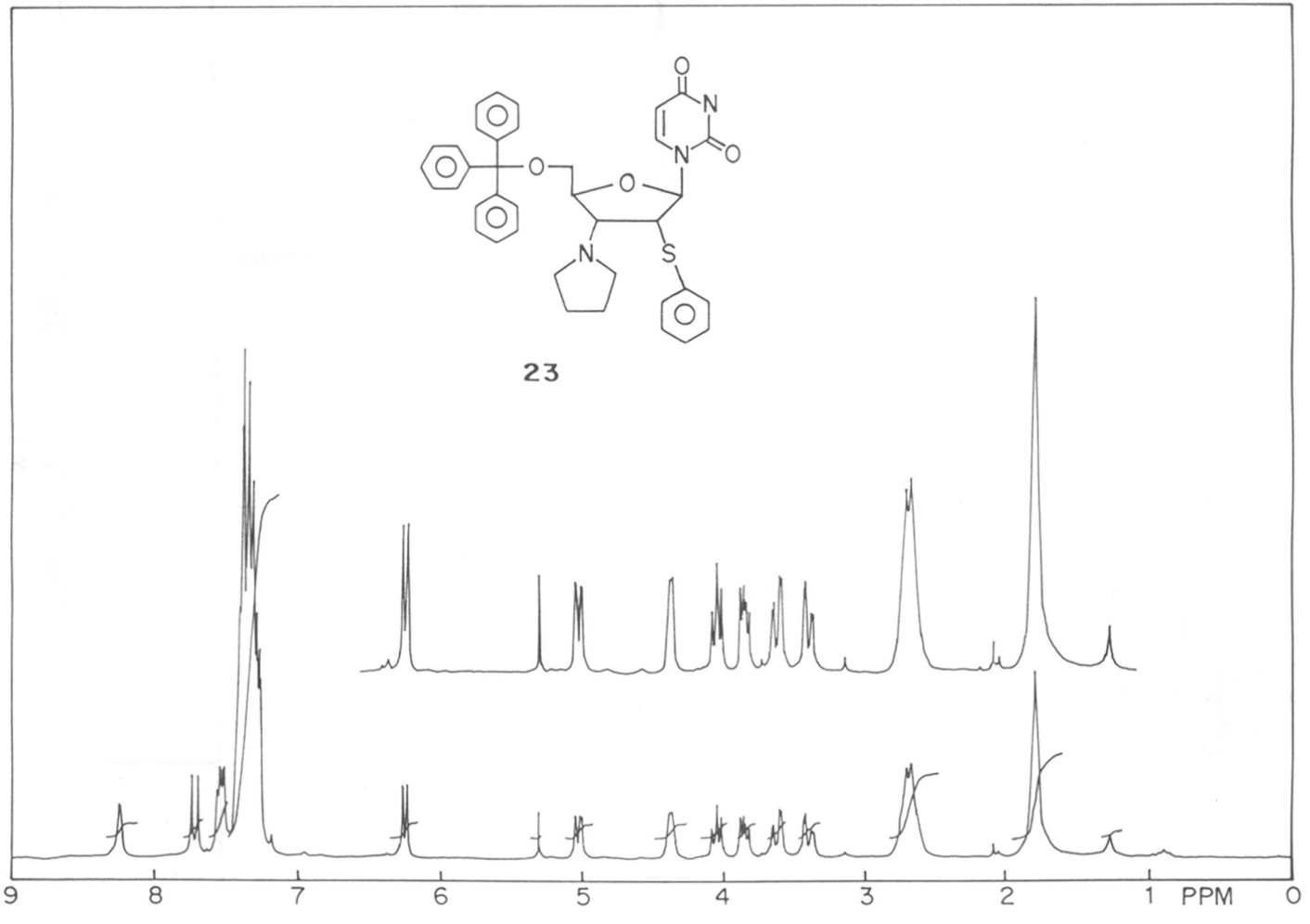

O
N
O
O
N
O
N
22d
8
7
6
5
4
3
2
1
0 PPM


22d
180
160
140
120
100
80
60
40
20
PPM



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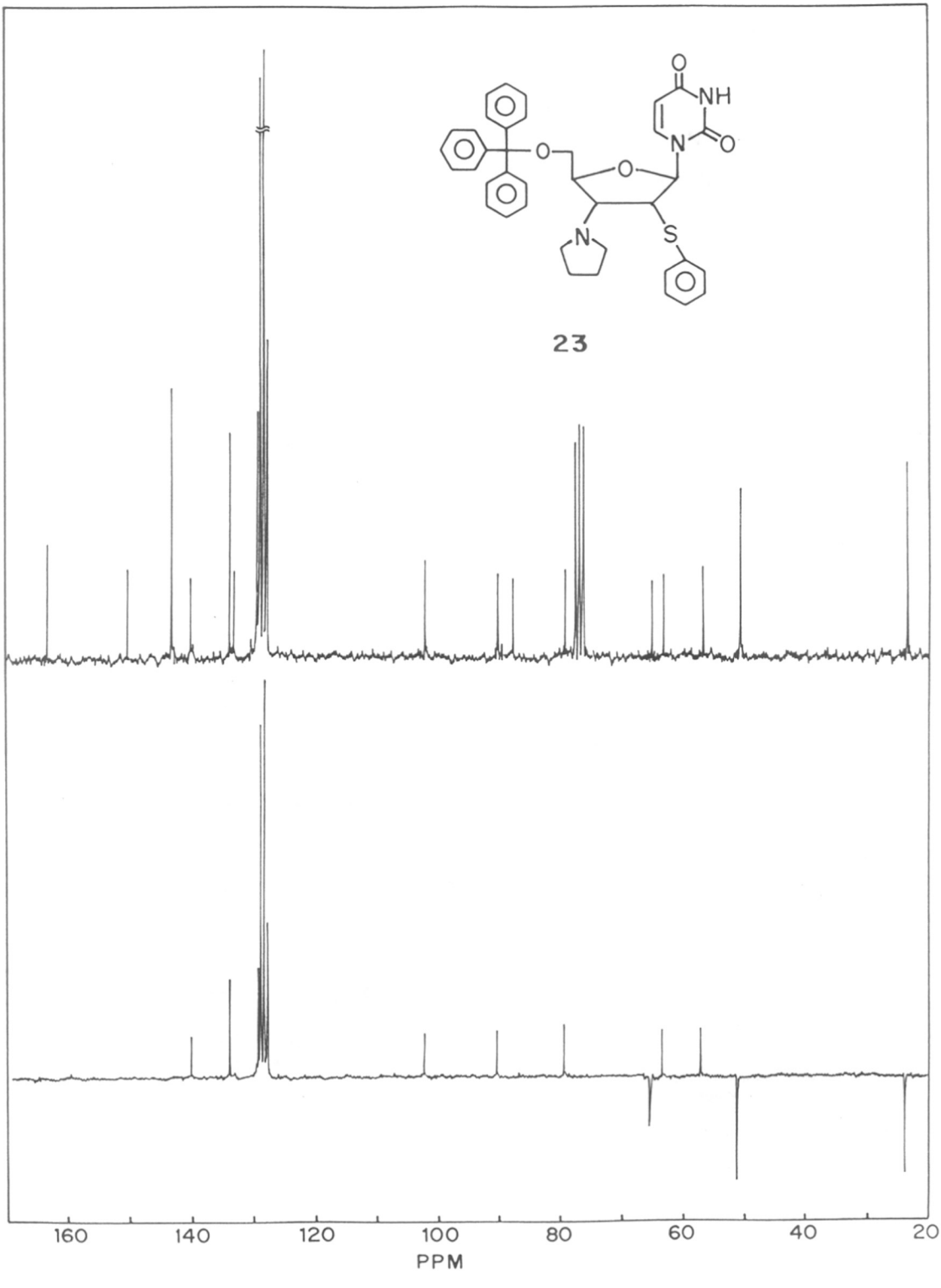

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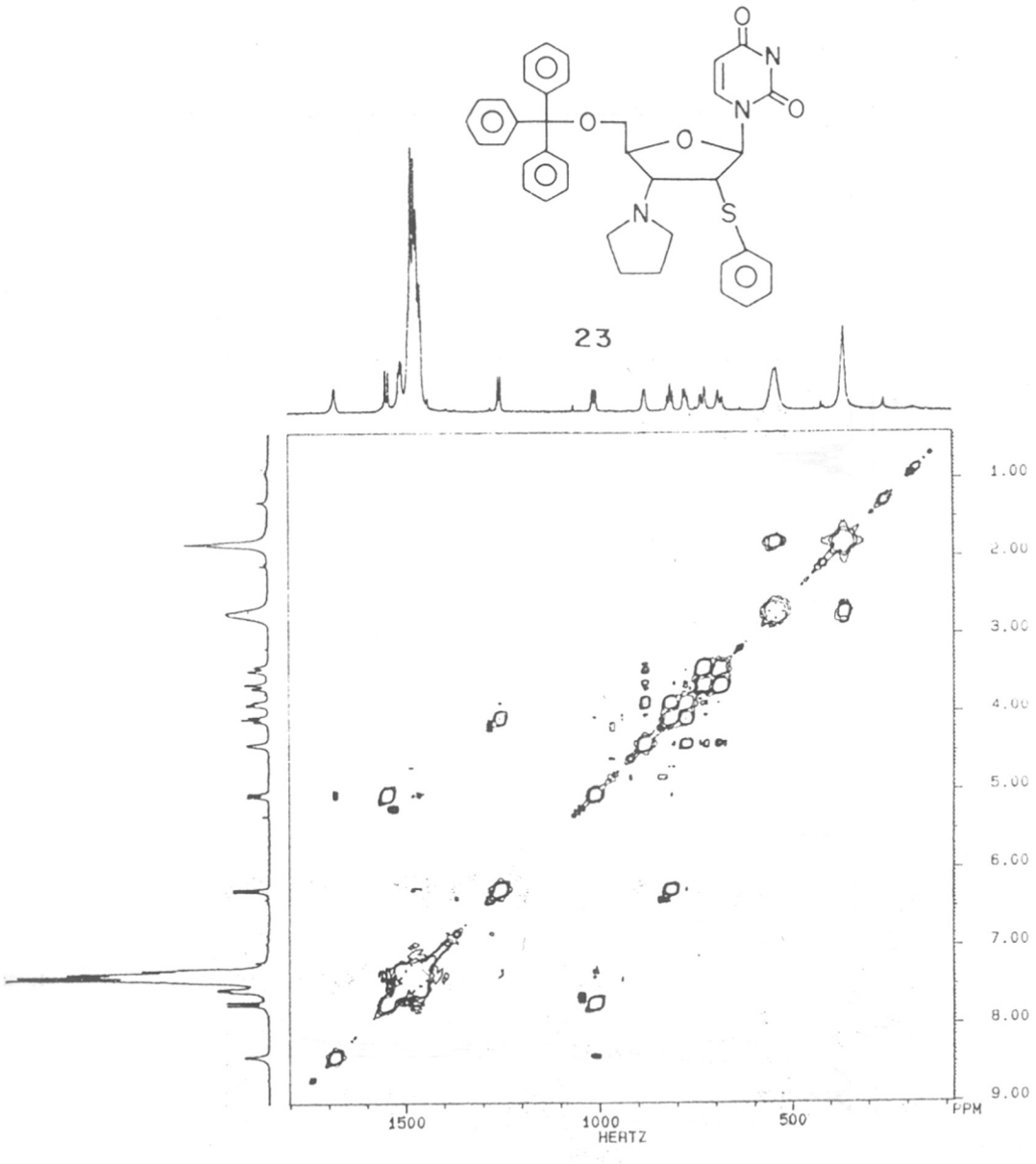
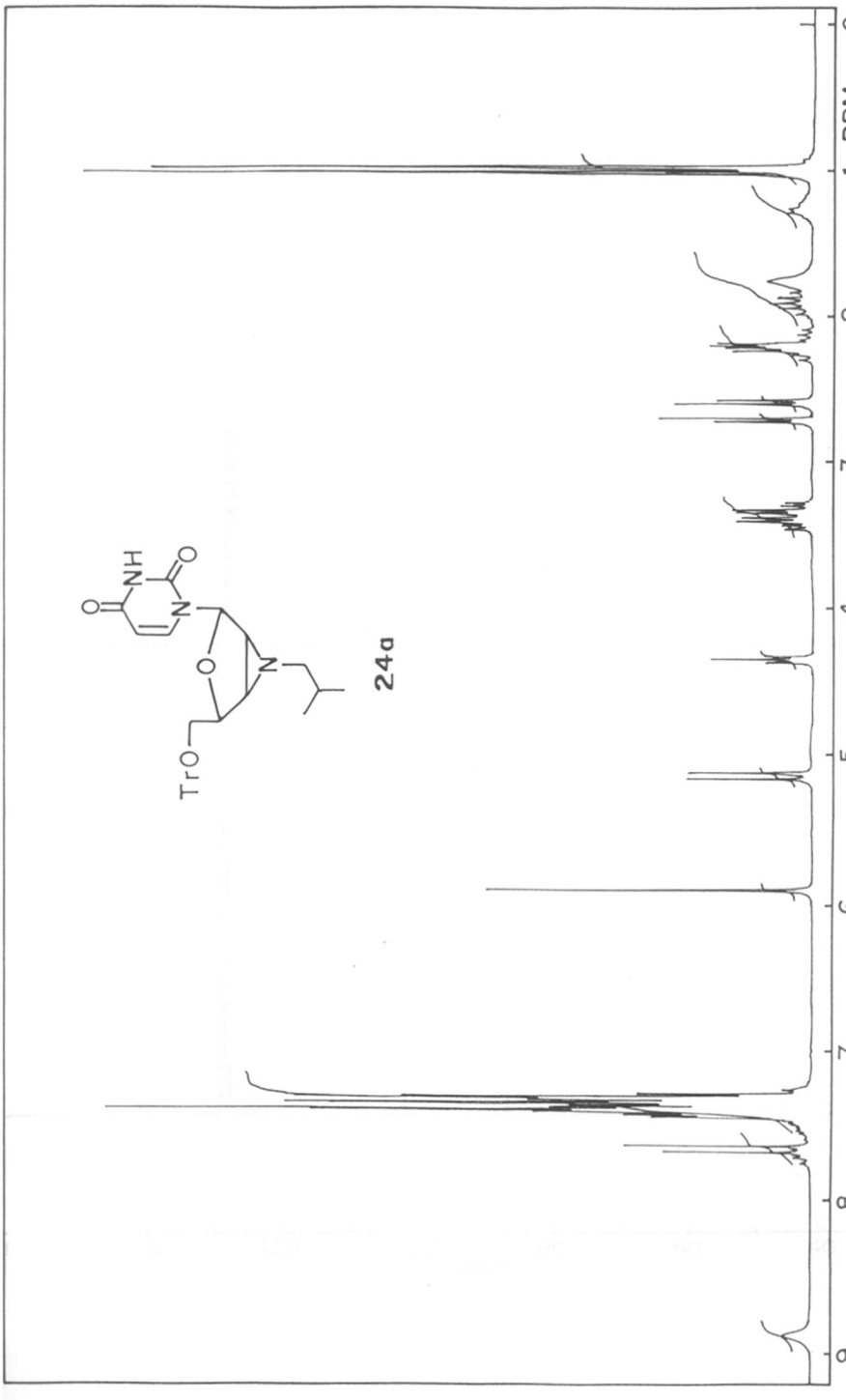
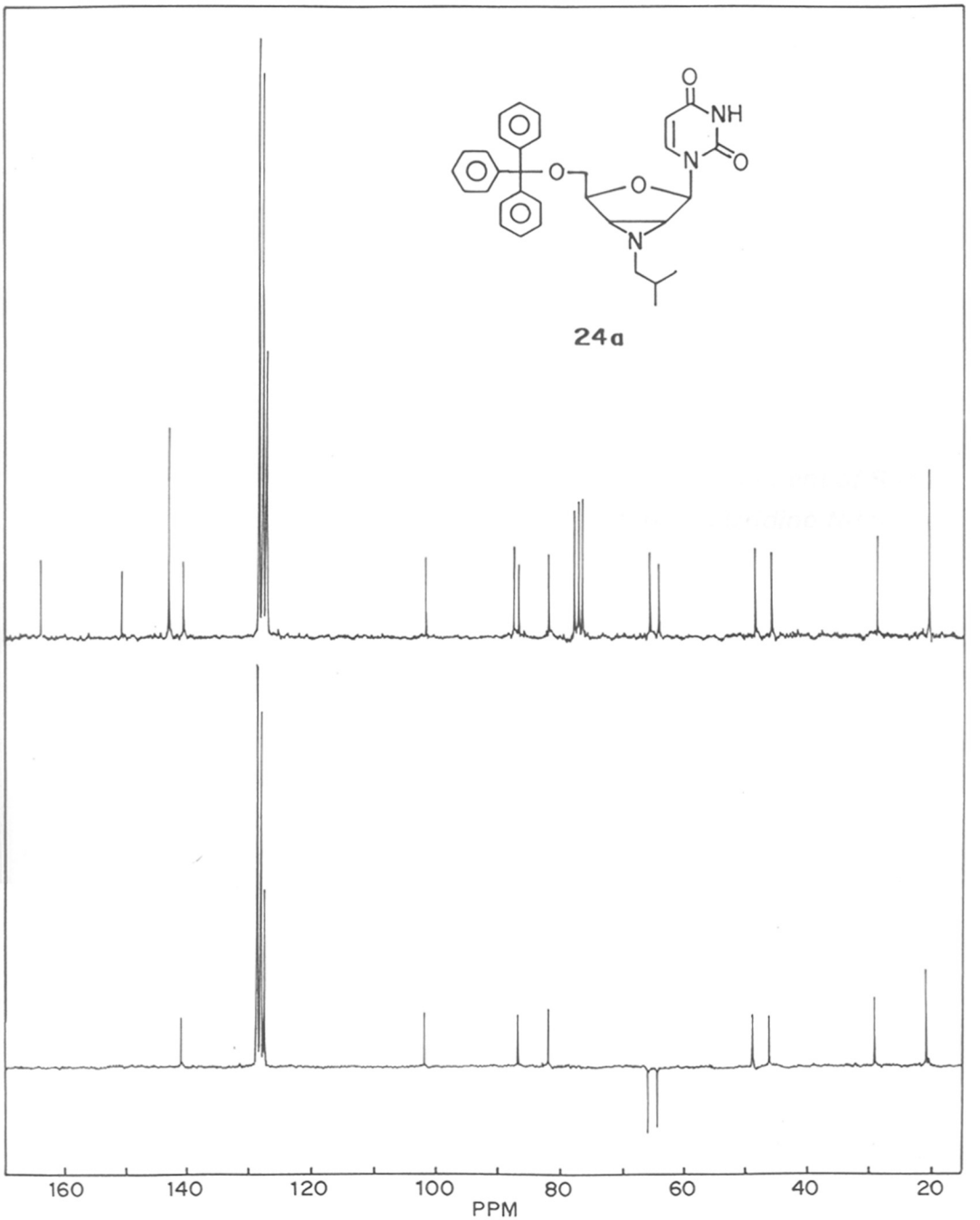

O
N
N
O
O
O
N
S
23
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
1500
1000
500
HERTZ
PPM


NH
O
O
N
O
N
TrO
24a
9
8
7
6
5
4
3
2
1 PPM
0



24a

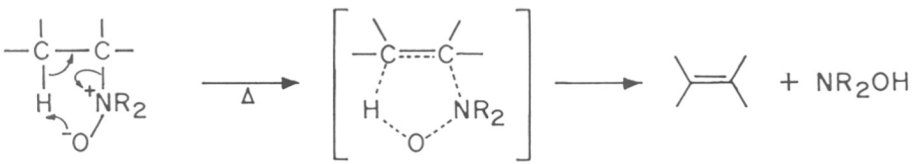
CHAPTER-II

Studies on the Thermal Degradation and Rearrangement of Sugar Modified Uridine N-Oxides

2.1. Introduction:

Tertiary amines are oxidised *in vitro* and *in vivo* to amine -N-oxides[1]. N-oxidation of trimethylamine was demonstrated in dogs and rabbits[2]. N,N-dimethylaniline was oxidised to the corresponding N-oxide by pork liver microsomal fractions and the presence of a reduced pyridine nucleotide and oxygen dependent N-oxide synthatase was indicated[3]. N-methyl pyrrolidine moiety of the natural (2'S)-(-)-nicotine and N-methyl piperidine moiety of (-) methyl anabasin were biotransformed to their respective diastereoisomeric N-oxides[4,5]. Tertiary amine N-oxides are also interesting because under pyrolytic conditions, they undergo two major reactions: a) N-oxides having β-hydrogen atoms undergo an elimination reaction known as Cope elimination[6-12] with the formation of olefins **2** and hydroxylamines **3** (**Scheme-2.1**);

Scheme-2·1



1 T.S. **2** **3**

and b) Meisenheimer rearrangement of an alkyl or aryl group from N to O for N-oxides without β-hydrogen[13-17] to form substituted hydroxylamine **5** (**Scheme-2.2**). It has been shown

Scheme-2·2

4 **5**

R^1 = allyl, benzyl, neopentyl

R^2, R^3 = alkyl, Aryl

recently that some piperidine N-oxides containing cyclopropyl ring at N-1 position, formed descyclopropyl secondary amines in the presence of trifluoro acetic anhydride; this reaction may serve as a model for the mechanism based inactivation of monoamine oxidase B in cyclopropylamines[18].

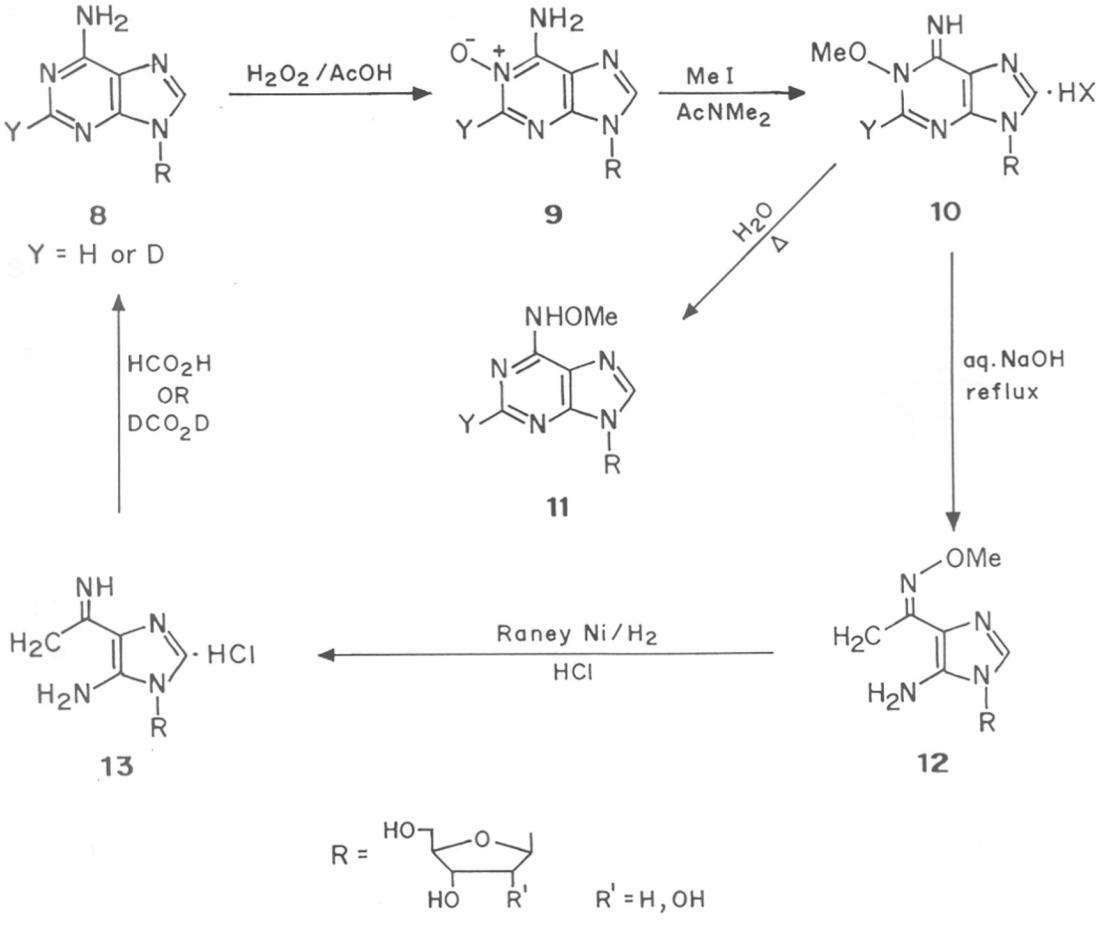
There are quite few reports on the synthesis and behavior of N-oxides derived from purine nucleobases[19-24]. Interestingly, adenine-1-oxide **6** was shown to get oxidised[19] by xanthine oxidase to 8-hydroxyadenine-1-N-oxide **7** (**Scheme-2.3**). Adenosine-1-oxide **8**[21,22] (Y=H) on

Scheme - 2·3

6 **7**

treatment with methyl iodide produced the 1-methoxy derivative **10** which when refluxed with aqueous sodium hydroxide gave monocyclic N-alkoxy carboxamidine **12**. **12** on catalytic reduction in the presence of hydrochloric acid produced the corresponding monocyclic carbamidine hydrochloride **13.** Cyclisation of **13** to adenosine-2-d **8** (Y=D) by incorporation of a deuterated C_1 unit was effected in formic acid-d_2. Compound **10** when heated in water produced the rearranged product **11** (**Scheme-2.4**). Similarly, adenosine-1-oxide **8** (Y=H) was converted to adenosine-2-d **8** (Y=D) by "fission and reclosure" technology. A series of adenosine-1-N-oxides were synthesised and shown to be active against vaccinia virus *in vitro* and *in vivo*[23]. Adenine-N-oxide which was generated within the DNA when exposed to hydrogen peroxide, was reductively repaired by γ-glutamyl cysteinyl glycine (glutathione) under irradiation with a sunlamp to give back adenine[24]; this repair reaction was also shown[24] to work in case of adenosine-1-N-oxide to adenosine. However, as far as our knowledge goes in the literature, no study has been done on the synthesis and properties of N-oxides of the sugar modified aminonucleosides.

Scheme - 2·4

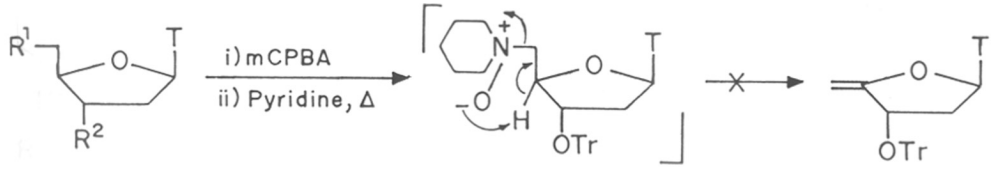


2.2. Present Work:

In the previous chapter (Chapter-I) we reported the synthesis of a series of sugar modified aminonucleosides by opening the known 5'-O-trityl-2',3'-O-anhydro-*lyxo*uridine epoxide by amines under controlled conditions[25]. The aminoalcohols obtained from the reactions of secondary amines and uridine epoxide turned out to be excellent substrates for the present study. Aminonucleosides were generally converted to the corresponding N-oxides by reacting with m-CPBA. N-oxides, except compound **15**, were not isolated.

Reactions of N-oxide derived from 5'-deoxy-5'-N-piperidino-3'-O-tritylthymidine 14c: Compound **14c** was synthesised by tritylating compound **14a**[26] with trityl chloride in presence of catalytic amount of DMAP followed by treatment with piperidine. Compound **14c** was treated with m-CPBA in dichloromethane to get the corresponding N-oxide **15**. This compound however did not produce the desired product **16** or any piperidine ring-opened product[9] when heated in pyridine; unreacted **15** was recovered in 75% yield (**Scheme-2.5**).

Scheme - 2·5

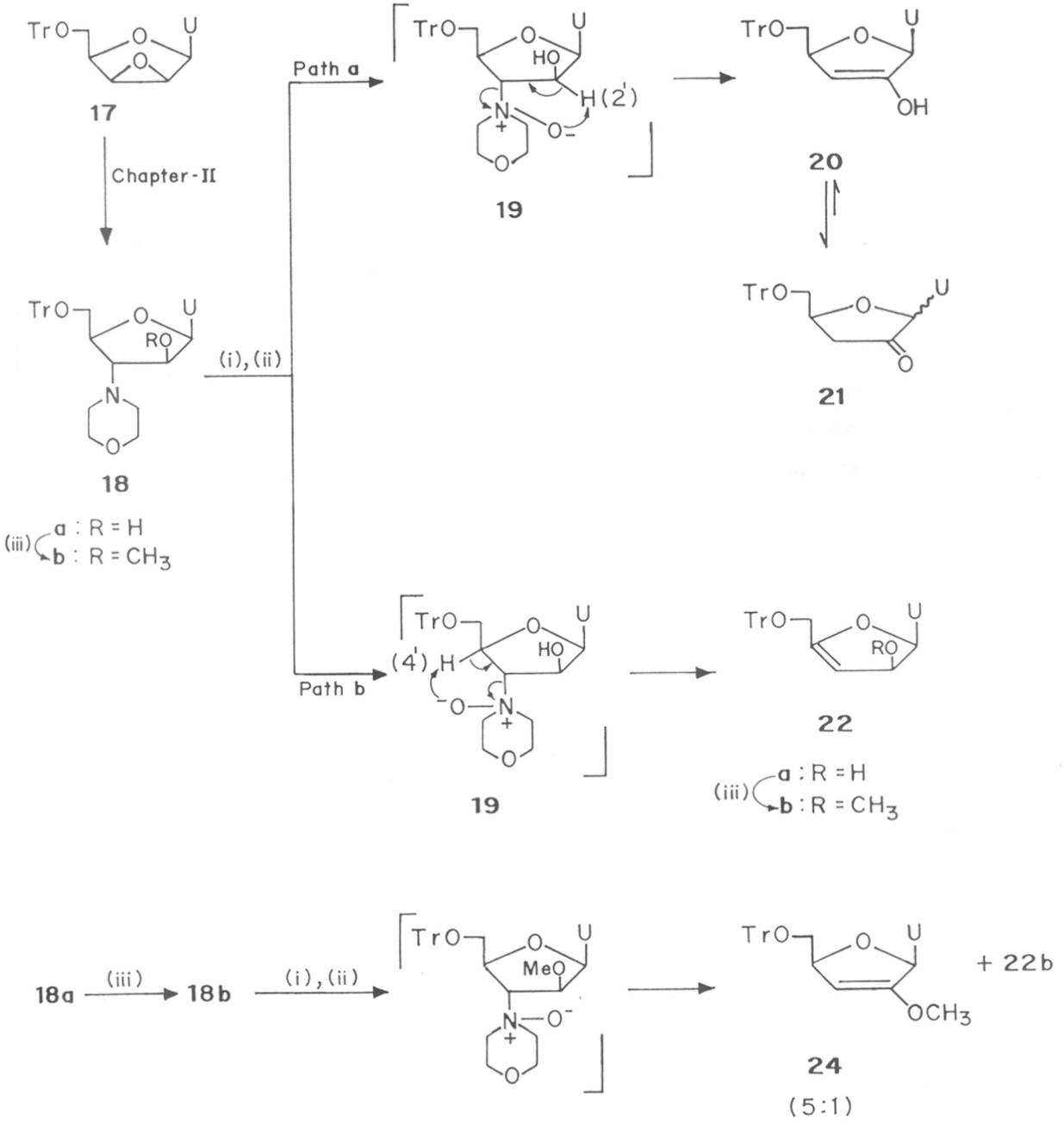


a : R^1 = OTs ; R^2 = OH
b : R^1 = OTs ; R^2 = OTr
c : R^1 = N⟨⟩ ; R^2 = OTr

Reaction of N-oxides derived from 5'-O-trityl-3'-deoxy-3'-N-morpholino-*ara*uridine 18a: The amine oxide **19** derived from the m-CPBA oxidation aminoalcohol **18a**[25], when heated in pyridine underwent elimination to produce a mixture of three compounds (**Scheme-2.6**). The analysis of the mixture revealed the presence of three products, namely a mixture of the α- and β- anomer of the 2'-keto uridine **21** (63%) and the 3'-deoxy-3'-ene derivative **22a** (29%).

Reactions of N-oxides derived from 5'-O-Trityl-3'-deoxy-3'-N-morpholino-2'-O-methyl-*ara*uridine 18b: Compound **18a** was methylated by treatment with methyl iodide and sodium hydride in dioxane . The methylated compound **18b** was oxidised to compound **23** and the amine oxide **23** was heated in pyridine. Again a mixture of compounds **24** and

Scheme - 2·6



(i) mCPBA , $CHCl_3$ (ii) Pyridine, 100°C (iii) NaH , MeI , Dioxane

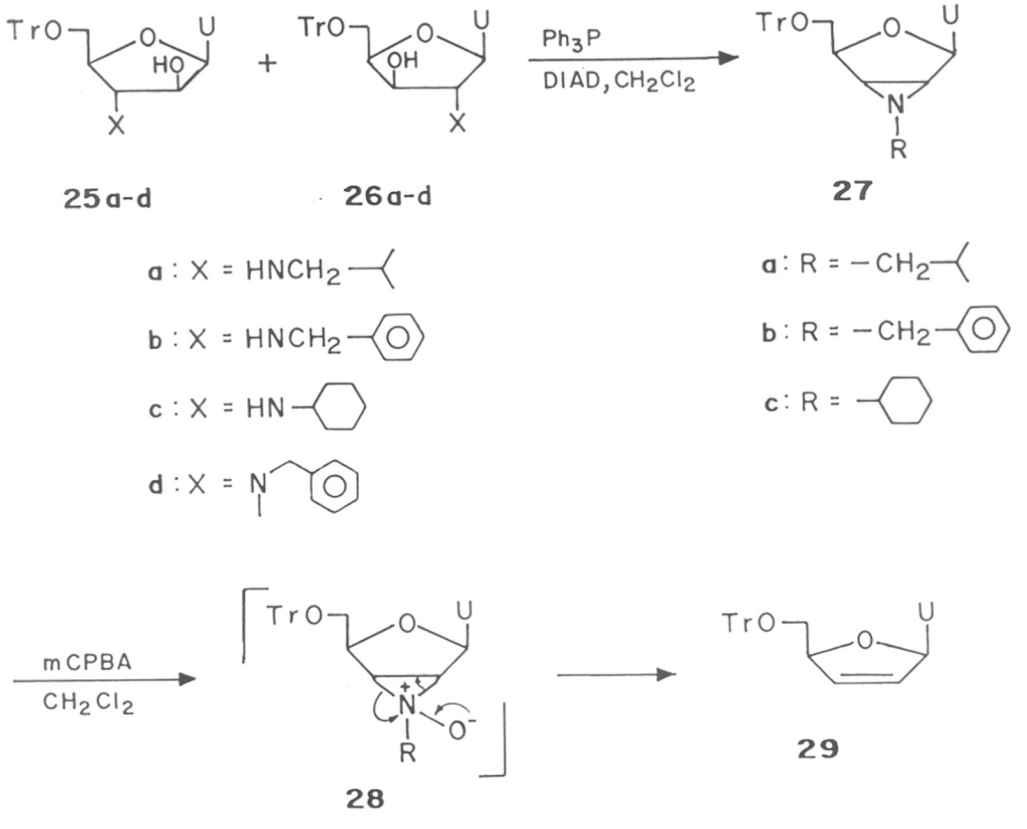
22b were obtained in a ratio 5:1 (^{1}H-NMR) (**Scheme-2.6**). Although these compounds could not be separated, **22a** was methylated and the product **22b** was added to the mixture of **24** and **22b**. The ^{1}H-NMR of this mixture showed the enhancement of the peaks corresponding to the minor component, proving thereby that the minor compound was indeed compound **22b**.

Reactions of N-oxides derived from N-alkyl aziridines 27a-c: In the previous chapter (Chapter-I) we reported a facile synthesis of 2',3'-dideoxy-2',3'-(N-isobutyl) epimino uridine **27a** from a mixture of 2'-deoxy-2'-N-isobutylamino-*ara*- and 3'-deoxy-3'-N-isobutylamino-*xylo*uridines **25a** and **26a** respectively. Compounds **27b** and **27c** were synthesised from the mixtures of **25b/26b** and **25c/26c** respectively following the same methodology. Compounds **27a-c** were treated with m-CPBA in dichloromethane at ambient temperature; the only nucleoside based product that was isolated from all these reactions was 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl) uracil **29** in 45%, 62% and 52% yields respectively after two steps (**Scheme-2.7**).

Four membered ring formation from uridine N-oxides: We have reported in the previous chapter (Chapter-I) that compounds of the type **30a** could be easily synthesised[25] from a mixture of 5'-O-trityl-2'-deoxy-2'-pyrrolidino-*xylo*- and 5'-O-trityl-3'-deoxy-3'-pyrrolidino-*ara*uridines. Compound **30a** was oxidised with m-CPBA and the N-oxide was heated in pyridine at elevated temperature. An oxazetidine derivative **31a** was isolated from the reaction mixture in 72% yield. The same product **31a** was isolated in 74% yield when compound **32a** was oxidised and heated in pyridine. Similarly, compound **30b** and **32b** were converted to **31b** in 80% and 54% yields respectively. The oxazetidine product obtained from the thermal degradation of the N-oxide of **30c** was somewhat unstable. A close examination of the ^{1}H-NMR and HRMS revealed (see later) that the product was infect the aminoalcohol **38c** and not the expected oxazetidine **31c**. Compound **30d**, however, produced an inseparable mixture of products. Conversion of **30a-c** to oxazetidines **31a-c** showed that this reaction is general in nature. (**Scheme- 2.8**).

Rearrangement reactions of uridine N-oxides: The regioisomer of **32a, 34a** was (for synthesis of **34a-c**, see experimental) oxidised and the N-oxide was heated in pyridine. The

Scheme-2·7

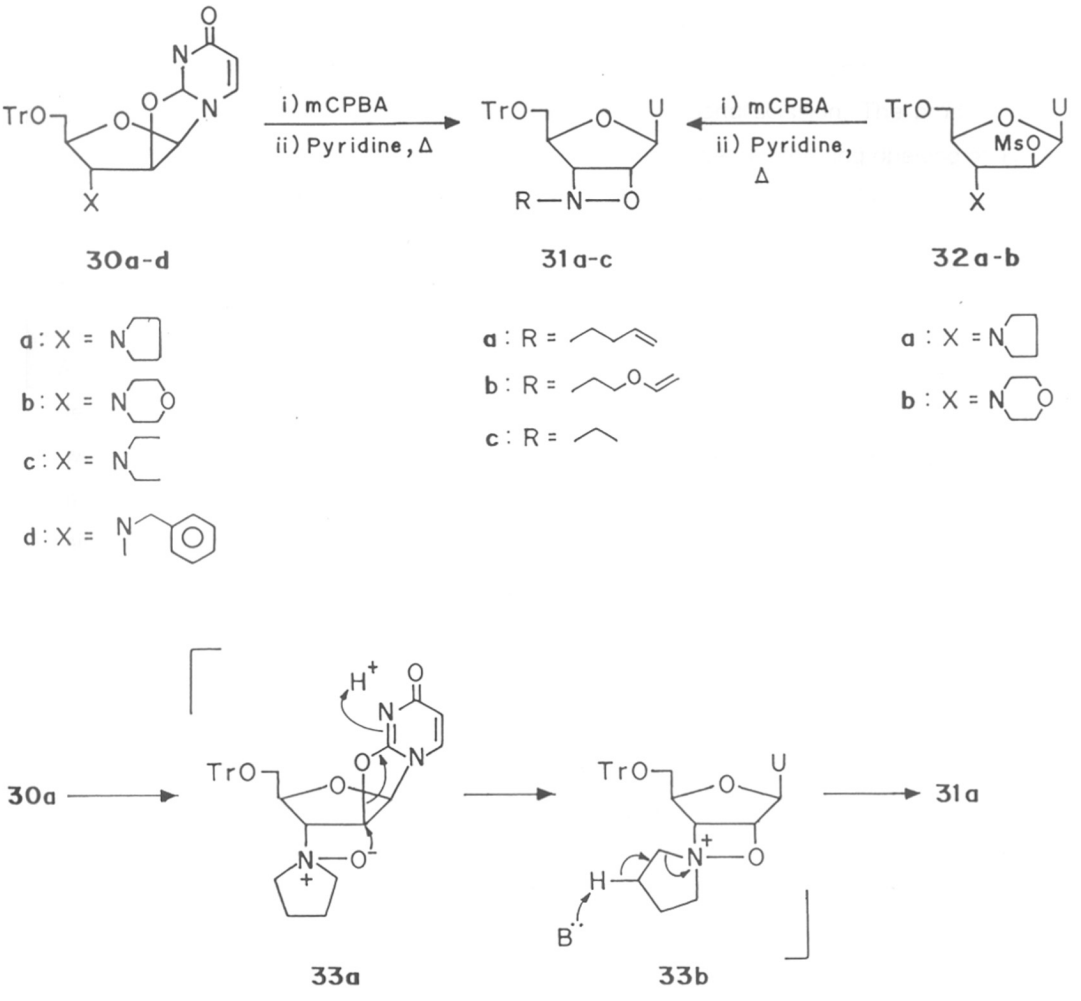


N-oxide **37a**, underwent rearrangement to produce compound **35a**. The 2'-deoxy-2'-N-morpholino-*xylo* **34b** and 2'-deoxy-2'-N-(N-benzyl)methylamino-*xylo* **34c** derivatives under the same sets of reaction conditions rearranged to compound **35b** and **35c** respectively in a similar fashion (**Scheme 2.9**).

2.3. Structural Assignment:

The structures of all new compounds were assigned unambiguously by chemical as well as spectroscopic means. The key compounds, such as, **31a-b**, **38c** and **35a-c** were also characterised by HRMS analysis. In fact the correct structure of the product obtained from the thermal degradation of the N-oxide of **30c** was originally based on HRMS data. The (MH)+ value at m/z 514 ($C_{30}H_{31}N_3O_5$+1) suggested the structure **38c** and not **31c** which would have

Scheme-2·8

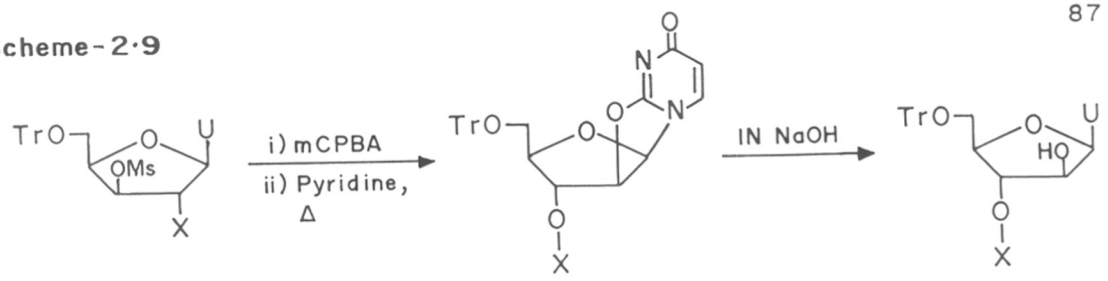


generated a peak at m/z 512 ($C_{30}H_{29}N_3O_5$+1). This assignment was further supported by the appearance of the H-6 peak of **38c** at 8.05 ppm (approx. 8.0 ppm for both **38a** and **38b**). H-6 signals of **31a** and **31b**, on the other hand merged with aromatic signals. Moreover, unlike the H-1' signals of **31a** (5.89 ppm, d, J=1.7 Hz) and **31b** (5.80 ppm, d, J=1.6 Hz), H-1' of **38c** appeared at 5.83 ppm as a singlet. Attempted acetylation (pyridine/acetic anhydride) of compound **31b** failed, proving thereby, that compound **31b** did not have any free amino- or hydroxyl groups. However, the following experiments were done to establish the structures

of the oxazetidine derivatives **31a-c**. We expected that under catalytic hydrogenation/hydrogenolysis, N-O bonds of compounds **31a-c** would cleave to generate 3'-deoxy-3'-N-alkylaminouridines. Therefore, we subjected **31a** to catalytic transfer hydrogenation using 4% formic acid as the hydrogen source. Interestingly, under the reaction conditions, N-butenyl moiety cyclised[27] back to pyrrolidine following the N-O bond scission. The product was, however, *not* similar to the *ara*- and *xylo*- derivatives obtained by the ring opening of **17** by pyrrolidine[25]. The product was, therefore, 3'-deoxy-3'-N-pyrrolidino-5'-O-trityluridine **38a**. Compound **38a** on mesylation followed by DBU treatment at room temperature produced the known 2,2'-O-anhydro derivative **30a**. Similarly, **31b** was converted to **30b** (**Scheme 2.10**).

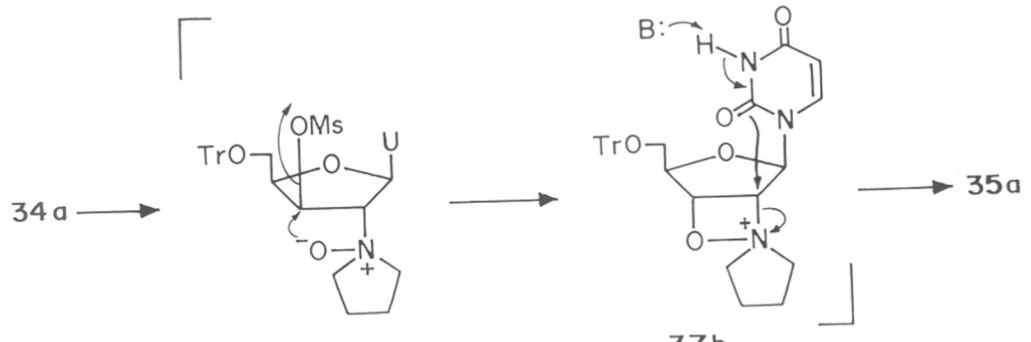
Although the spectroscopic data of compounds **35a** and **35b** were almost similar, the third derivative in the series **35c** produced a significantly different ^{1}H-NMR spectrum where the two peaks tentatively assigned as H-1' (6.09 and 6.13 ppm for compounds **35a** and **35b** respectively) and H-2' (5.38 and 5.29 ppm for compounds **35a** and **35b** respectively) were missing. Instead, there were two additional signals in the aromatic region. Interestingly, however, the ^{13}C-spectrum of compound **35c** was readily comparable to those of compound **35a** (**Figure 2.1**) and **30d** (**Figure 2.2**). Although the deshielding of H-1' proton towards aromatic region with intact amino group and the absence of mesyl group indicated towards the presence of an enamine type functionality[28] in the structure of the compound **35c**, the ^{13}C-NMR spectra were similar to those of 2,2'-O-anhydro derivatives **35a** and **35b**; moreover, the presence of a signal at around 110 ppm (signal arising of C-5 for 2,2'-O-anhydro derivatives) and absence of peak at around 101-102 ppm (signal arising of C-5 for ara-uridines[25] strongly argued in favour of the presence of a 2,2'-O-anhydro ring structure rather than a double bond. However, to confirm the structure of compound **35c** unambiguously, we subjected compounds **35b** and **35c** to alkaline hydrolysis[25], under which the 2,2'-O-anhydro bridge was known to undergo a scission to generate *ara*-nucleosides **36b** and **36c.** The ^{13}C-NMR spectra of compounds **36b** and **36c** were comparable (**Figure-2.3**) and in both the cases signals appeared at around 101-102 ppm. Moreover, the H-1' signal of compound **36c** appeared at the expected region, i.e. 5.98 ppm (6.11 for **25d** and 6.10 for **36b**) (**Figure-2.4**). This experiment established unambiguously that compound **35c** was indeed a 2,2'-O-anhydro derivative.

Scheme-2·9



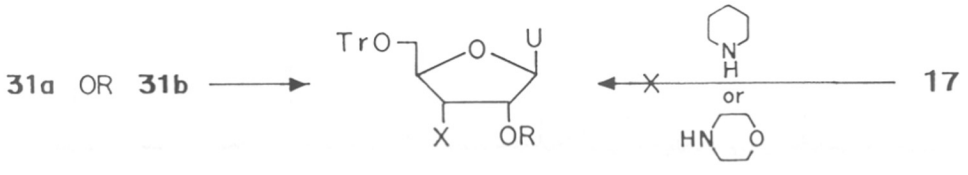
34a-c **35a-c** **36b-c**

a : X = N ; **b** : X = N O ; **c** : X = N



37a **37b**

Scheme-2·10



(ii) → **38a** : X = N ; R = H

(ii) → **39a** : X = N ; R = Ms

(ii) → **38b** : X = N O ; R = H

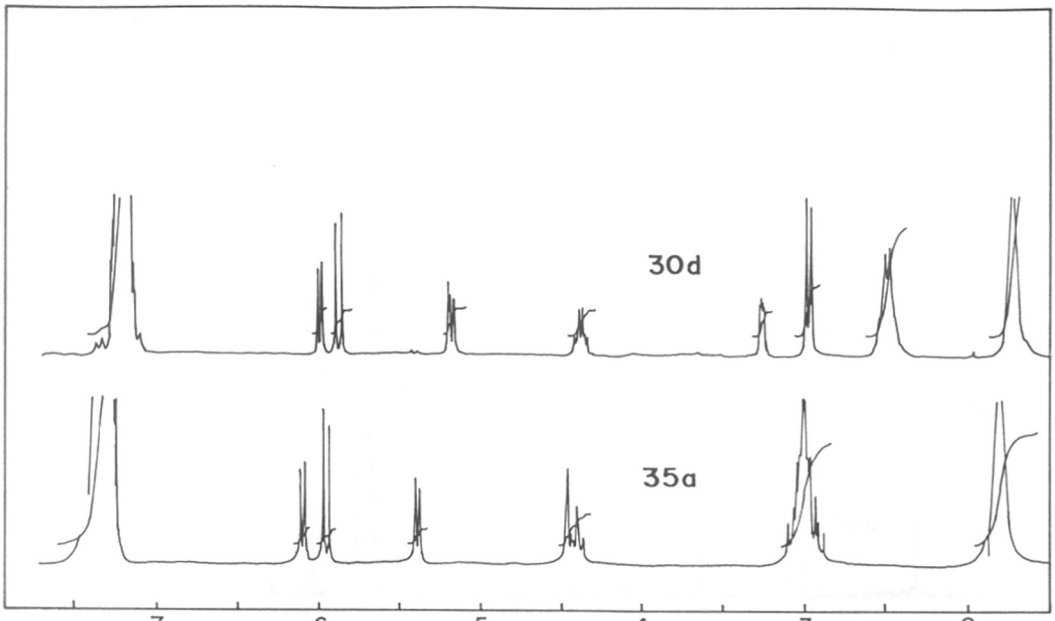
(ii) → **39b** : X = N O ; R = Ms

38c : X = NH ; R = H

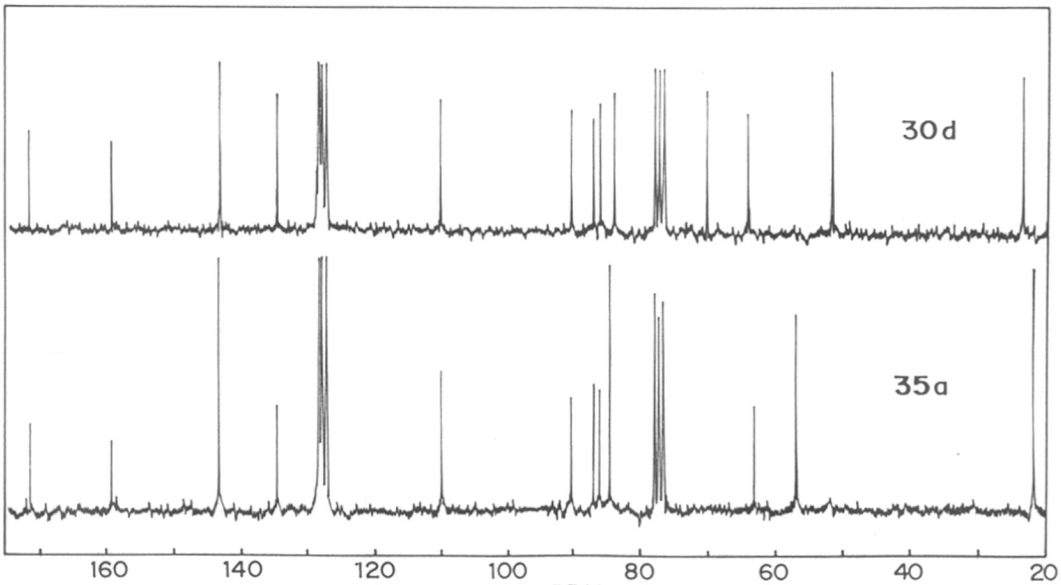
39a —(iii)→ **30a** ; **39b** —(iii)→ **30b**

(i) Pd/C , HCOOH , MeOH , 80°C ; (ii) MsCl , Pyridine, 0°C

(iii) $CHCl_3$, DBU , RT



PANEL A



PANEL B

Figure-2·1

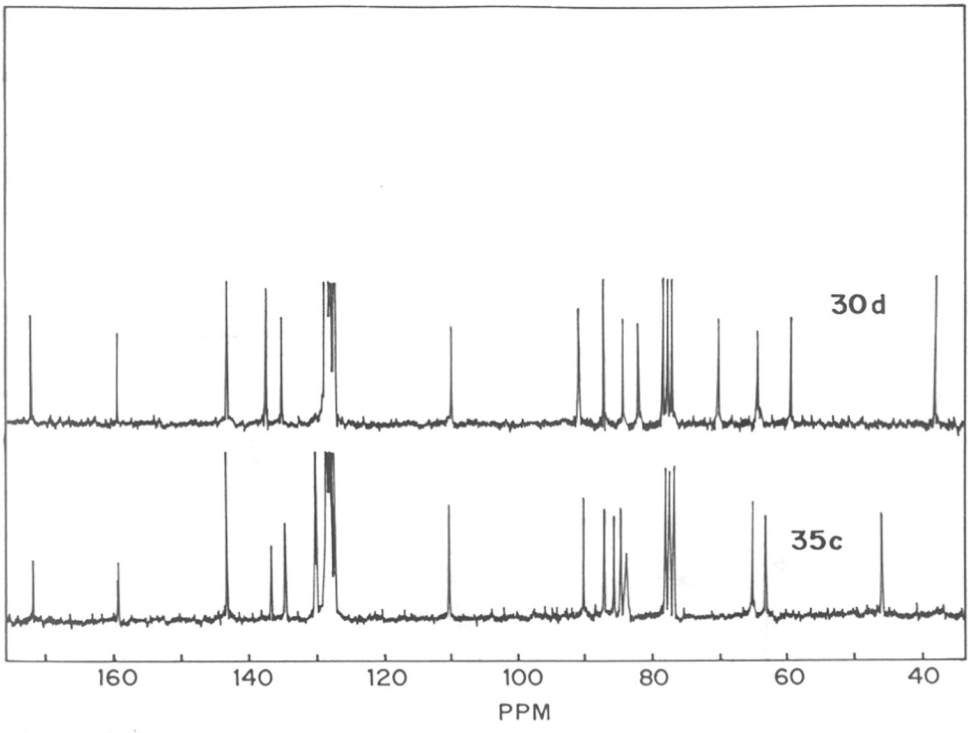


Figure - 2·2

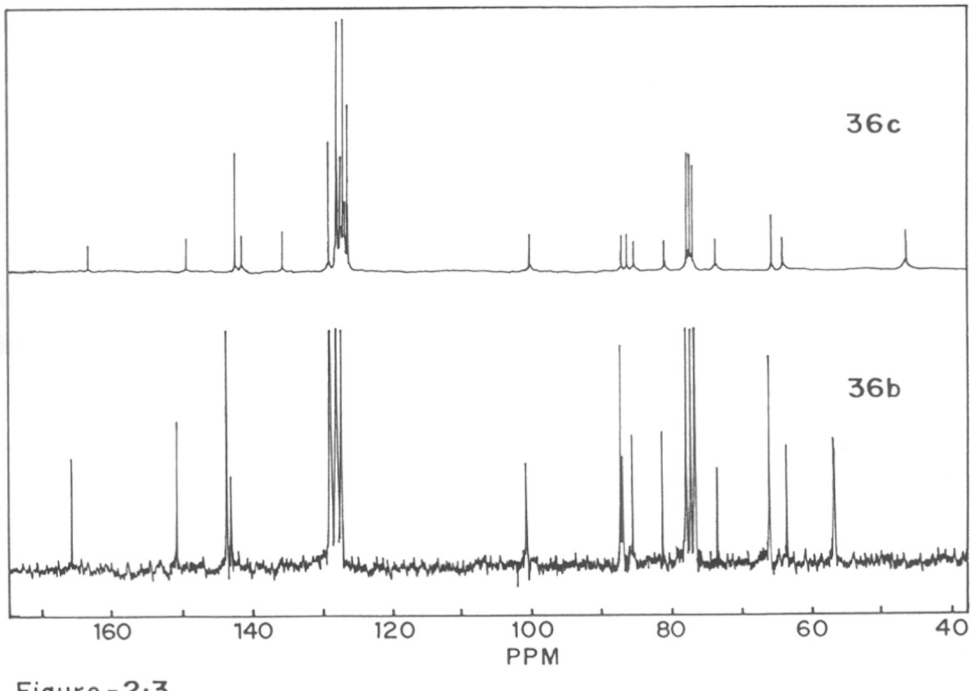


Figure - 2·3

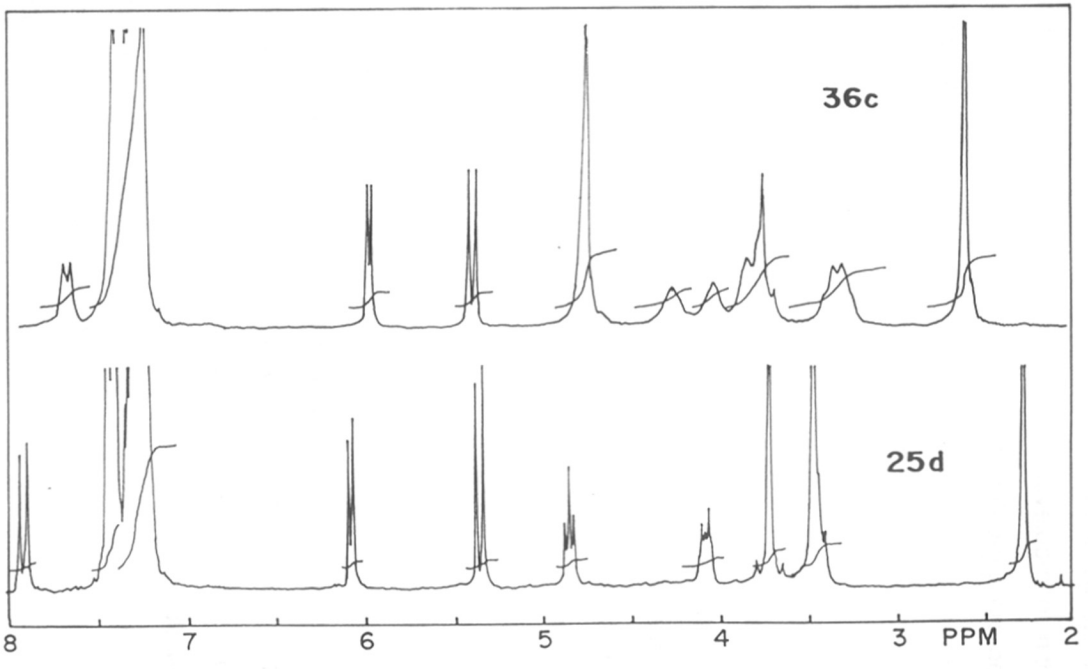


Figure - 2·4

2.4. Discussion:

The occurrence of unsaturations in the sugar part of nucleoside antibiotics, such as augustmycin A[29-31] has triggered the interest of organic chemists for the creation of unsaturations in various positions of nucleosides[32]. The development in this area was further stimulated with the recent approval of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl) thymine (d_4T) for the treatment of AIDS[33,34]. In view of the fact that N-oxides were indeed used[6-12] in general for the preparation of olefines, we studied the thermal breakdown pattern of compounds such as 5'-deoxy-5'-piperidino-3'-O-tritylthymidine **14c** and 3'-deoxy-3'-morpholino-5'-O-trityl-*ara*uridine **18**. Thermal degradation study of compound **15** derived from compound **14c** did not produce the desired product. It may be argued that the formation of the five membered transition state which was required[9,12] for the stereoselective *syn* elimination process of amine oxide was not possible. It was envisaged, however, that an amine oxide connected to the 2' or 3' sites of the carbohydrate moiety of nucleosides would be better suited to initiate proton abstraction from the β- position because of the conformational flexibilities of the furanose rings. In fact the amine oxide **19** derived from the aminoalcohol **18a**[25], when heated in pyridine underwent elimination to produce a mixture of compounds (**Scheme-2.6**). The analysis of the mixture revealed the presence of three products, namely a mixture of the α- and β- anomer of the 2'-keto uridine **21** (63%) and the 3'-deoxy-3'-ene derivative **22a** (29%). Formation of **21** and **22a** may be explained by involving two different reaction pathways as depicted in **scheme-2.6**. As both H-1' and H-4' are β-to the amine oxide **19**, removal of either of the proton was possible. Mixture of 2'-keto uridines **21** would be formed if the reaction followed *path a*; and *path b* would generate compound **22a**. In order to enhance the electropositive character of C-2' carbon (i.e. to enhance the acidity of H-2'), the 2'-O-methyl derivative **18b** was synthesised from **18a** (see experimental). Oxidative degradation of compound **18b** follows the same reaction pathways to afford a mixture of compounds **24** and **22b** (5:1). It may be assumed from the reactions of N-oxides **19** and **23** that in both the cases five membered transition state formation between H-2'/ C-2'/ C-3'/ N^+-O^- was more facile than between H-4'/ C-4'/ C-3'/ N^+-O^-.

The most successful elimination reaction of N-oxide was observed with the amine oxides generated from the cyclic tertiary amines or N-alkyl aziridines **27a-c**. There are two

examples[35a,35b] on the conversion of methyl 4,6-O-benzyledene-2,3-dideoxy-2,3-epimino-α-D-alloside and the corresponding manno-side to methyl 4,6-O-benzylidine-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside through the formation of the N-nitrosoepimine intermediate. To the best of our knowledge, deamination *via* N-alkylaziridine N-oxides[36] has not been studied with carbohydrates in general and nucleosides in particular. Compounds **27a-c** when oxidised with m-CPBA produced 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl) uracil **29** .The formation of an N-oxide of general structure **28** may be assumed which collapsed to compound **29** through an elimination process (**Scheme 2.7**). As almost all the reactions applicable to uridine are also applicable to ribothymidine, it may be concluded logically that the above synthetic route could be an alternative method of choice for the synthesis of d_4T from ribothymidine. Moreover as it is well-known[1] that relatively lipophilic xenobiotics are converted into polar, water soluble metabolites (such as amine-oxides) by endogenous enzymes in mammals, it may be argued that epimino nucleosides with free 5'-hydroxyl group may as well act as pro-drugs for compounds such as d_4T, provided the epimino-nucleosides are recognised by the N-oxide synthetase[3] present in the biological system.

As there was no specificity of proton abstraction in case of N-oxides such as **19** or **23**, we decided to introduce rigidity in the molecule to see whether the lack of conformational mobilities dictates the type of product formation. Oxidative degradation study of amine oxides derived from compound **30a-c** produced oxazetidine derivatives **31a-c**. Formation of products **31a-b** were unexpected as according to earlier report[9], in case of Cope reaction, ring cleavage did not occur when the ring size was six membered and occurred easily as "the ring size increased from seven to eight atoms". It may be argued that in presence of a leaving group at the β position (in this case, C2'), attack by nucleophilic O^- of N-oxide **33a** is possibly a preferred route than Cope elimination. (Formation of **35a-c** from **34a-c** also supports this view; see **Scheme 2.9**). Subsequent Hofmann elimination of the oxazetidinium ion **33b** generates the observed oxazetidine **31a**. Compound **31b-c** also followed similar reaction pathways to produce compound **31b-c** (**Scheme 2.8**).

The interesting conversion of **30a-c** to **31a-c** or **32a-b** to **31a-b** led us to study the behavior of the regioisomers of **32a-b**, **34a-c** under the similar reaction conditions. Thus, compound **34a** was (for synthesis of **34a-c**, see experimental) oxidised and the N-oxide was heated in

pyridine. To our surprise, we found that a product completely unrelated (^{1}H-NMR) to compound **31a** was obtained. The 1H-NMR and 13C-NMR data of compound **35a** were very close to those[25] of compound **30a** except for the peaks arising from H-3' and C-3' positions (**Figure-2.1**). On the basis of spectroscopic evidence we concluded that oxazetidine intermediate **37b** was formed by the displacement of the C-3' mesylate and subsequently the C-2 oxygen attacked the C-2' position from the top as the 2,2'-O-anhydro ring formation was known[37] to be a highly facile reaction in presence of a leaving group at the C-2' position; the electron deficient pyrrolidium moiety acted as a leaving group and remained connected to the C-3' position through an oxygen atom after C2'-N(+) bond scission took place.

The conversion of **34a-c** to **35a-c**, in essence, involved the scission of C-N bonds of the intermediate N-oxides (for example, **37a**) followed by C-O bond formation. This N -> O migration of an alkyl group (in our case a furanosyl moiety) *via* N-oxide led us to compare the present rearrangements with Meisenheimer rearrangement. It may be noted that even in case of reported Meisenheimer rearrangements, the reactions were triggered by the attack of the nucleophilic oxides of amine oxides to the electron deficient centers of the other functional groups attached to nitrogen. This was followed by N(+)-C bond scission (**Scheme 2.11**). The only difference between our reactions and the actual Meisenheimer rearrangements reported earlier was that, a part of the system under study, i.e. the methanesulfonyl

Scheme - 2·11

Meisenheimer Rearrangement
(Ref : 13)

group was eliminated. However, as far as the amine oxide portion was concerned, the reaction resembled a [2,2] sigmatropic rearrangement.

2.5. Conclusion:

It has been demonstrated in this chapter that nucleoside N-oxides may be used as versatile intermediates for generating a wide variety of compounds. To the best of our knowledge, this work also constitutes the first report on the use of reactions related to Cope reaction and Meisenheimer rearrangement for the functionalisation of nucleosides.

Melting points were uncorrected. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin layer chromatography was performed on Merck precoated 60 F_{254} plates. Compounds were visualized under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 60-100 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 a Bruker ACF200 NMR spectrometer (δ scale) using TMS or solvent chloroform-d as internal standards. ^{13}C-NMR (75 MHz) spectra were also recorded with a Bruker MSL300 NMR spectrometer. Mass spectra were recorded on a Finnigan MAT 1020B GC/MS. HRMS were recorded on VG Autospec-M using LSIMS technique with cesium ion (22Kv). Glycerol was used as matrix.

Synthesis of 5'-deoxy-5'-N-piperidino-3'-O-tritylthymidine 14c:

To a solution of 5'-O-tosylthymidine **14a**[26] (1g, 2.5mmol) in pyridine (25ml), trityl chloride (1.1g. 4mmol) and DMAP (0.1g) was added and the reaction mixture was heated at 110°C for 15h. The pyridine solution was poured into saturated $NaHCO_3$ solution and filtered. The residue was dissolved in EtOAc, dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel column to produce compound **14b** in 30% yield. Compound **14b** was dissolved in DMSO (3ml) and piperidine (1ml) was added. The clear solution was stirred overnight at room temperature and then heated at 75°C for 24h. The reaction mixture was then poured into saturated $NaHCO_3$ solution and filtered. The residue was dissolved in CH_2Cl_2, dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel column to get the title compound .

Yield: 86%

mp: 147-151°

^{1}H NMR: ($CDCl_3$):δ 7.55-7.25 (m, 16H, trityl, H-6), 6.21 (t, 1H, H-1'), 4.06 (m, 2H, H-3', H-4'), 2.41-2.30 (m, 8H, H-2', H-2", H-5', H-5", -CH_2-N-CH_2-), 1.88 (s, 3H, -CH_3), 1.59-1.40 (m, 6H, -CH_2-CH_2-CH_2-).

^{13}H NMR: ($CDCl_3$):δ 163.4, C-4, 149.7, C-2, 143.0, trityl, 135.7, 127.9, 127.2, 126.6, trityl, 109.7, C-5, 86.8, trityl, 85.7, C-1', 80.3, C-4', 75.2, C-3', 58.1, C-5', 53.0, $-CH_2-N-CH_2-$, 36.9, C-2', 22.9, 21.6, $-CH_2-CH_2-CH_2-$, 11.3, $-CH_3$.

Oxidative degradation of 5'-deoxy-5'-N-piperidino-3'-O-tritylthymidine 14c:

To a solution of compound **14c** (0.25g, 0.45mmol) in dichloromethane (20ml), m-CPBA (0.25g, 1.4mmol) was added and the reaction mixture was stirred at ambient temperature for 1h. Dichloromethane was removed under reduced pressure and the residue was dissolved in pyridine (20ml). The pyridine solution was heated at 90°C for 7h. There was no reaction (TLC).

Oxidative degradation of 5'-O-trityl-3'-deoxy-3'-N-morpholino-*ara*uridine 18a:

To a solution of **18a**[25] (0.34 g, 0.61 mmol) in chloroform (20 ml), m-CPBA (0.27 g, 1.5 mmol) was added and the mixture was stirred at room temperature for 0.5h. Chloroform was removed under reduced pressure and the residue was dissolved in pyridine (20 ml). The pyridine solution was heated at 100°C for 10h. Pyridine was removed under reduced pressure and residual pyridine was coevaporated with toluene. The oily residue was dissolved in EtOAc (60 ml) and the solution was washed with saturated $NaHCO_3$ (2 x 20 ml) solution followed by water (2 x 50 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness and the residue was purified over silica gel to give 5'-O-trityl-3'-deoxy-2'-ketouridines **21** (63%) and 5'-O-trityl-3'-deoxy-3',4'- didehydro uridine **22a**.

Compound 22a:

Yield: 29%

mp: 99-101°C

^1H NMR: ($CDCl_3$):δ 10.65 (s, 1H, NH), 7.55-7.20 (m, 16H, H-6, trityl), 6.52 (d, 6.4Hz, 1H, H-1'), 5.62 (d, 8.0Hz, 1H, H-5), 5.42 (s, 1H, H-3'), 5.27 (d, 6.3Hz, 1H, H-2'), 3.76 (s, 2H, H-5', H-5").

^{13}H NMR: ($CDCl_3$):δ 165.4, C-4, 158.5, C-2, 150.8, C-4', 143.6, trityl, 143.17, C-6, 128.8, 128.2, 127.5, trityl, 101.3, C-5, 101.1, C-3', 87.6, trityl, 87.1, C-1', 71.9, C-2', 59.4, C-5'; MS (EI) m/z 225 (2, M-trityl).

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-morpholino-2'-O-methyl-*ara*uridine 18b:

To a suspension of NaH (0.06 g, 2 mmol) in dioxane (10 ml), a solution of **18a**[25] (0.35 g, 0.63 mmol) in dioxane (5 ml) was added and the mixture was stirred at room temperature for 0.5h. Methyl iodide (0.71 g, 5 mmol) was added dropwise and the reaction mixture was stirred at room temperature. After 24h the mixture was poured into saturated NH_4Cl solution (50 ml) and extracted with dichloromethane (3 x 20 ml). The combined dichloromethane extract was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give **18b**.

Yield: 69%

mp 106-109°C

^{1}H NMR: ($CDCl_3$):δ 8.93 (bs, 1H, NH); 7.78 (d, 8.2Hz, 1H, H-6); 7.48-7.27 (m, 15H, trityl); 6.16 (d, 5.2Hz, 1H, H-1'); 5.49 (dd, 1.9Hz, 8.2Hz, 1H, H-5); 4.05 (m, 2H, H-2', H-4'); 3.68 (t, 4H, $-CH_2-O-CH_2-$); 3.42 (m, 2H, H-5', H-5"); 3.30 (s, 3H, $-OCH_3$); 3.24 (m, 1H, H-3'); 2.57 (m, 4H, $-CH_2-N-CH_2-$).

^{13}C NMR: ($CDCl_3$):δ 163.9, C-4, 150.8, C-2, 143.5, trityl, 142.1, C-6, 128.7, 127.9, 127.3, trityl, 101.3, C-5, 87.1, trityl, 84.2, C-1', 80.0, C-4', 77.0, C-2', 69.7, C-3', 66.9, $-CH_2-O-CH_2$, 63.4, C-5', 58.4, $-OCH_3$, 50.9, $-CH_2-N-CH_2$; MS (EI) m/z 326 (23, M-trityl).

Oxidative degradation of compound 18b:

To a solution of **18b** (0.24 g, 0.42 mmol) in chloroform (15 ml), m-CPBA (0.2 g, 1.1 mmol) was added and the solution was stirred at room temperature for 0.5h. Chloroform was removed under reduced pressure and the residue was dissolved in pyridine (15 ml). The pyridine solution was heated at 80°C for 9h. Pyridine was evaporated under reduced pressure and

the residual pyridine was coevaporated with toluene. The residue was dissolved in EtOAc (60 ml) and the solution was washed with saturated $NaHCO_3$ (3 x 25 ml) solution followed by water (2 x 50 ml). The EtOAc part was dried over Na_2SO_4 and evaporated to dryness to give mixture of products **24** and **22b** (5:1) which could not be separated.

Compound 24:

^1H NMR: ($CDCl_3$):δ 8.75 (bs, 1H, NH), 7.69 (d, 8.2Hz, 1H, H-6), 7.49-7.24 (m, 15H, trityl), 6.80 (m, 1H, H-1'), 5.16 (dd, 2.2Hz, 8.1Hz, 1H, H-5), 4.96 (m, 2H, H-3', H-4'), 3.75 (s, 3H, $-OCH_3$), 3.40 (m, 2H, H-5', H-5").

^{13}H NMR($CDCl_3$): δ 163.7, C-4, 153.3, C-2', 151.2, C-2, 143.5, trityl, 140.8, C-6, 128.9, 128.1, 127.5, trityl, 102.8, C-5, 97.4, C-3', 87.4, trityl, 85.6, C-1', 82.9, C-4', 65.7, C-5', 58.4, $-O-CH_3$.

Synthesis of 5'-O-trityl-2'-O-methyl-3'-deoxy-3',4'-didehydrouridine 22b from compound 22a:

To a suspension of NaH (0.02 g, 0.6 mmol) in dioxane (5 ml), **22a** (0.05 g, 0.1 mmol) in dioxane (5 ml) was added and the mixture was stirred for 0.5h. Methyl iodide (0.14 g, 1 mmol) was then added and the reaction mixture was stirred at room temperature for 48h. The solution was poured into saturated NH_4Cl solution (20 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic part was dried over Na_2SO_4 and evaporated to dryness. The solid residue was purified over silica gel to give **22b**.

Yield: 48%

mp 76-78°C

^1H NMR: ($CDCl_3$):δ 8.8 (bs, 1H), 7.55-7.25 (m, 16H), 6.62 (d, 6.8Hz, 1H), 5.72 ((d, 8.0Hz, 1H), 5.42 (d, 1H), 4.61 (d, 1H), 3.75 (s, 2H), 3.25 (s, 3H).

Synthesis of 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)uracil 29:

General Method: A mixture of **17**[25] and the appropriate amine (5 eq) in DMSO (3 ml/mmol) was heated at 90-95°C. After the disappearance of the starting material (tlc) the reaction mixture was diluted with EtOAc (40 ml/mmol) and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness and the solid residue was purified by column chromatography to furnish a mixture of **25a-c** and **26a-c**. The mixture of **25a-c** and **26a-c** and triphenylphosphine (1.5eqv) was dissolved in dichloromethane (20 ml/mmol) and the solution was cooled using an ice-bath under argon. To this ice-cold solution, diisopropylazodicarboxylate (2 eq) was added slowly. The ice-bath was removed and the reaction mixture was stirred at ambient temperature for 6-8h. The solution was evaporated to dryness and the mixture was purified by column chromatography to produce **27a-c**. Compounds **27a-c** were treated with m-CPBA (1 eq) in dichloromethane (15 ml/mmol). After 2-8h at ambient temperature, dichloromethane was removed under reduced pressure and the residue was dissolved in EtOAc (25 ml/mmol). The EtOAc solution was washed with saturated aqueous K_2CO_3 solution (3 x 25 ml) followed by water (3 x 25ml). The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The colored material was purified by column chromatography to obtain **29** in 45%, 62% and 52% overall (based on compound **17** in 3 steps) yield from **27a**, **27b** and **27c** respectively.

mp: 189-191°C (EtOAc-pet ether, lit.[38] 188-191°C).

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-pyrrolidino-2,2'-O-anhydrouridine 30a:

The synthesis of the title compound has been described in chapter-I.

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-morpholino-2,2'-O-anhydrouridine 30b:

This compound was prepared following the same for the synthesis of compound **30a** in 61% overall yield from compound **17.**

mp 96-98°C·

^{1}H NMR: ($CDCl_3$):δ 7.38-7.24 (m, 16H, H-6, trityl), 6.09 (d, 6.0Hz, 1H, H-1'), 5.96 (d, 7.6Hz, 1H, H-5), 5.35 (dd, 1.4Hz, 5.9Hz, 1H, H-2'), 4.45 (m, 1H, H-4'), 3.71 (t, 4H, $-CH_2-O-CH_2$), 3.37 (m, 1H, H-3'), 3.01 (m, 2H, H-5', H-5"), 2.60-2.40 (m, 4H,$-CH_2-N-CH_2$).

^{13}C NMR: ($CDCl_3$):δ 171.8, C-4, 159.5, C-2, 143.5, trityl, 134.9, C-6, 128.6, 128.0, 127.4, trityl, 110.1, C-5, 90.6, C-1', 87.3, trityl, 84.6, C-2', 81.6, C-4', 71.9, C-3', 66.8, $-CH_2-O-CH_2$, 64.3, C-5', 50.3, $-CH_2-N-CH_2$.

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-diethylamino-2,2'-O-anhydrouridine 30c:

To a solution of **17**[25] (0.94 g, 2 mmol) in DMSO (10 ml), diethylamine (2.2 g, 30 mmol) was added and the reaction mixture was heated at 70°C for 76h. Excess diethylamine was removed under reduced pressure. The brown colored solution was dissolved in EtOAc (100ml) and washed with water (3 x 50 ml). The mixture of isomers was purified over silica gel to give an isomeric mixture of amino alcohols (0.71 g, 66%). The mixture was converted to **30c** as above in 40% yield.

mp: 74-76°C.

^{1}H NMR: ($CDCl_3$):δ 7.50-7.20 (m, 15H, trityl); 6.06 (d, 6.0Hz, 1H, H-1'); 5.95 (d, 7.4Hz, 1H, H-5); 5.29 (dd, 6.1Hz, 1.8Hz, 1H, H-2'); 4.32 (q, 1H, H-4'); 3.73 (m, 1H, H-3'); 3.02 (m, 2H, H-5', H-5"); 2.54 (m, 4H, $-CH_2-N-CH_2-$); 1.05 (m, 6H, 2x$-CH_3$).

^{13}C NMR: ($CDCl_3$):δ 171.9, C-4; 159.5, C-2; 143.4, trityl; 134.9, C-6; 128.5, 128.0, 127.4, trityl; 110.0, C-5; 90.5, C-1'; 86.9, trityl; 84.7, C-2'; 82.8, C-4'; 68.3, C-3'; 64.0, C-5'; 44.6, $-N-CH_2$; 13.5, $-CH_3$.

Synthesis of 5'-O-trityl-3'-deoxy-3'-N-(N-benzyl) methylamino-2,2'-O-anhydrouridine 30d:

A mixture of **17**[25] (1.41 g, 3 mmol), N-benzylmethylamine (2 g, 16 mmol) in DMSO (15 ml) was heated at 100°C for 15h. After usual work up the *xylo*- and *ara*- isomers were separated on basic alumina column.

5'-O-trityl-2'-deoxy-2'-N-(N-benzyl) methylamino-*xylo*uridine 26d:

Yield: 24%.

mp: 93-96°C

^{1}H NMR: ($CDCl_3$):δ 7.62 (d, 8.1Hz, 1H, H-6),7.46-7.27 (m, 20H, aromatic), 6.17 (d, 4.6Hz, 1H, H-1'), 5.60 (d, 8.1Hz, 1H, H-5), 4.52 (m, 1H, H-3'), 4.18 (q, 1H, H-4'), 3.69-3.50 (m, 5H), 3.22 (m, 1H, H-2'), 2.33 (s, 3H, -CH_3).

^{13}C NMR: ($CDCl_3$):δ 164.1, C-4; 150.6, C-2; 143.5, trityl; 141.7, C-6; 138.35, 128.7, 128.5, 128.1, 127.4, aromatic; 102.6, C-5; 87.7, trityl; 86.2, C-1'; 81.1, C-4'; 77.1, C-3'; 72.6, C-2'; 62.6, C-5'; 59.7,-N-CH_2; 39.1,-CH_3.

MS (EI) m/z 478 (14, M-uracilyl).

5'-O-trityl-3'-deoxy-3'-N-(N-benzylmethylamino)-*ara*uridine 25d:

Yield: 53%

mp: 97-100°C

^{1}H NMR: ($CDCl_3$):δ 7.90 (d, 8.0Hz, 1H, H-6), 7.53-7.24 (m, 20H, aromatic), 6.11 (d, 4.8Hz, 1H, H-1'), 5.37 (d, 8.0Hz, 1H, H-5), 4.89 (bs, 1H, H-2'), 4.45 (bs, 1H), 4.10 (m, 1H, H-4'), 3.71 (s, 2H, -N-CH_2), 3.40 (m, 3H, H-5', H-5"), 2.28 (s, 3H, -CH_3).

^{13}C NMR: ($CDCl_3$):δ 165.6, C-4, 150.9, C-2, 143.8, trityl, 139.0, C-6, 128.9, 128.4, 128.0, 127.3, aromatic, 100.6, C-5, 87.1, trityl, 86.6, C-1', 78.4, C-4', 71.1, C-2', 69.6, C-3', 64.6, C-5', 59.7, benzyl-CH_2, 38.3, -CH_3.

MS (EI) m/z 346 (3, M-trityl), 477 (5, M-uracil).

The title compound was prepared from compounds **25d** and **26d** following the procedure

described for compound **30a** in 62% yield.

mp: 85-87°C

^{1}H NMR: ($CDCl_3$):δ 7.45-7.25 (m, 20H, aromatic), 6.07 (d, 6.0Hz, 1H, H-1'), 5.96 (d, 7.4Hz, 1H, H-5), 5.37 (dd, 6.0Hz, 1.4Hz, 1H, H-2'), 4.48 (m, 1H, H-4'), 3.61 (m, 3H, H-3', -N-CH_2), 3.00 (m, 2H, H-5', H-5"), 2.30 (s, 3H, -CH_3).

^{13}C NMR: ($CDCl_3$):δ 171.9, C-4; 159.3, C-2; 143.2, trityl; 137.4, C-6; 135.0, 128.6, 128.3, 127,8, 127.3, 127.1, aromatic; 109.6, C-5; 90.4, C-1'; 86.7, trityl; 83.9, C-2'; 81.6, C-4'; 69.8, C-3'; 63.9, C-5'; 59.1,-N-CH_2; 37.8,-CH_3.

MS (EI) m/z 328 (45, M-trityl).

Synthesis of 5'-O-trityl-3'-deoxy-2',3'(N-butenyl-1,2-oxazetidino) uridine 31a:

Method A: To a solution of **30a** (0.54 g, 1 mmol) in dichloromethane (20 ml), m-CPBA (0.41 g, 2.4 mmol) was added and the reaction mixture was stirred at room temperature for 1h. Dichloromethane was removed and the residue was dissolved in pyridine (25 ml). The pyridine solution was heated at 75°C for 9h. Pyridine was removed under reduced pressure by coevaporation with toluene. The residue was dissolved in EtOAc (100 ml) and washed with saturated $NaHCO_3$ (3 x 25 ml) and water (50 ml). The EtOAc part was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give **31a** (72%).

Method B: To a solution of 5'-O-trityl-3'-deoxy-3'-N-pyrrolidino*ara*uridine[25] (0.46 g, 0.85 mmol) in pyridine (10 ml), mesyl chloride (0.5 g, 4.2 mmol) was added dropwise at 0°C. After the addition, the reaction mixture was kept at +4°C overnight. The brown solution was poured into cold saturated $NaHCO_3$ solution. The precipitate was filtered and washed thoroughly with water. The residue was dissolved in dichloromethane, dried over Na_2SO_4 and evaporated to dryness at <30°C to generate 5'-O-trityl-3'-deoxy-3'-pyrrolidino-2'-O-mesyl*ara*uridine **32a**. Compound **32a** was dissolved in chloroform (25 ml), m-CPBA (0.35 g, 2 mmol) was added and the mixture was stirred at ambient temperature. After 1h, the solvent was evaporated and the residue was dissolved in pyridine (20 ml). The pyridine solution was heated at 75°C.

After 4.5h the solution was poured into saturated $NaHCO_3$ solution. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over Na_2SO_4 and evaporated to dryness. The solid residue was purified over silica gel to give **31a** (74% for three steps).

mp: 107-109°C

^{1}H NMR: ($CDCl_3$):δ 9.01 (bs, 1H, NH); 7.60-7.23 (m, 16H, H-6, trityl); 5.89 (d, 1.74Hz, 1H, H-1'); 5.53 (dd, 8.0Hz, 2.0Hz, 1H, H-5), 5.12 (d, 3.9Hz, 1H), 4.52 (dd, 6.0Hz, 1.8HZ, 1H), 4.08 (m, 2H), 3.54 (m, 2H), 3.08 (m, 1H), 2.54 (q, 1H), 2.0 (m, 4H).

^{13}C NMR: ($CDCl_3$):δ 163.6, C-4; 150.2, C-2; 143.7, trityl; 141.3, C-6; 128.8, 128.0, 127.3, trityl; 102.6, C-5; 98.9, =CH; 92.5, C-1'; 87.3, trityl; 83.3/83.1, C-2'/C-4'; 70.0, C-3'; 63.6, C-5'; 54.0,=CH_2; 31.0, 23.9, -N-CH_2-CH_2.

HRMS (FAB+, MH+): for $C_{32}H_{32}N_3O_5$ calcd. 538.2341 obsd. 538.2375.

Synthesis of 5'-O-trityl-3'-deoxy-2',3'(N-vinyloxyethyl-1,2-oxazetidino) uridine 31b:

Method A: Compound **30b** (0.27 g, 0.5 mmol) was oxidised as above and the N-oxide was heated in pyridine at 75°C for 8h. After usual work-up the crude product was purified over silica gel (80%). **Method B:** 5'-O-Trityl-3'-deoxy-3'-N-morpholino-2'-O-mesyl*ara*uridine **32b** was synthesized from **18a** (0.41 g, 0.73 mmol) using a literature procedure[28]. Compound **32b** was oxidised as above and the N-oxide was heated in pyridine at 75°C for 4h. After usual work-up **31b** was purified over silica gel (54% for three steps).

mp: 127-130°C

^{1}H NMR: ($CDCl_3$):δ 9.20 (bs, 1H, NH); 7.47-7.21 (m, 16H, H-6, trityl); 5.80 (d, 1.6Hz, 1H, H-1'); 5.58 (dd, 8.0Hz, 1.8Hz, 1H, H-5); 4.75 (d, 6.4Hz, 1H), 4.44 (s, 1H), 4.22 (d, 13.2Hz, 1H), 4.03 (m, 1H), 3.84 (m, 3H), 3.53 (m, 3H), 2.61 (m, 2H).

^{13}C NMR: ($CDCl_3$):δ 163.7,C-4; 150.2, C-2; 143.6, trityl; 141.8, C-6; 128.8, 127.9, 127.3, trityl; 102.7, C-5; 94.05, vinyl -CH_2; 87.6, C-1'; 87.1, trityl; 82.4, C-4'; 82.1, C-2'; 71.9, C-3'; 65.6, 65.1, 64.3, -O-CH_2, vinyl-CH; 48.8, -N-CH_2.

HRMS (FAB+, MH+): for $C_{32}H_{32}N_3O_6$ calcd. 554.2291 obsd. 554.2293.

5'-O-Trityl-3'-deoxy-3'-N-ethyluridine 31c:

Compound **30c** (0.19 g, 0.35 mmol) was oxidised as above and the N-oxide was heated in pyridine at 75°C for 5h. After usual work-up the crude product was purified over silica gel to give **31c**.

Yield: 56%

mp: 108-110°C

^1H NMR: ($CDCl_3$):δ 8.05 (d, 8.0Hz, 1H, H-6); 7.45-7.24 (m, 15H, trityl); 5.83 (s, 1H, H-1'); 5.39 (d, 8.0Hz, 1H, H-5); 4.26 (d, 5.0Hz, 1H, H-2'); 3.98 (m, 1H, H-4'); 3.50 (m, 3H, H-3', H-5', H-5"); 2.69 (m, 2H, -N-CH_2); 1.13 (t, 3H, -CH_3).

^{13}C NMR: ($CDCl_3$):δ 164.1, C-4; 151.1, C-2; 143.6, trityl; 140.8, C-6; 128.9, 128.2, 127.5, trityl; 102.2, C-5; 92.4, C-1'; 87.6, trityl; 82.6, C-4'; 73.6, C-2'; 61.9, C-5'; 58.4, C-3'; 42.9, -N-CH_2; 15.6,-CH_3.

HRMS (FAB+, MH+): for $C_{30}H_{32}N_3O_5$ calcd. 514.2341 obsd. 514.2365.

Synthesis of 5'-O-trityl-3'-deoxy-3'-O- pyrrolidino-2,2'-O-anhydrouridine 35a:

5'-O-Trityl-2'-deoxy-2'-pyrrolidino*xylo*uridine[25] (0.37 g, 0.68 mmol) was mesylated following the literature procedure[28]. The crude mesylated product, 5'-O-trityl-3'-O-mesyl-2'-deoxy-2'-pyrrolidino*xylo*uridine **34a** was oxidised as above and the N-oxide was heated in pyridine at 75°C for 4.5h. After usual work-up **35a** was purified over silica gel.

Yield: 57%

mp: 89-91°C

^{1}H NMR: ($CDCl_3$):δ 7.38-7.23 (m, 16H, H-6, trityl); 6.09 (d, 5.7Hz, 1H, H-1'); 5.95 (d, 7.4Hz, 1H, H-5); 5.38 (d, 5.7Hz, 1H, H-2'); 4.42 (m, 2H, H-3', H-4'); 2.99 (m, 6H, H-5', H-5", $-CH_2-N-CH_2$); 1.81 (bs, 4H, $-CH_2-CH_2$).

^{13}C NMR: ($CDCl_3$):δ 171.8, C-4; 159.5, C-2; 143.3, trityl; 134.8, C-6; 128.5, 128.1, 127.4, trityl; 110.1, C-5; 90.4, C-1'; 87.0, trityl; 86.2, C-2'; 84.5 (C-3' and C-4'); 63.2, C-5'; 56.9, $-CH_2-N-CH_2-$; 21.9, $-CH_2-CH_2-$.

HRMS (FAB+, MH+): for $C_{32}H_{32}N_3O_5$ calcd. 538.2341 obsd. 538.2344.

Synthesis of 5'-O-trityl-3'-deoxy-3'-O- morpholino-2,2'-O-anhydrouridine 35b:

5'-O-Trityl-2'-deoxy-2'- morpholino*xylo*uridine[25] (0.31 g, 0.55 mmol) was mesylated following the literature procedure[28]. The crude mesylated product, 5'-O-trityl-3'-O-mesyl-2'-deoxy-2'-morpholino*xylo*uridine **34b** was oxidised as above and the N-oxide was heated in pyridine at 75°C for 4.5h. After usual work-up **35b** was purified over silica gel.

Yield: 70%

mp: 95-98°C

^{1}H NMR: ($CDCl_3$):δ 7.45-7.25 (m, 16H, H-6, trityl); 6.13 (d, 5.8Hz, 1H, H-1'); 5.95 (d, 7.4Hz, 1H, H-5); 5.29 (d, 5.8Hz, 1H, H-2'); 4.54 (m, 1H, H-3'); 4.41 (m, 1H, H-4'); 3.91 (d, 2H) and 3.58 (t, 2H) $-CH_2-O-CH_2$; 3.10 (m, 3H), 2.92(m, 1H) H-5', H-5", $N-CH_2$; 2.72 (m, 2H, $-N-CH_2$).

^{13}C NMR: ($CDCl_3$):δ 171.7, C-4; 159.4, C-2; 143.3, trityl; 134.8, C-6; 128.4, 128.1, 127.5, trityl; 110.2, C-5; 90.3, C-1'; 87.1, trityl; 86.1, C-2'; 84.5, 83.7, 66.1, $-CH_2-O-CH_2$; 62.9, C-5; 56.8, 56.3,$-CH_2-N-CH_2$.

HRMS (FAB+, MH+): for $C_{32}H_{32}N_3O_6$ calcd. 554.2291 obsd. 554.2306.

Synthesis of 5'-O-trityl-3'-O-(N-benzyl) methylamino-2,2'-O-anhydrouridine 35c:

Compound **26d** (0.2 g, 0.33 mmol) was mesylated following the literature procedure[28]. The crude mesylated product, 5'-O-trityl-3'-O-mesyl- 2'-deoxy-2'-N-(N-benzylmethylamino)-*xylo*uridine **34c** was oxidised as above and the N-oxide was heated in pyridine at 80°C for 8h. After usual work-up **35c** was purified over silica gel.

Yield: 62%

mp: 78-80°C

^{1}H NMR: ($CDCl_3$):δ 7.32-7.25 (m, 22H, H-6, aromatic), 7.11 (d, 7.2Hz, 1H, H-1'), 5.89 (d, 7.5Hz, 1H, H-5), 4.25 (m, 2H, H-3', H-4'), 3.76 (q, 2H, H-5', H-5"), 2.89-2.72 (m, 5H, -O-CH_2, -CH_3).

^{13}C NMR: ($CDCl_3$):δ 171.6, C-4, 159.2, C-2, 143.2, trityl, 136.6, C-6, 134.6, 130.0, 128.5, 128.4, 127.9, 127.4, aromatic, 110.1, C-5q, 90.0, C-1', 86.9, trityl, 85.5, C-2', 84.5, C-4', 83.7, C-3', 64.9, C-5', 63.0, -N-CH_2, 45.8, -CH_3.

HRMS (FAB+, MH+): for $C_{36}H_{34}N_3O_5$ calcd. 588.2498 obsd. 588.2502.

Synthesis of 5'-O-trityl-3'-O-morpholino-*ara*uridine 36b:

To a solution of **35b** (0.28 g, 0.5 mmol) in ethanol (30 ml), 10ml of water and 4ml of 1N NaOH were added and the reaction mixture was stirred at room temperature for 4h. The solution was neutralized with 1N HCl and then saturated $NaHCO_3$ (50 ml) was added. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give **36b** .

Yield: 77%

mp: 105-107°C

^{1}H NMR: ($CDCl_3$):δ 7.70 (d, 8.1Hz, 1H, H-6), 7.49-7.21 (m, 15H, trityl), 6.10 (d, 3.8Hz, 1H, H-1'), 5.35 (d, 8.1Hz, 1H, H-5), 4.52 (m, 2H, H-4'), 4.31 (t, 1H, H-2'), 4.06 (m, 1H, H-3'), 3.84 (m, 2H, H-5', H-5"), 3.15 (m, 4H, $-CH_2-O-CH_2-$), 3.22 (d, 1H), 3.07 (d, 1H), 2.70 (m, 2H), $-CH_2-N-CH_2-$.

^{13}C NMR: ($CDCl_3$):δ 165.6, C-4, 150.6, C-2, 143.7, trityl, 143.1, C-6, 128.9, 128.0, 127.3, trityl, 100.6, C-5, 87.2, trityl, 86.9, C-1', 85.5, C-4', 81.3, C-2', 73.5, C-3', 66.2, $-CH_2-O-CH_2-$, 63.7, C-5', 56.9, 56.7, $-CH_2-N-CH_2-$.
MS (EI) m/z 328 (5, M-trityl), 470 (3, M-uracilyl).

Synthesis of 5'-O-trityl-3'-O-(N-benzyl) methylamino-*ara*uridine 36c:

Prepared from compound **35c** following the same method as above in 86% yield.

mp: 85-87°C

^{1}H NMR: ($CDCl_3$):δ 7.65 (d, 8.1Hz, 1H, H-6), 7.44-7.26 (m, 15H, trityl), 5.98 (d, 4.3Hz, 1H, H-1'), 5.39 (d, 8.1Hz, 1H, H-5), 4.25 (bs, 1H, H-2), 4.05 (bs, 1H, H-4'), 3.77 (m, 4H, H-3', benzyl-CH_2), 3.38 (m, 2H, H-5', H-5"), 2.62 (s, 3H, $-CH_3$).

^{13}C NMR: ($CDCl_3$):δ 164.7, C-4, 150.4, C-2, 143.4, trityl, 142.5, C-6, 137.4, 129.7, 128.6, 128.2, 127.7, 127.5, 127.1, aromatic, 100.4, C-5, 87.0, trityl, 86.2, C-1', 85.3, C-4', 80.8, C-2', 73.1, C-3', 65.0, benzyl-CH_2, 63.4, C-5, 45.8, $-CH_3$.

MS (EI) m/z 362 (3, M-trityl).

Compound 30a from 31a:

To a solution of **31a** (0.23 g, 0.43 mmol) in 4% formic acid in methanol (25 ml), Pd/C (0.22 g, 10% Pd) was added. The suspension was heated at 80°C for 15 mins. The mixture was cooled at room temperature and filtered. Pyridine (5 ml) was added to the filtrate and solvents

were evaporated to dryness under reduced pressure to obtain crude **38a**. Mesyl chloride (1 ml, 13 mmol) in pyridine (5 ml) was added to a solution of **38a** in pyridine (15 ml) at 0°C. The reaction mixture was left at +4°C overnight. The brown solution was poured into saturated $NaHCO_3$ solution. The precipitate was filtered, washed with water and dried. The residue was dissolved in EtOAc. The solution was dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. The brown residue was purified over silica gel to obtain **39a**. To a solution of **39a** in chloroform (20 ml), DBU (0.1 g, 0.6 mmol) was added. The solution was left at room temperature for 1.75h. The solution was washed with water, dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was purified over silica gel to give **30a** (0.14 g, 62% for three steps).

Compound 30b from 31b:

To a solution of **31b** (0.25 g, 0.45 mmol) in 4% formic acid in methanol (50 ml), Pd/C (0.3 g, 10% Pd) was added. The suspension was heated at 80°C for 8 hrs. The mixture was cooled at room temperature and filtered. Pyridine (10 ml) was added to the filtrate and solvents were evaporated to dryness under reduced pressure. The residue was partitioned between EtOAc and water. The organic part was dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness. The residue was purified over silica gel to give **38b**. Compound **38b** was mesylate to **39b** as above. Compound **39b** was converted to **30b** by treatment with DBU (0.06 g, 25% for three steps).

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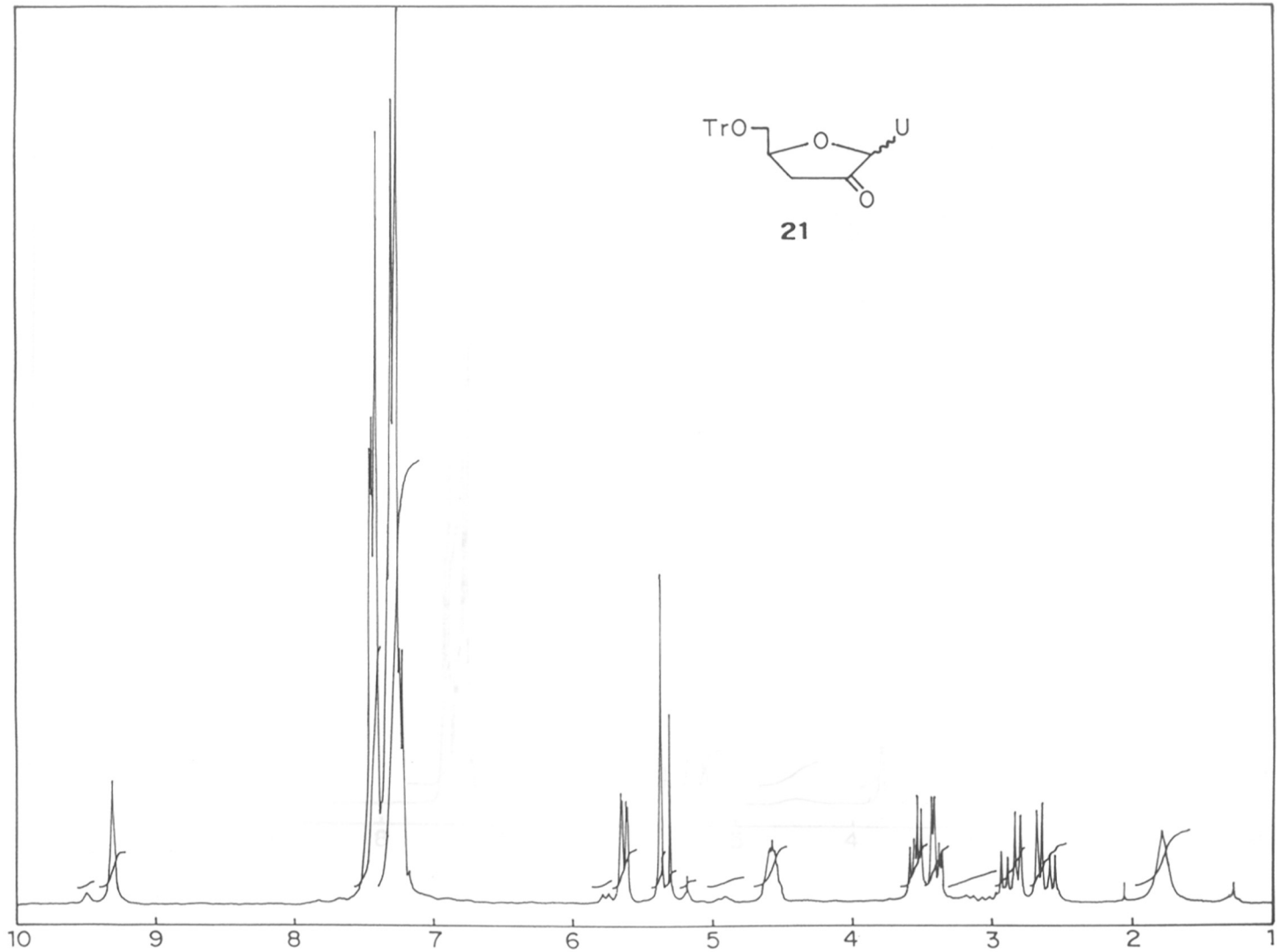

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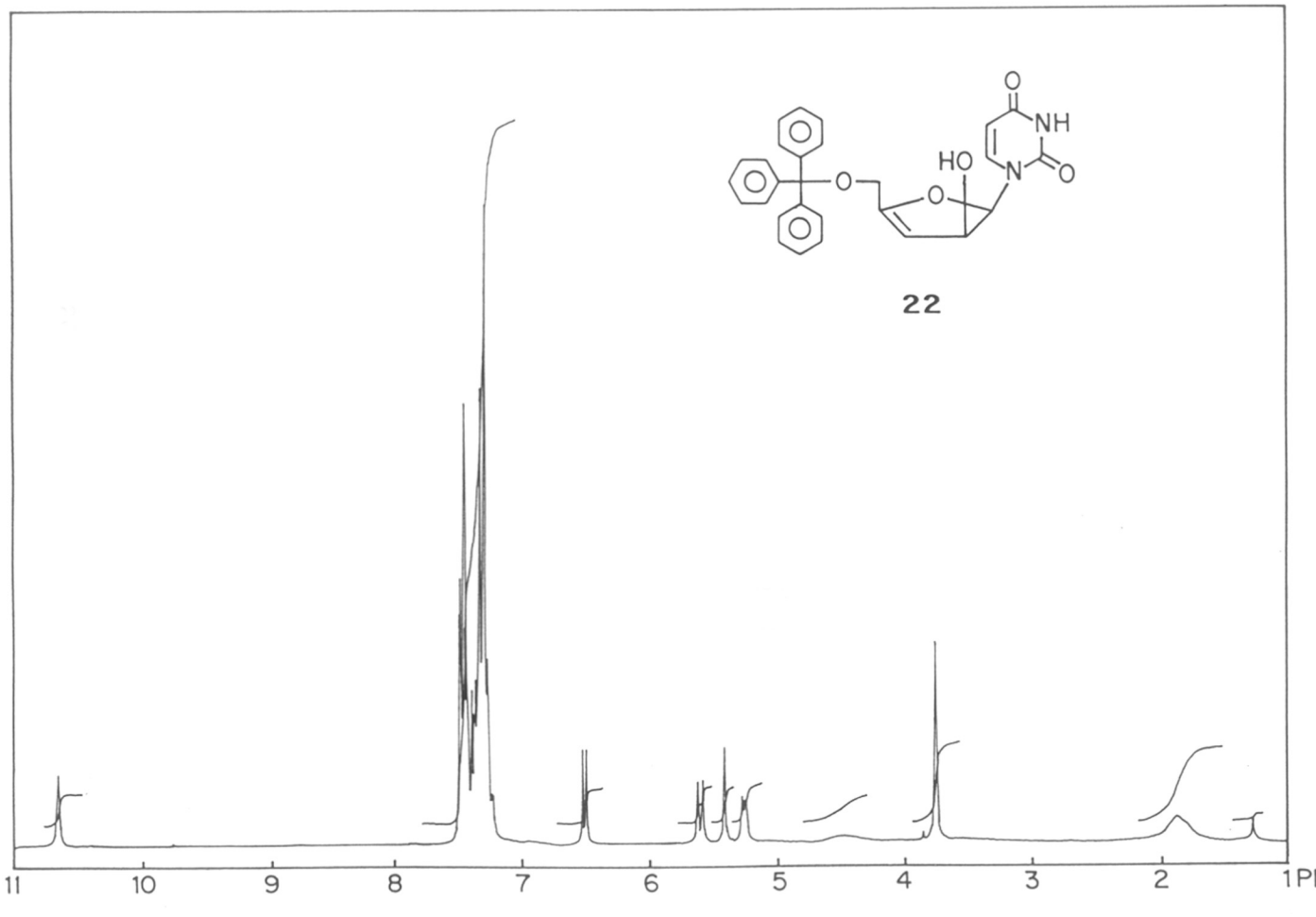
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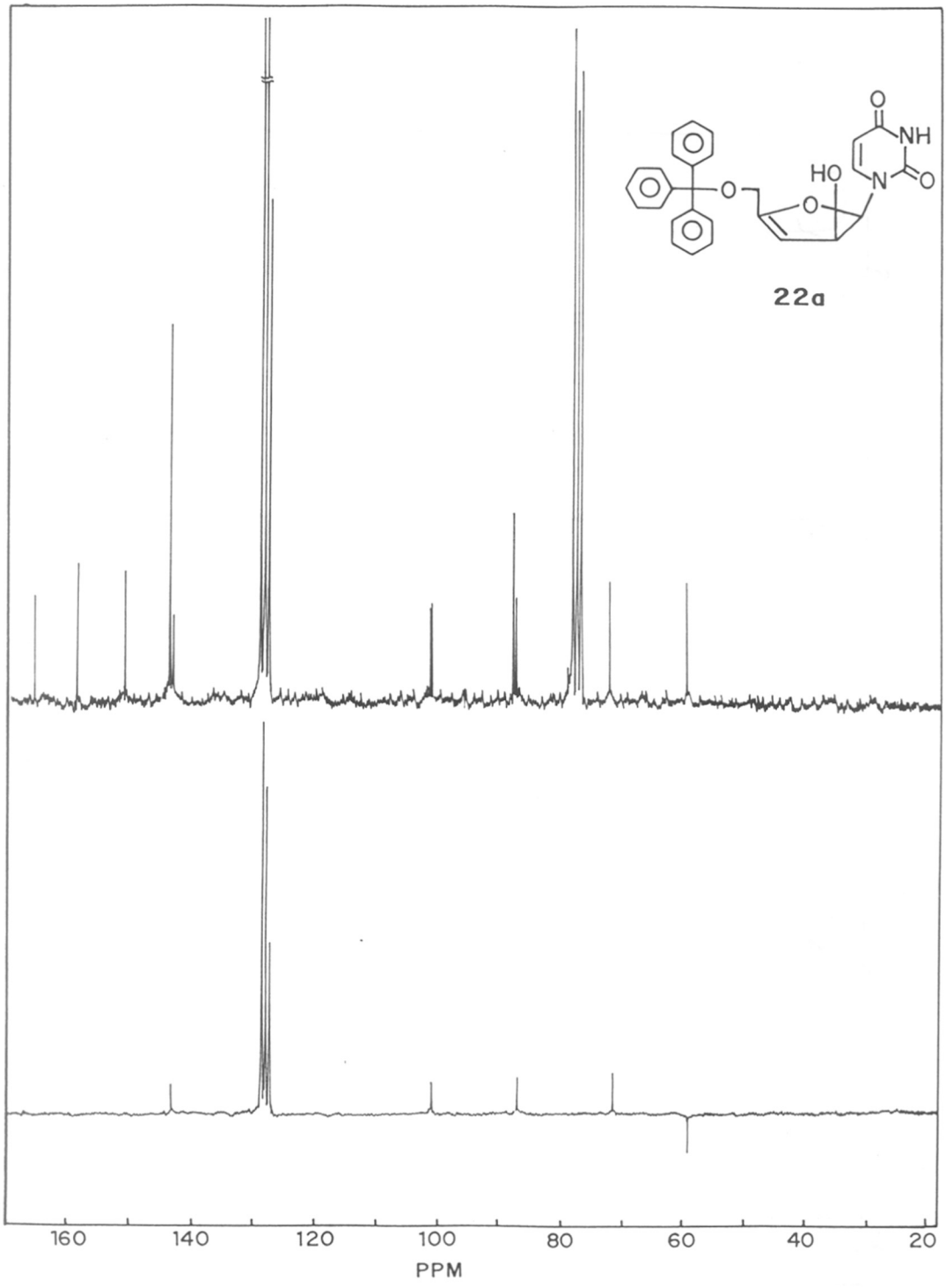

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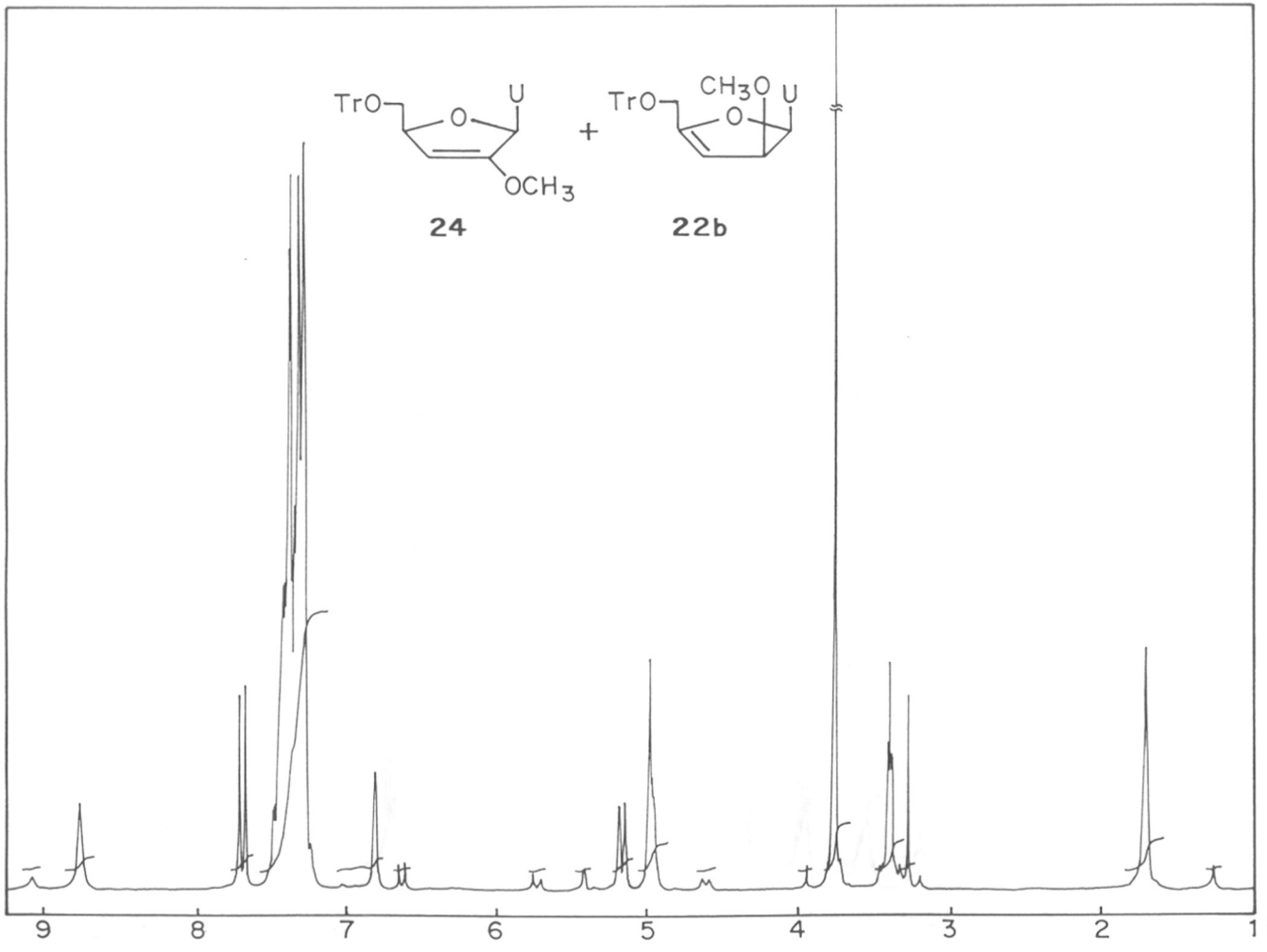
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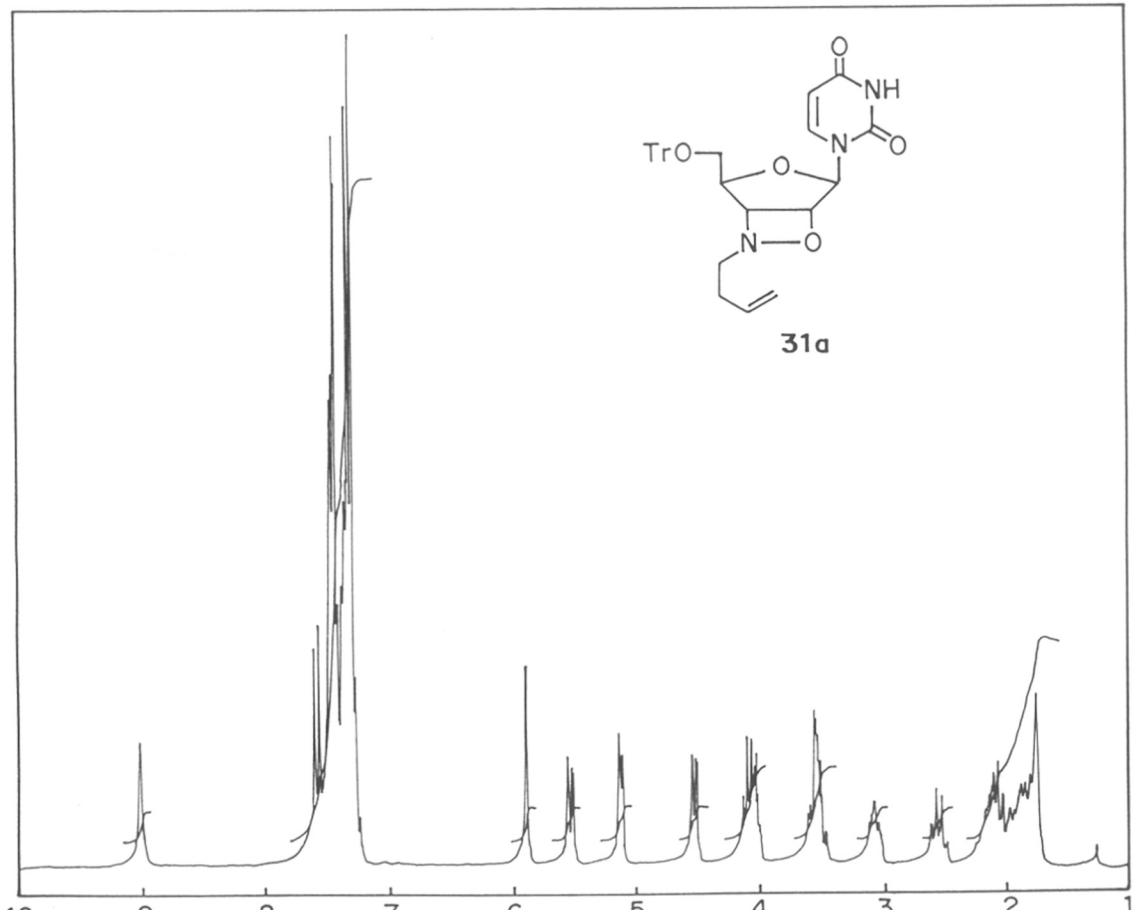

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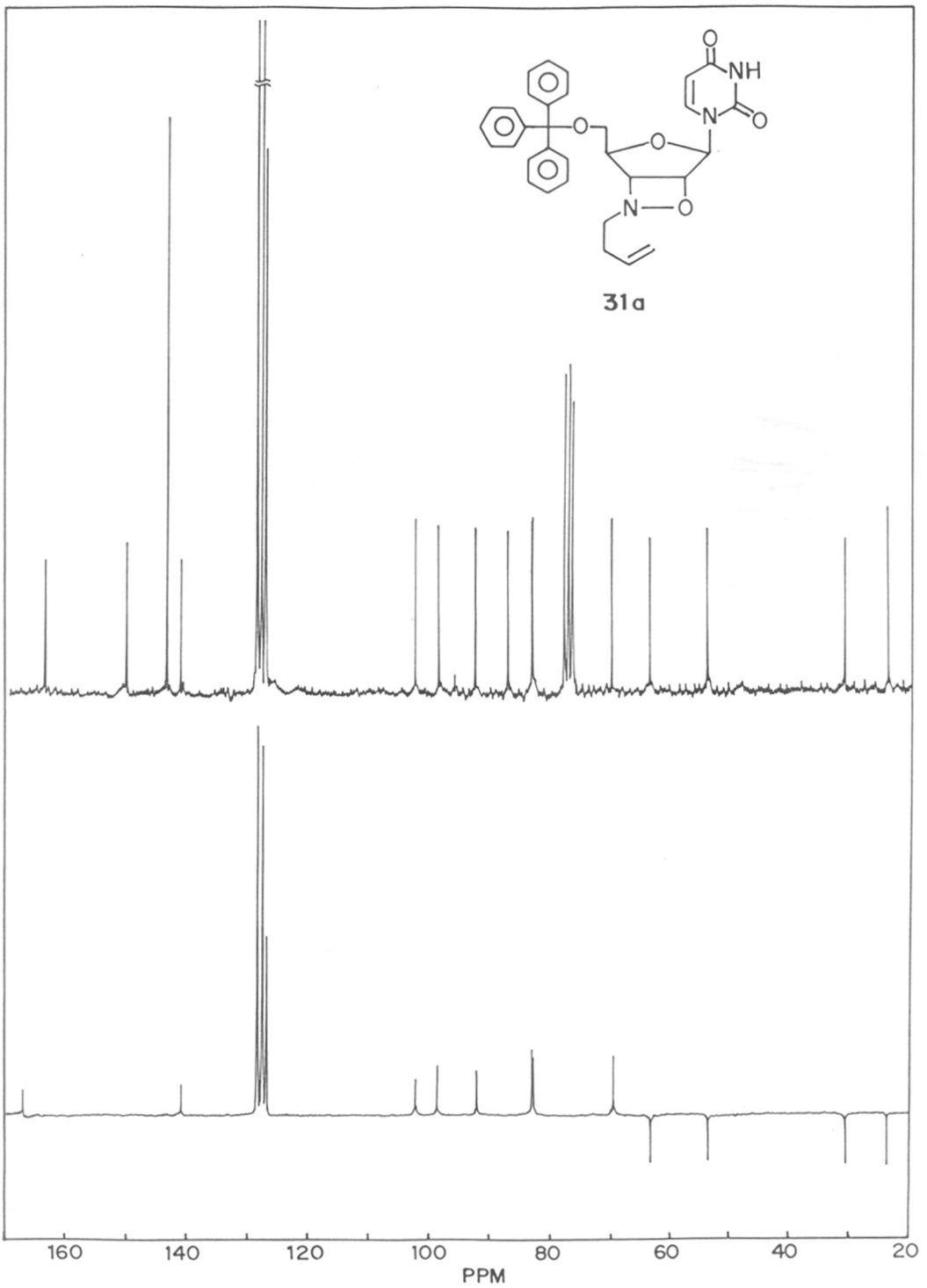
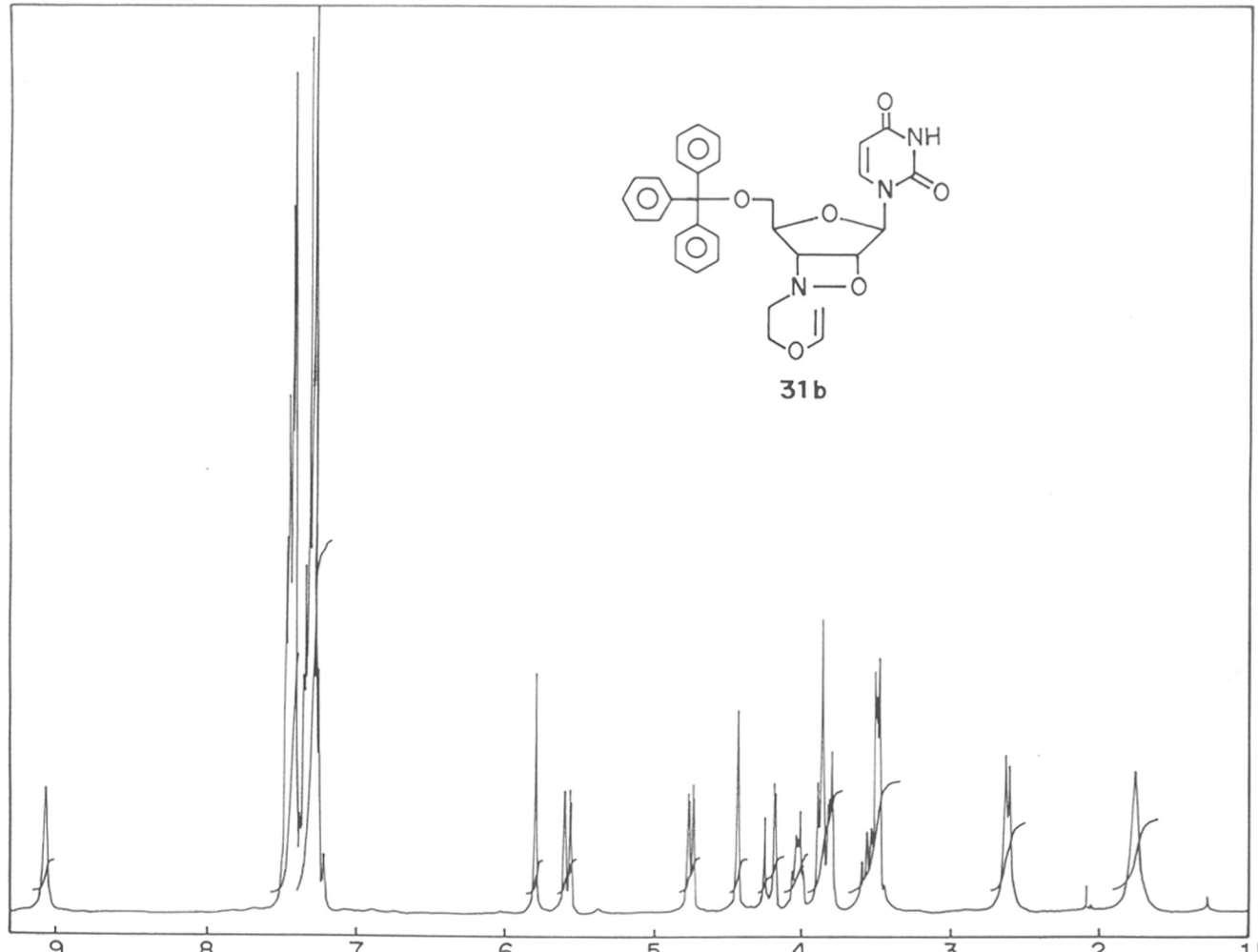
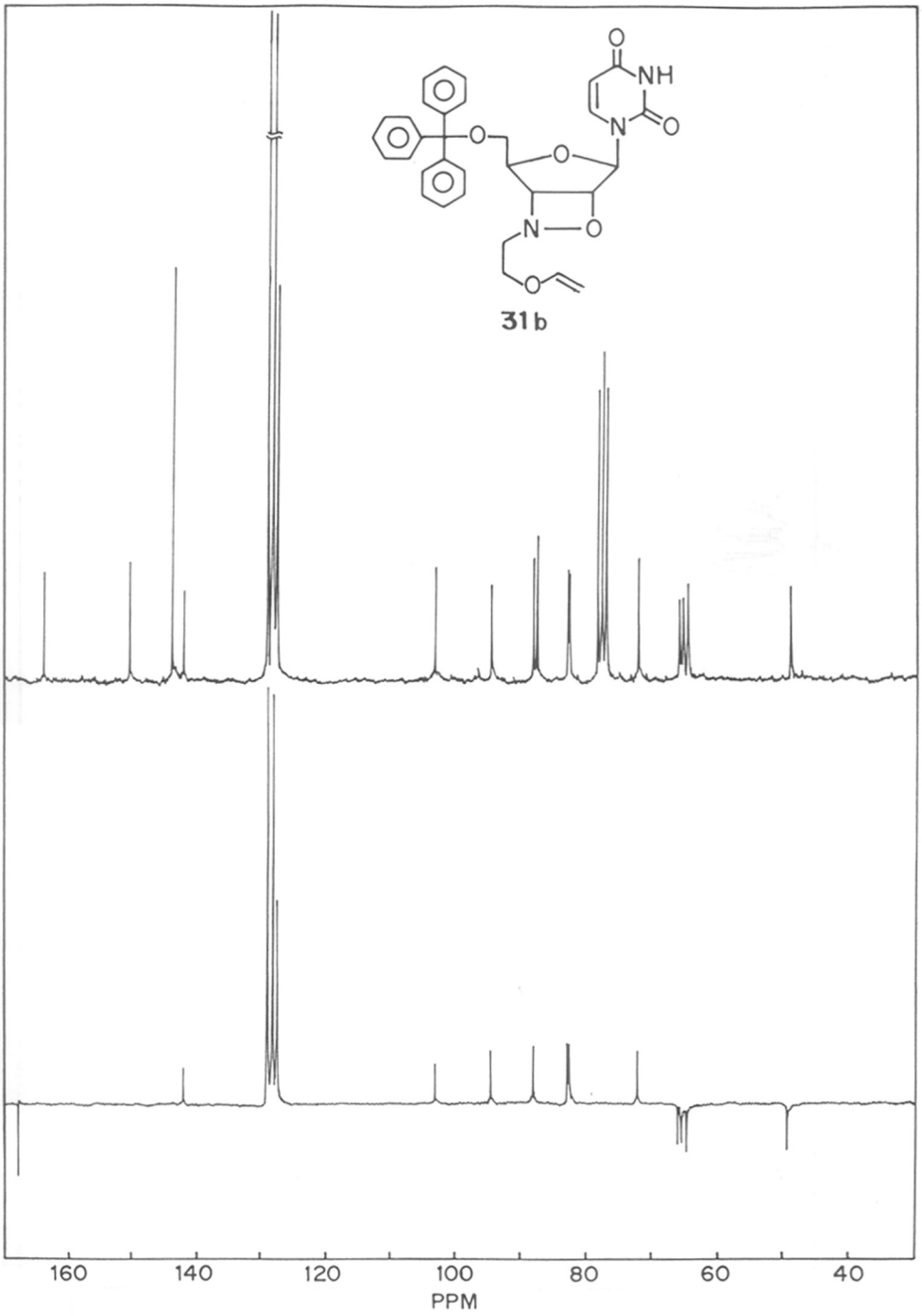


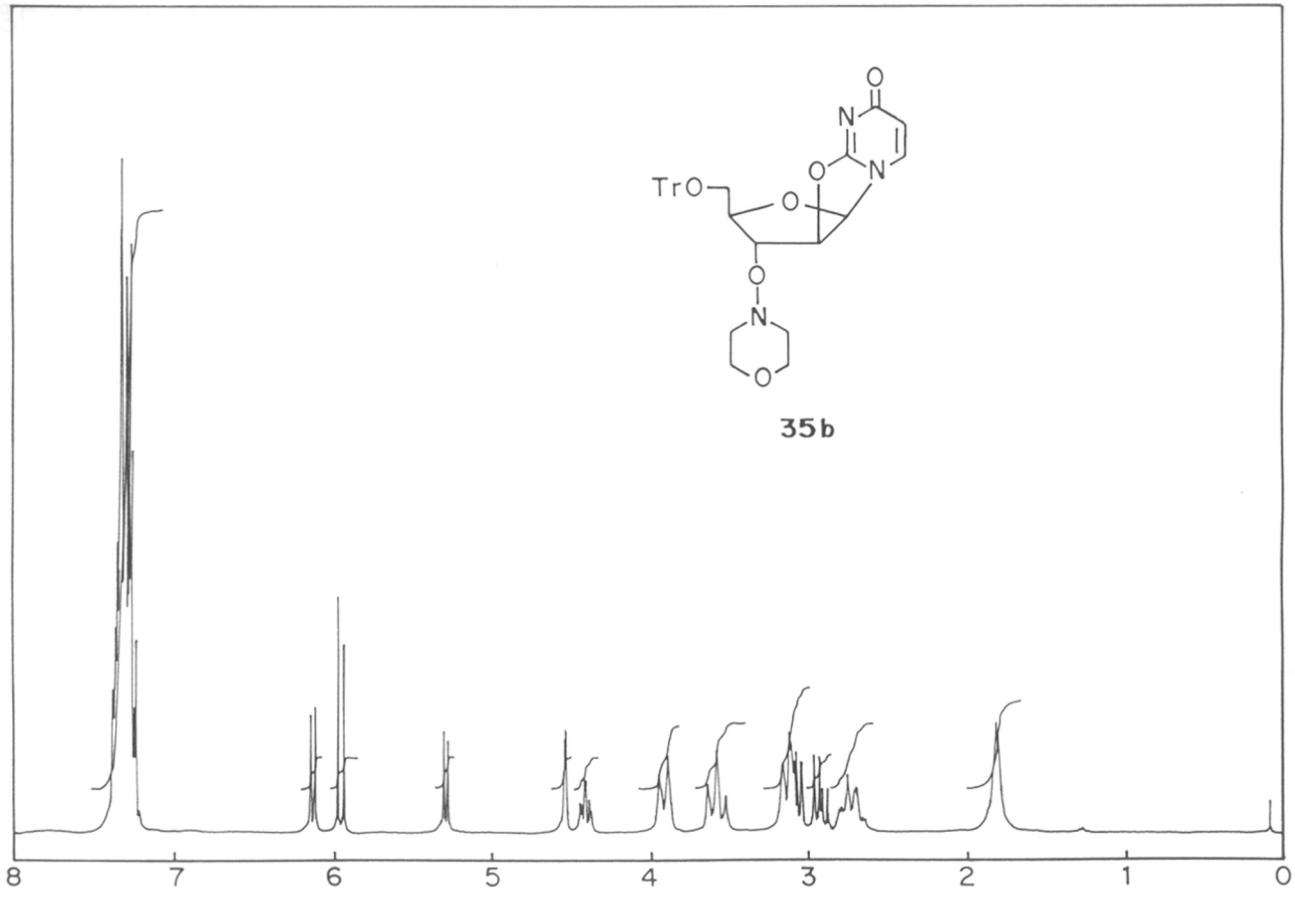
31a



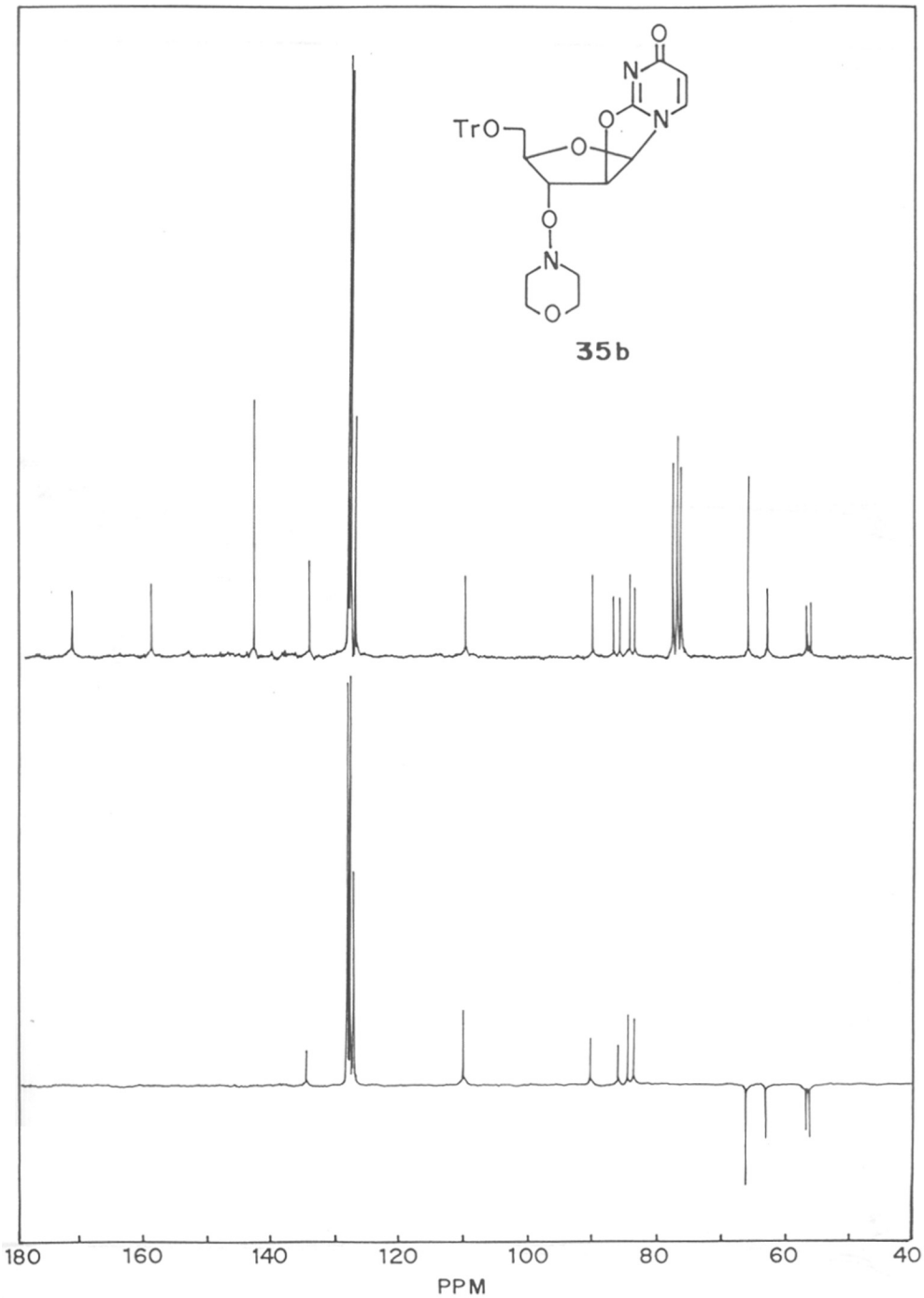
31b



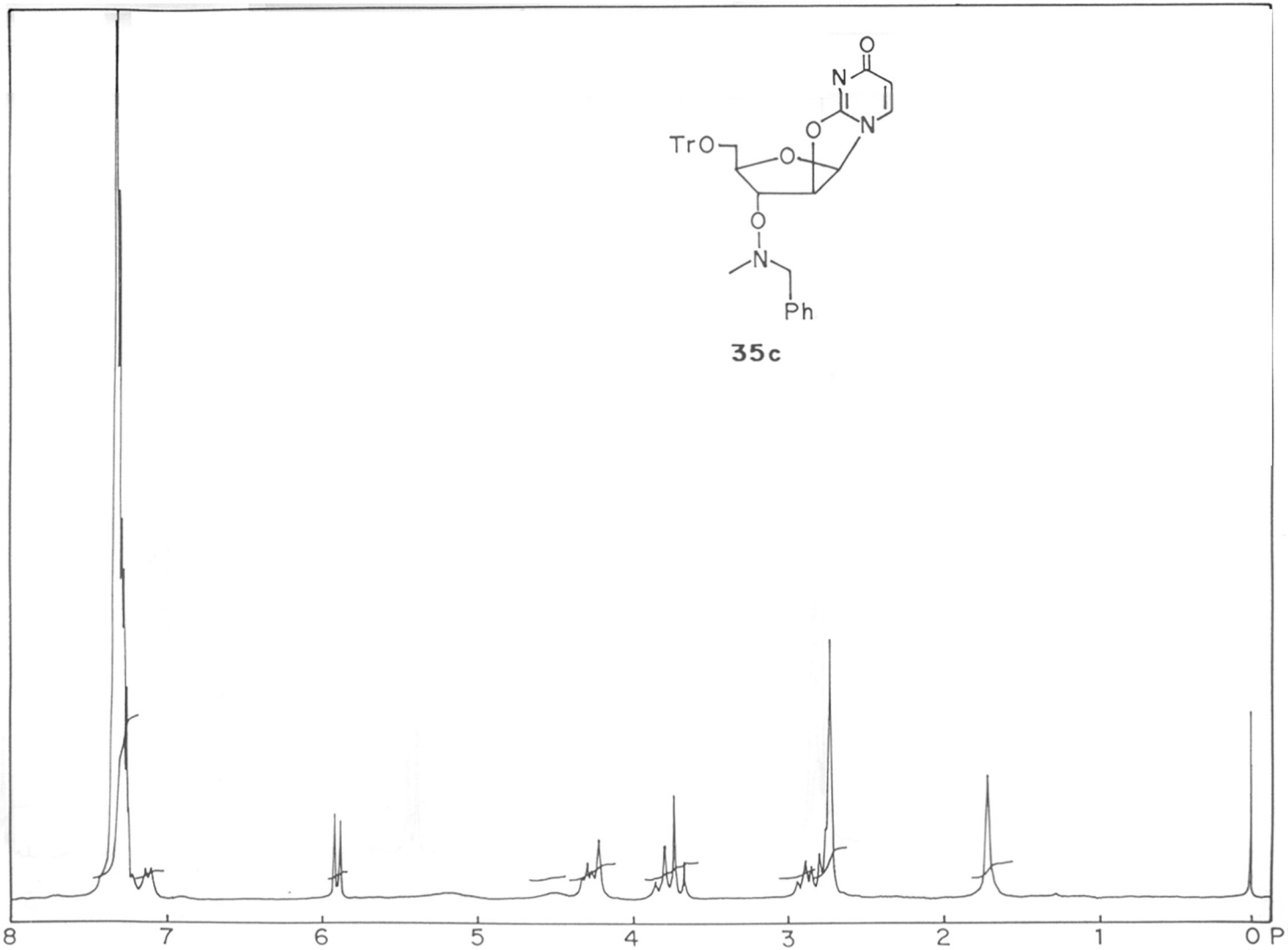
31b



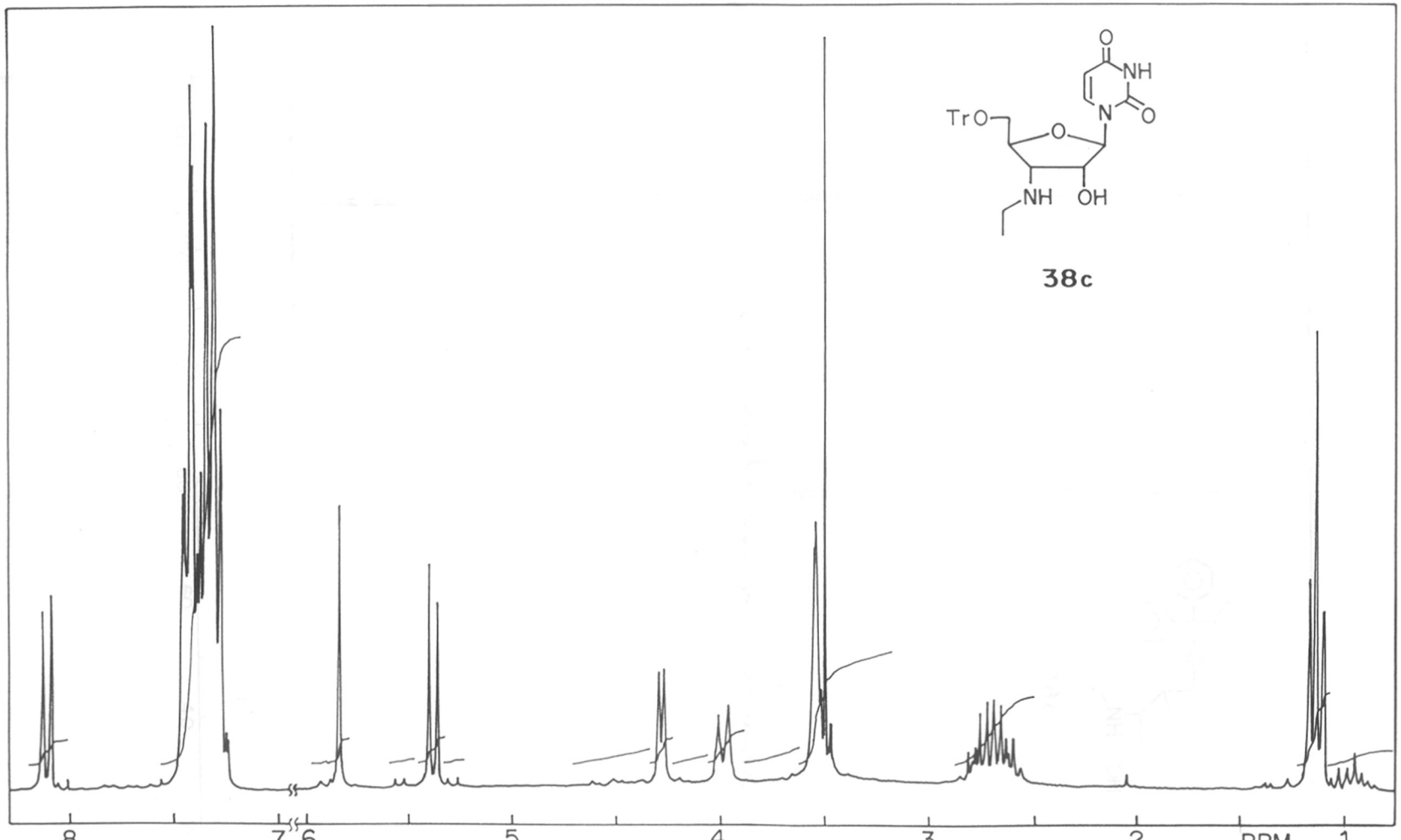
35b

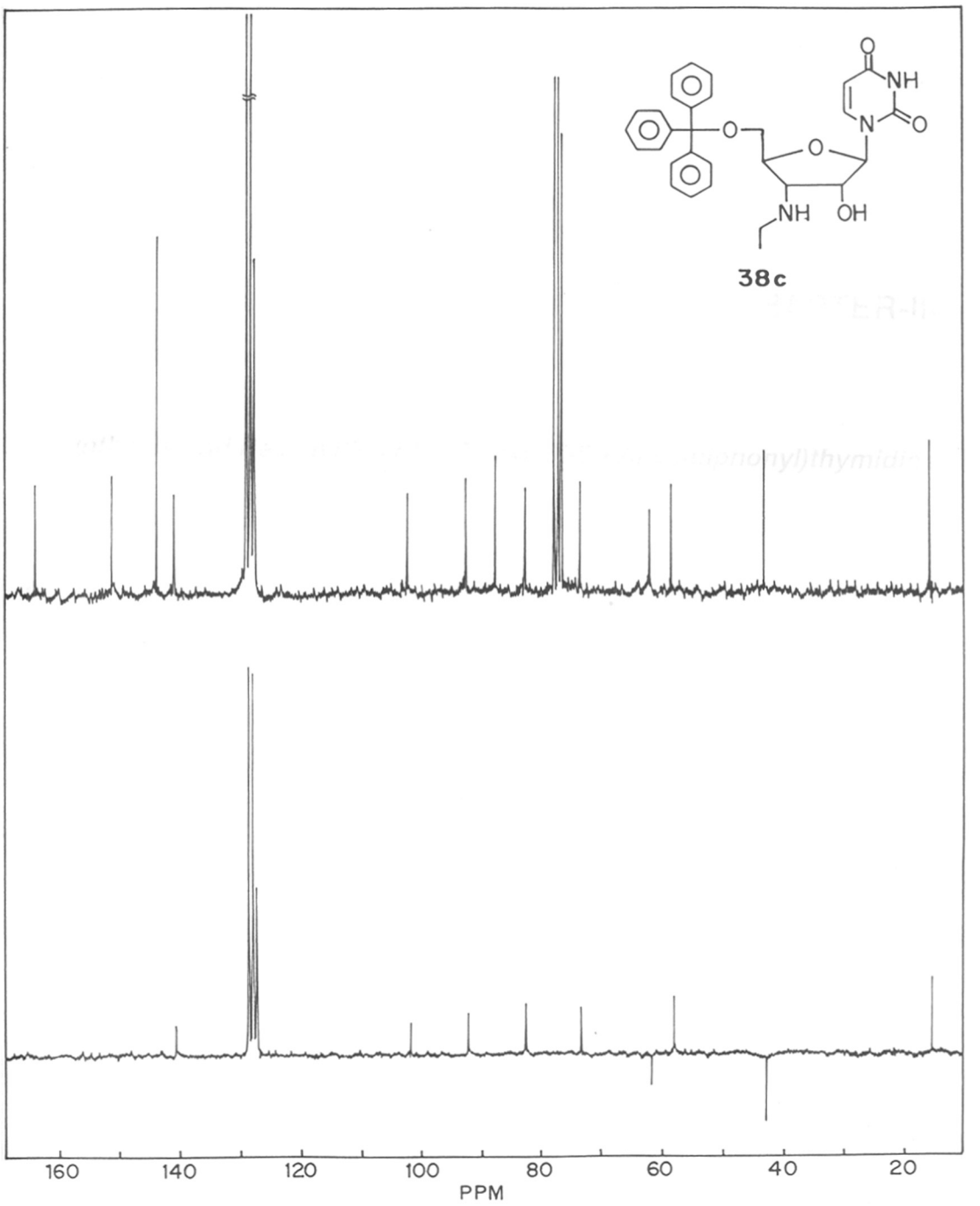


35b



35c


TrO
O
NH
N
O
O
NH
OH
38c
8
7
6
5
4
3
2
PPM
1



38c

CHAPTER-III

Synthesis and Reactivities of 3'-Deoxy-3'-S-(Vinylsulphonyl)thymidine

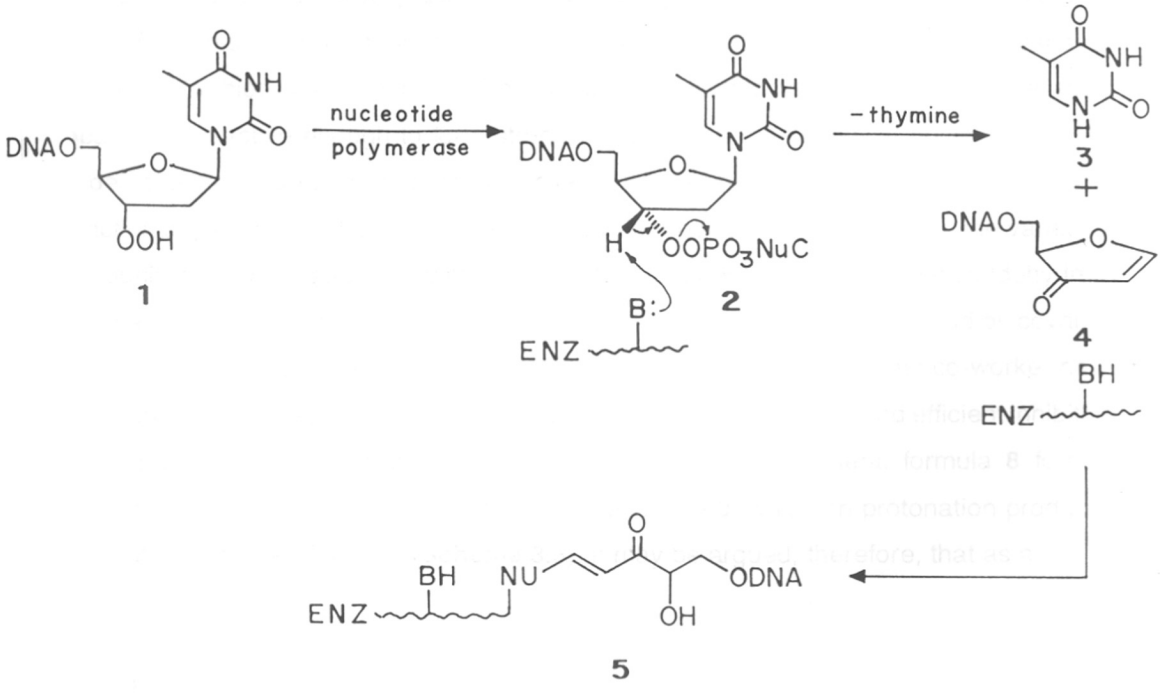
3.1. Introduction:

Since the discovery of anti-HIV activity of 3'-deoxy-3'-azidothymidine (AZT)[1], enormous progress has been made in the synthesis of new 3'-deoxy-3'-substitutednucleosides in general and 3'-deoxy-3'-substitutedthymidines in particular due to urgent need for better therapeutic agents[2]. One common strategy attempts to discover a drug which can interfere with a stage in the viral replicative cycle without damaging the normal processes of the host cell. In general, all these compounds get incorporated into the nascent DNA chain through the action of viral reverse transcriptase and act as chain terminators since they lack the 3'-hydroxyl group for chain processing (**Chapter-I, Scheme-1.1**). More recently, in the absence of well-defined rules for the selection of functional groups to be attached at the 3'-site of thymidine for the synthesis of potential anti-AIDS derivatives, several groups have reported the synthesis of 3'-deoxy-3'-substitutedthymidine analogues carrying three-atom functionalities[3-15] in order to mimic the triatomic structure[16] of the azido functionality of AZT.

Some of these 3'-modified nucleosides carrying three-atom functionalities, were however, designed not only as DNA chain terminators but it was expected that they might as well form covalent linkages with viral reverse transcriptase. These compounds were equipped with functional groups at the 3'-position of the nucleoside which were formulated on consideration of two potential binding modes. The first class of inhibitors is comprised of mechanism-based or "Trojan horse" substrates[17] whose reactive functionalities are unmusked as a consequence of their incorporation into the DNA chain. The electrophilic intermediates, may react with the residues in the active site of the enzyme. Thus compound **1** gets incorporated into the DNA through the 3'-hydroperoxy group to give **2**. The more acidic 3'-proton of **2** is picked up by enzyme base leading to the formation of a highly reactive intermediate **4** which is attacked by the nucleophilic sites of the enzymes (**Scheme 3.1**). Members of the second class of inhibitors are equipped with reactive functional groups at the 3'-position. This reactive functional group of **6** may interfere with the action of the enzyme by the direct formation of a covalent bond to form a drug enzyme adduct **7** (**Scheme 3.2**).

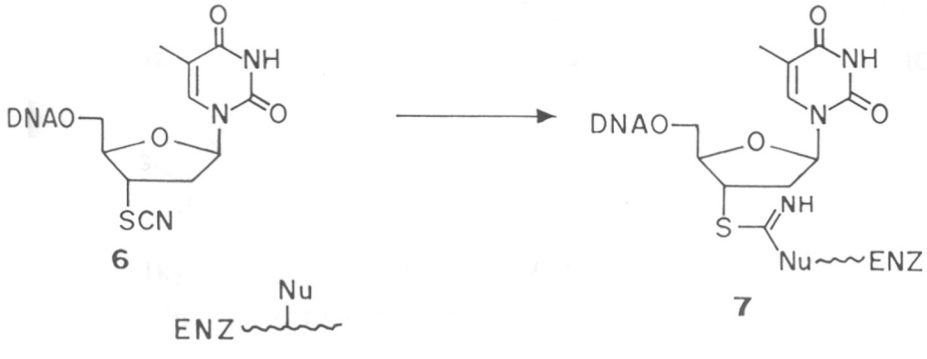
It is obvious that the synthesis of the second cass of compounds, that is, nucleosides containing electron deficient functional groups would be more easily available rather than introducing "Trojan horse" groups. Examples of nucleosides containing electron deficient

Scheme - 3·1



CLASS-A

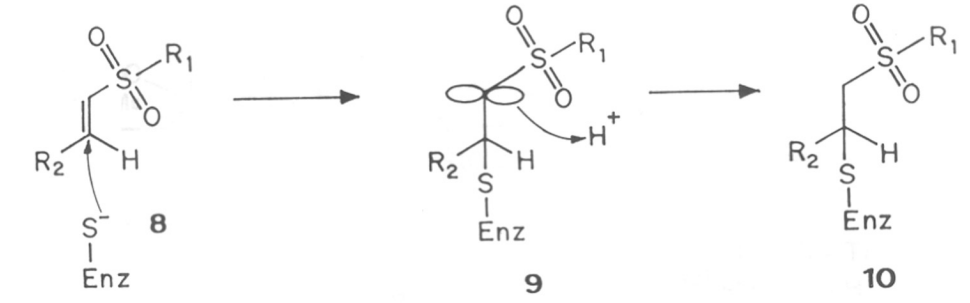
Scheme - 3·2



CLASS-B

reactive functionalities are very few and earlier attempts[6] along this line, however, were not successful. This was evident from the very low activity of 3'-deoxy-3'-thiocyano or 3'-deoxy-3'-*iso*thiocyanothymidines. Thiocyanate or isothiocyanate groups were most probably not reactive enough to form strong bonding with the biological nucleophiles. We decided, therefore, to incorporate, at the 3'-site, an electrophilic group such as vinyl-sulphone, a functionality known[18,19] for its efficiency for covalent bond formation with a wide variety of nucleophiles. It was also known[20] that vinyl sulphones inactivated glyceraldehyde-3-phosphate dehydrogenase by inducing the oxidation of cysteine residue and\or covalent binding to cysteine residue in active site. In yet another report, Palmer and co-worker have demonstrated that dipeptides containing vinyl sulphones are selective and efficient inhibitors of cysteine proteases[21]. These peptide Michael acceptors of general formula **8** formed covalent bond with the active site of the enzyme to give **9** which on protonation produced deactivated enzyme adduct **10** (**Scheme 3.3**). It may be argued, therefore, that as a

Scheme-3·3



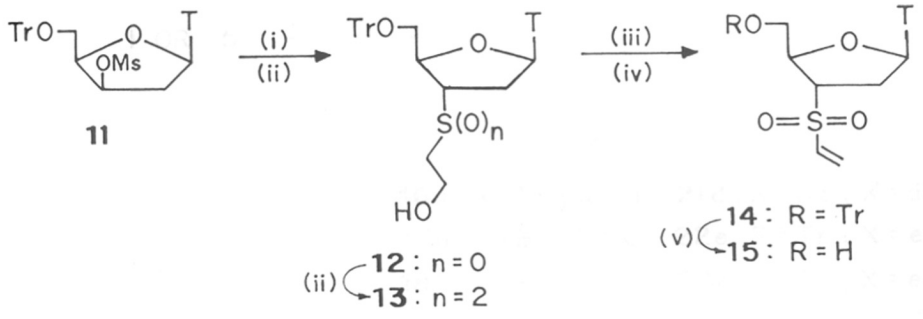
consequence of the high reactivity of vinyl-sulphones, 3'-deoxy-3'-(vinylsulphonyl)thymidine

and related derivatives may interact more efficiently with natural or mutated enzymes. However, unlike nitrogen-mustards[22], the vinyl-sulphone group would react with only one nucleophile at a time.

3.2. Present Work:

Synthesis of 3'-deoxy-3'-S-(vinylsulphonyl)thymidine 14: 1-(5-O-Trityl-3-O-mesyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **11** (ref. 4) was treated with marcaptoethanol in DMF in the presence of an organic base to give compound **12** in 64% yield (see discussion). Compound **12** was easily oxidised by magnesium monoperoxypthalate (MMPP) in methanol at ambient temperature to the corresponding sulphone **13** in 75% yield. Compound **13** was converted to the mesylated derivative in pyridine at +4°C and the same pyridine solution was heated at 60°C for 0.5h to produce the desired vinylsulphone derivative **14** in 71% overall yield (**Scheme-3.4**).

Scheme-3·4

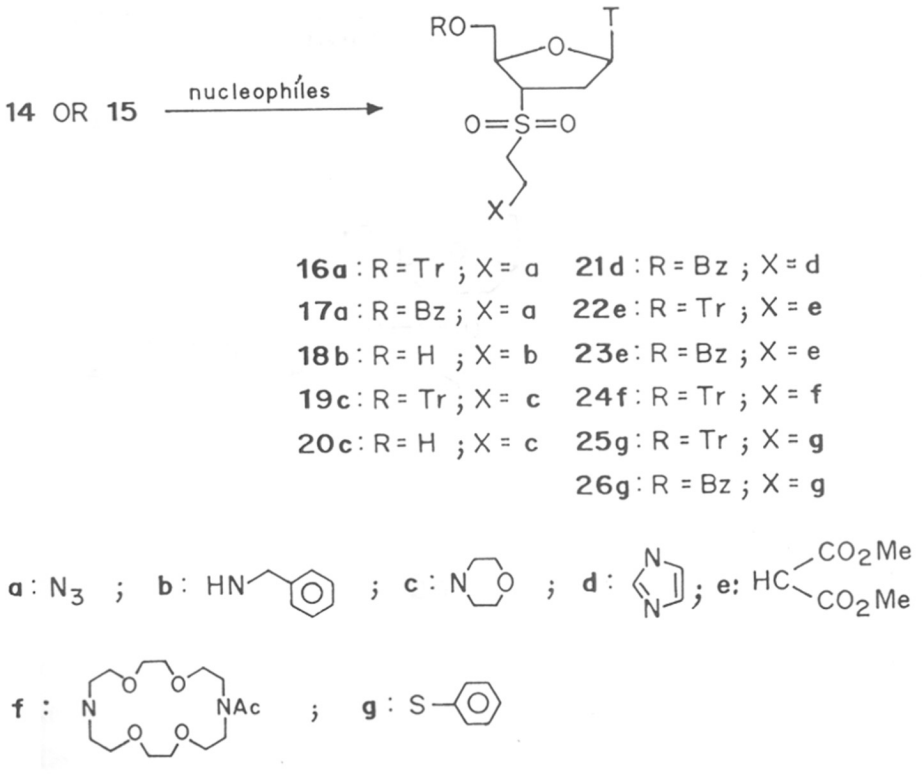


(i) HS⌒OH , DBU , DMF (ii) MMPP, MeOH (iii) MSCl / Py (iv) Py, 60°C
(v) 80% HOAc

Deprotection of 5'-O-trityl-3'-deoxy-3'-S-(vinylsulphonyl)thymidine: Compound **14** could be detritylated, if necessary, to the free hydroxy derivative **15** in 85% yield by heating it in 80% aqueous acetic acid solution.

Reactions of 3'-Deoxy-3'-S-(vinylsulphonyl)thymidine with nucleophiles: Either the protected vinylsulphone **14** or the deprotected derivative **15** were reacted with various nucleophiles in Michael fashion (*see experimental*). Nucleophiles, such as, hydrazoic acid[23], morpholine, sodium salt of dimethylmalonate and thiophenol reacted smoothly with compound **14** to furnish compounds **16a**, **19c**, **22e**, and **25g** respectively in excellent to moderate yields. Similarly compound **15** reacted with benzylamine and imidazole in protic solvent at ambient temperature to produce compounds **18b** and **21d** (after benzoylation in case of **21d**) respectively in high yields. Except for the benzylamino and morpholino derivatives **18b** and **20c** respectively, all other compounds were isolated and characterised as their 5'-O-benzoyl derivatives. Compound **15** was also reacted with 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane and the product obtained was isolated as the N-acetyl derivative **24f** (**Scheme-3.5**).

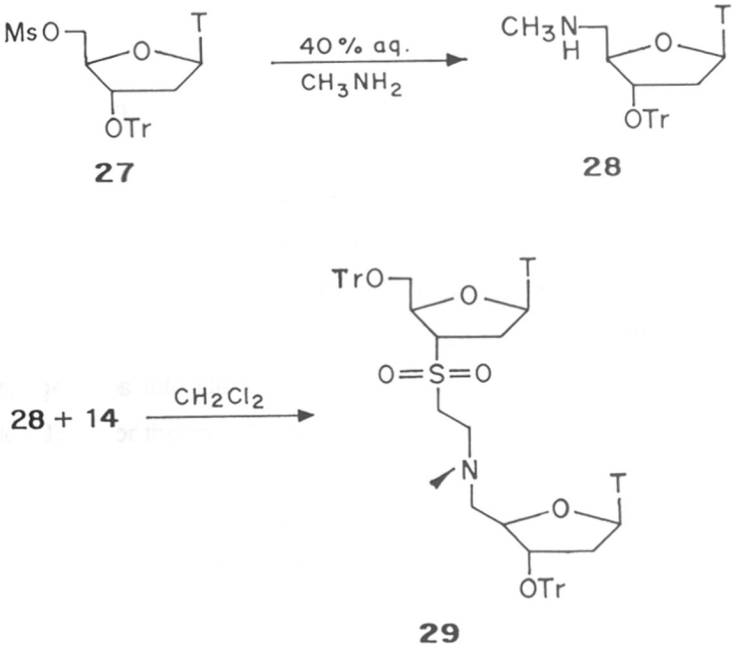
Scheme - 3·5



Deprotection of the Michael adducts 16a, 19c, 22e and 25g: Compounds **16a**, **22e** and **25g** were deprotected using 80% acetic acid at elevated temperature. Compound **19c** was deprotected using ion-exchange resins (IR 120H+). The deprotected products of **16a**, **22e** and **25g** were converted to the benzoyl derivatives **17a**, **23e** and **26g** respectively in high yields. Compound **20c**, the deprotected derivative of **19c** was isolated as the 5'-free hydroxy compound.

Synthesis of 3'-deoxy-5'-O-trityl-3'-[S-{1-(thymine-1-yl)-1,2,5-trideoxy-3-O-trityl-β-D-erythropentofuranos-5-yl}-N-(methyl)-ethylsulphonyl] thymidine 29: 5'-O-Trityl-3'-deoxy-3'-(vinylsulphonyl)thymidine **14** was treated with 3'-O-trityl-5'-deoxy-5'-N-methylamino thymidine **28** in dichloromethane to produce non-phosphate linked dimer **29** in 76% yield (**Scheme-3.6**).

Scheme-3.6



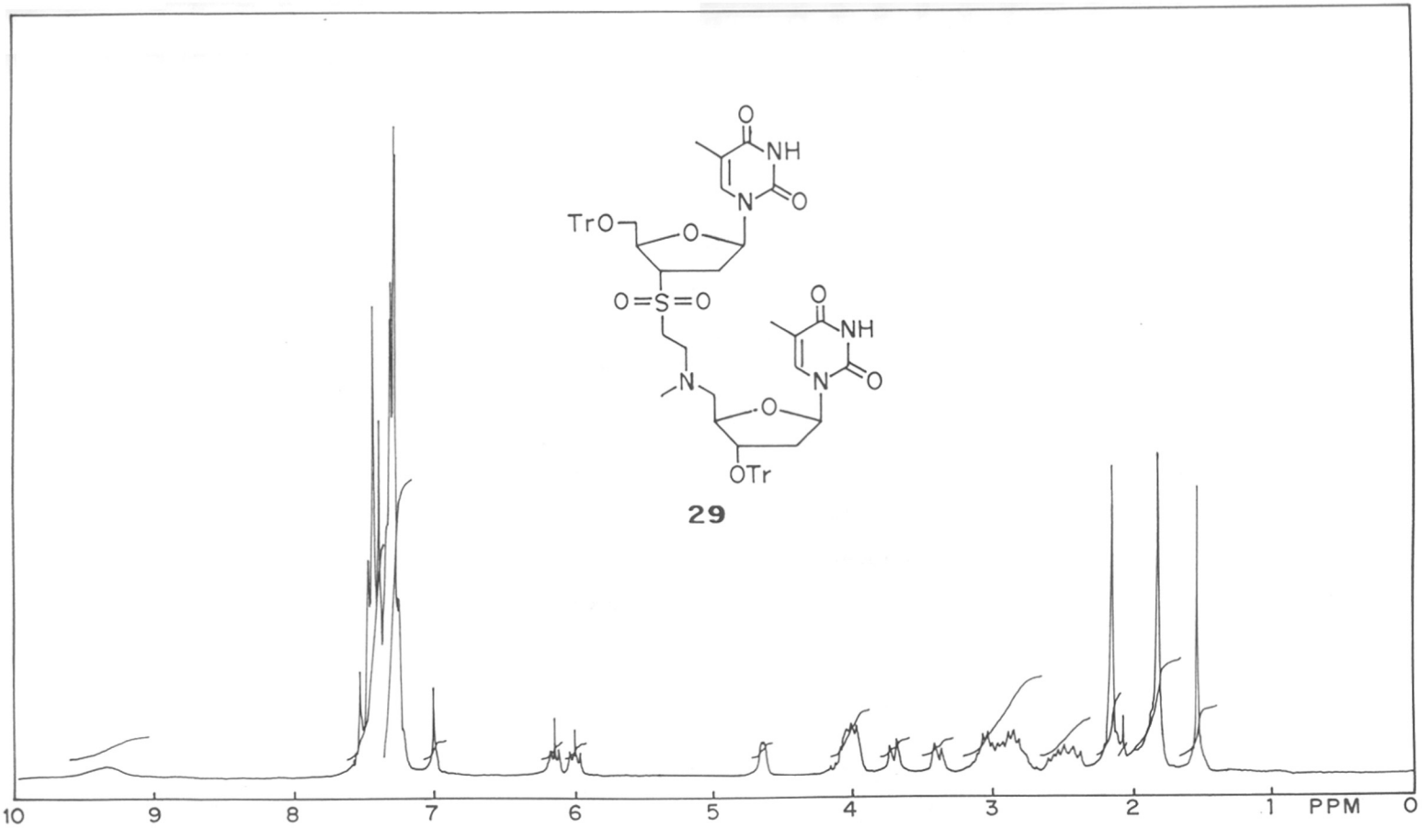
3.3. Structural Assignment:

The structures of all new compounds were assigned unambiguously by spectroscopic means. ^{1}H-NMR of all compounds are consistent with the structures assigned. The proton signals of compounds **13, 14** and **21d** were assigned on the basis of COSY analysis. The ^{1}H NMR signals at 6.45 ppm and 6.13 ppm and ^{13}C NMR signals at ~134 ppm and 133 ppm of compound **14** indicated the presence of olefinic protons and carbons in the molecule. At the same time disappearance of these signals in the products derived from the reactions of **14** and various nucleophiles and appearance of extra peaks at ~3-4ppm (^{1}H-NMR) and extra CH_2 peaks at ~40ppm and ~50 ppm (^{13}CNMR) clearly indicated the presence of ethyl sulphone spacer in the products. The presence IR band at 2090 cm^{-1} in compounds **16a** and **17a** also indicates the presence of azido groups in these compounds. Additional proof for the structures of new compounds were provided by exact mass measurement experiments. The structure of compound **29** was, however, tentatively assigned on the basis of ^{1}H-NMR spectra only (**Figure-3.1**).

3.4. Discussion:

A limited number of modified nucleosides, having alkyl/aryl- sulphoxide or sulphone functionalities at the C-3' position were synthesised in the past and some of these were subjected to biological screening[3,15,24-26]. However, none of these synthetic methodologies was general in nature and all of them produced only a handful of compounds. As far as our knowledge goes into literature, there is only one[18,19] report on the use of vinyl-sulphone functionalities for the modification of the carbohydrate moieties of nucleosides. In this case vinyl-sulphone moieties of 3'-enesulphone uridine or adenosine were, however, used as tools for the functionalisation of the 2'-positions of uridine or adenosine; the aryl sulphone was later removed reductively to generate 2',3'-dideoxy-2-funtionalised nucleosides (**Scheme-1.13** in Chapter-I)

In another development, it was shown earlier that the 4'' amino group of the 3'-spiro moiety of the modified nucleoside TSAO, a HIV-1 specific inhibitor interacted[27] with the carboxylic group of Glu-138 of HIV-1 reverse transcriptase (**Figure-3.2**). It is interesting to note that



29

Figure-3·1

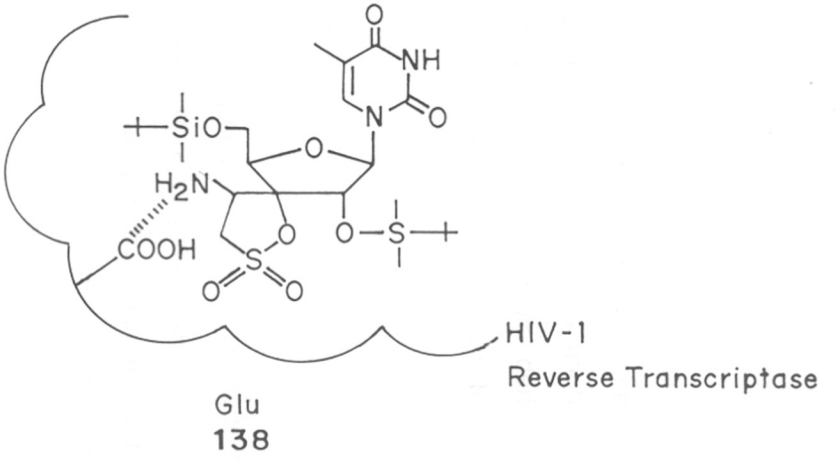

O
NH
N
O
SiO
O
H_2N
COOH
O
S
O
O
O
O
S
HIV-1
Reverse Transcriptase
Glu
138

Figure - 3·2

unlike in case of AZT, the amino group of TSAO, which is not directly linked to the C-3' centre, interacts[27] with the enzyme through a spacer - in this case the spiro functionality. The unusual spiro group, namely, spiro-5''-(4''-amino-1'', 2''-oxathiole-2'', 2''-dioxide), incidentally carries a sulphur atom in its highest oxidised state[24].

Unlike the previous report[18,19], the 3'-deoxy-3'-S-(vinylsulphonyl)thymidine that we propose to synthesise will retain the sulphone group. We envisaged that the studies related to the reactivities of compounds **14** or **15** with various nucleophiles would on one hand prove the efficiency of interaction of the newly designed molecule. The vinyl-sulphone moiety, on the other hand, can be used for attaching various functionalities to generate new classes of modified nucleosides where a group will be attached to the C-3' of a nucleoside through a flexible (unlike the rigid spiro spacer mentioned above) ethyl sulphone spacer[28]. These new modified nucleosides (**Scheme-3.5**) themselves might act as DNA chain terminators. Interestingly, a group of quaternary ammonium derivatives[29] generated from various 3'-O-(aminoalkyl) thymidines showed activity against Herpes Simplex Virus.

In the conversion of **11** to **12**, 1,1,3,3-tetramethylguanidine (TMG) produced the desired product in moderate yield. We observed that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished **12** in better yield (64% as opposed to 53%). 1-(2,3-Dideoxy-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)thymine was the other product formed in the reaction which could be removed from the mixture very easily by column chromatography. It should be mentioned that 5'-O-trityl-2,3'-O-anhydrothymidine as a substrate instead of compound **11** produced compound **12** in a much lower yield. In cases where the product of the Michael addition reactions were expected to be stable towards acidic detritylation conditions, compound **14** was used as the substrate. Compound **14** on treatment with sodium azide in methanol did not produce the desired product but a mixture of hydrazoic acid[23] and sodium azide gave the desired product. The reactions of benzylamine and imidazole with the deprotected compound **15** in methanol were performed to establish the point that the functional group that we have devised is indeed reactive enough in hydroxylic solvent at ambient temperature.

Several unnatural DNA/RNA fragments were synthesised where the phosphate backbones were replaced by sulphur[24] linkages; in quite a few of these reports, sulphur is present in its

highest oxidation state[30-34]. However, in almost all of these cases no general synthetic methodology evolved which would generate a group of similar type of oligomers. We presumed that 3'-deoxy-3'-S-(vinylsulphonyl)thymidine **14** may be reacted with various suitably 5'-functionalised nucleosides to generate a wide variety of sulphone linked dinucleotides. To demonstrate the usefulness of **14** for the synthesis of such dinucleotides, we have synthesised a dimer **29**. It is obvious that this methodology could be used for the synthesis of a wide variety of backbone modified oligomers.

3.5. Conclusion:

We have synthesised a reactive triatomic analogue of AZT, 3'-deoxy-3'-S-(vinylsulphonyl)thymidine **15** (and **14**) from easily accessible starting material. We have also established that these vinyl-sulphone nucleosides do indeed react very efficiently with a variety of nucleophiles; these experiments established further that compounds **14** or **15** may also be used to generate new classes of modified nucleosides where the functional groups are attached to the C-3' of a nucleoside through flexible ethyl sulphone spacer[28].

3.6. Experimental:

Melting points were uncorrected. Thymidine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merck 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 or solvent chloroform-d as internal standards. All mass spectrometric experiments were carried out on a VG Analytical 70-250-SE normal geometry double focussing mass spectrometer. Accurate mass measurements were carried out at 10 000 resolution using mixtures of polyethylene glycols as mass calibrants.

Synthesis of 3'-deoxy-3'-S-(2-hydroxyethylthio)-5'-O-tritylthymidine 12:

A mixture of marcaptoethanol (30mmol) and DBU (12.5mmol) in DMF (20ml) was heated at 60°C for 10m. Compound **11** (5mmol) was then added at a time. The mixture was heated at 60°C for 7h. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate solution. The white residue was filtered and was washed with water. The residue was then dissolved in ethyl acetate and the solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on silica gel column to give **12.**

Yield: 64%

m.p: 56-8°C

^{1}H-NMR: ($CDCl_3$):δ 7.76 (d, 1.1 Hz, 1H) H-6; 7.45-7.24 (m, 15H) trityl; 6.14 (dd, 1H) H-1'; 3.96 (m, 1H) H-4'; 3.66 (m, 4H) CH_2O, H-5'or H-5'' and H-3'; 3.36 (m, 1H) H-5'or H-5''; 2.54 (m, 4H) H-2', H-2'', CH_2S; 1.46 (d, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.4, C-4; 150.7, C-2; 143.4, trityl; 135.8, C-6; 128.8, 128.2, 127.6, trityl; 110.9, C-5; 87.4, trityl; 85.8/85.1, C-1'/C-4'; 62.4/61.5, CH_2O/C-5'; 41.0, CH_2S/C-3';

34.6, C-2'; 12.1, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{32}N_2O_5S$: 545.2112, found 545.2198.

Synthesis of 3'-deoxy-3'-S-(2-hydroxyethylsulphonyl)-5'-O-tritylthymidine 13:

To a solution of compound **12** (6.6mmol) in methanol (100ml) was added MMPP (80%, 21mmol). The mixture was stirred at room temperature for 6h (the reaction was complete within 0.5h as was evident from tlc; however, it was necessary to continue the stirring for the precipitation of the reagents to occur). The mixture was filtered and the residue was washed with methanol. The methanol solution was evaporated to dryness. The oily material thus obtained was dissolved in ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution (2x50ml) followed by water (2x50ml). The ethyl acetate solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on silica gel column to afford compound **13**.

Yield: 75%

m.p: 110-1°C

^{1}H-NMR: ($CDCl_3$):δ 7.59 (d, 1.0 Hz, 1H) H-6; 7.45-7.24 (m, 15H) trityl; 6.23 (t, 1H) H-1'; 4.66 (m, 1H) H-4'; 4.23 (m, 1H) H-3'; 4.05 (t, 2H) CH_2O; 3.70 (dd, 1H) and 3.45 (dd, 1H) H-5' and H-5''; 3.10 (m, 3H) CH_2SO_2, H-2' or H-2''; 2.58 (m, 1H) H-2' or H-2''; 1.47 (d, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.5, C-4; 150.7, C-2; 143.3, trityl; 135.9, C-6; 128.8, 128.2, 127.7, trityl; 111.5, C-5; 87.7, trityl; 85.5, C-1'; 77.2, C-4'; 64.3, C-5'; 62.1, C-3'; 56.3, CH_2O; 55.0, CH_2SO_2; 34.1, C-2'; 11.9, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{32}N_2O_7S$: 577.2010, found 577.1987.

Synthesis of 3'-deoxy-3'-S-(1-vinylsulphonyl)-5'-O-tritylthymidine 14:

A solution of methanesulphonyl chloride (16mmol) in pyridine (10ml) was added dropwise to an ice-cold solution of compound **13** (5.2mmol) in pyridine (25ml). The mixture was left overnight at +4°C. The mixture was then heated at 60°C for 0.5h. The reaction mixture was then cooled and carefully added to saturated aqueous sodium bicarbonate solution. The bicarbonate mixture was extracted with ethyl acetate (3x25ml). The organic layer was separated and was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on silica gel column.

Yield: 71%

m.p: 102-4°C

^{1}H-NMR: ($CDCl_3$):δ 7.60 (d, 1.2 Hz, 1H) H-6; 7.43-7.27 (m, 15H) trityl; 6.45 (m, 2H) $=CH_2$; 6.26 (t, 1H) H-1'; 6.13 (t, 1H) $CHSO_2$; 4.56 (m, 1H) H-4'; 3.90 (m, 1H) H-3'; 3.73 (dd, 1H) and 3.37 (dd, 1H) H-5' and H-5''; 2.90 (m, 1H) and 2.50 (m, 1H) H-2' and H-2''; 1.51 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.1, C-4; 150.4, C-2; 143.2, trityl; 135.3/134.4, C-6/$CHSO_2$; 132.9, $=CH_2$; 128.8, 128.2, 127.7, trityl; 111.7, C-5; 87.7, trityl; 85.1, C-1'; 78.3, C-4'; 63.8, C-5'; 61.5, C-3'; 33.6, C-2'; 12.0, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{30}N_2O_6S$: 559.1904, found 559.1943.

Synthesis of 3'-deoxy-3'-S-(1-vinylsulphonyl)-thymidine 15:

A mixture of compound **14** (3mmol) and aqueous acetic acid (80%, 20ml) was heated at 100°C for 15m. Acetic acid was removed under reduced pressure. The residual acetic acid and water were coevaporated with ethanol (2x15ml) and toluene (20ml). The residue was triturated with ether, filtered and the residue was purified by chromatography on silica gel column.

Yield: 85%

m.p: 205-6°C

^{1}H-NMR: ($CDCl_3$+DMSO-d_6):δ 7.68 (s, 1H) H-6; 6.97 (q, 1H) $CHSO_2$; 6.33 (t, 2H) $=CH_2$; 6.12 (t, 1H) H-1'; 4.35 (m, 1H) H-4'; 3.98 (m, 1H) H-3'; 3.78 (m, 1H) and 3.57 (m, 1H) H-5' and H-5''; 2.60 (m, 1H) and 2.29 (m, 1H) H-2' and H-2''; 1.77 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$+DMSO-d_6):δ 164.2, C-4; 150.7, C-2; 136.1/135.3, C-6/$CHSO_2$; 132.3, $=CH_2$; 110.3, C-5; 84.5, C-1'; 78.9, C-4'; 62.6, C-5'; 61.2, C-3'; 32.7, C-2'; 12.6, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{12}H_{16}N_2O_6S$: 317.0808, found 317.0827.

Synthesis of 3'-deoxy-3'-S-(2-azidoethylsulphonyl)-5'-O-tritylthymidine 16a:

To a suspension of sodium azide (0.9g) in methanol (20ml), a solution of conc. sulphuric acid (0.3mg) in methanol (5ml) was added dropwise at 0°C. After 10m. At the same temperature, the turbid solution was added to a methanolic (10ml) solution of compound **14** (0.62mmol). The mixture was stirred overnight at ambient temperature. Methanol was removed and the residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution followed by water. The ethyl acetate solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on silica gel column to give compound **16a**.

Yield: 83%

m.p: 92-3°C

IR: 2090cm^{-1}

^{1}H-NMR: ($CDCl_3$):δ 7.59 (d, 1.0 Hz, 1H) H-6; 7.45-7.25 (m, 15H) trityl; 6.27 (t, 1H) H-1'; 4.64 (m, 1H) H-4'; 4.17 (m, 1H) H-3'; 3.77 (m, 3H) CH_2N_3 and H-5' or H-5''; 3.42 (m, 1H) H-5' or H-5''; 3.07 (m, 3H) CH_2SO_2 and H-2' or H-2''; 2.53 (m, 1H) H-2' or H-2''; 1.49 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.2, C-4; 150.5, C-2; 143.2, trityl; 135.5, C-6; 128.7, 128.2, 127.7, trityl; 111.6, C-5; 87.7, trityl; 85.3, C-1'; 77.5, C-4'; 64.2, C-5'; 62.0, C-3'; 51.4, CH_2SO_2; 44.8,

CH_2N_3; 33.8, C-2'; 12.0, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{31}H_{31}N_5O_6S$: 602.2074, found 602.2055.

Synthesis of 3'-deoxy-3'-S-(2-azidoethylsulphonyl)-5'-O-benzoylthymidine 17a:

A solution of compound **16a** (0.5mmol) in aqueous acetic acid (80%, 15ml) was heated at 100°C. After 0.5h, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol followed by toluene. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (10ml) and benzoyl chloride (2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed thoroughly with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on silica gel.

Yield: 73%

m.p: 69-71°C

IR: 2090cm^{-1}

^{1}H-NMR: ($CDCl_3$):δ 8.04-7.19 (m, 6H) H-6 and phenyl; 6.06 (t, 1H) H-1'; 4.87 (m, 2H) and 4.64 (m, 1H) H-4', H-5' and H-5''; 4.23 (m, 1H) H-3'; 3.90 (m, 3H) CH_2N_3; 3.31 (m, 2H) CH_2SO_2; 3.02 (m, 1H) and 2.57 (m, 1H) H-2' and H-2''; 1.69 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 166.2, benzoyl CO; 164.2, C-4; 150.6, C-2; 135.7, C-6; 133.8, 129.7, 129.3, 128.8 phenyl; 111.4, C-5; 86.7, C-1'; 76.3, C-4'; 65.1, C-5'; 62.1, C-3'; 51.7, CH_2SO_2; 44.7, CH_2N_3; 33.6, C-2'; 12.3, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{19}H_{21}N_5O_7S$: 464.1241, found 464.1281.

Synthesis of 3'-deoxy-3'-S-(2-N-benzylaminoethylsulphonyl)-thymidine 18b:

A mixture of compound **15** (0.5mmol) and benzylamine (2.5mmol) in methanol (10ml) was stirred at ambient temperature for 0.5h. After removing methanol under reduced pressure, excess benzylamine was removed by trituration with ether. The residue was purified by chromatography on a basic alumina column.

Yield: 71%

m.p: 132-4°C

^{1}H-NMR: ($CDCl_3$+DMSO-d_6):δ 7.71 (s, 1H) H-6; 7.26 (m, 5H) phenyl; 6.18 (t, 1H) H-1'; 4.50 (m, 1H) H-4'; 4.25 (m, 1H) H-3'; 3.82 (m, 4H) H-5', H-5''and benzyl CH_2; 3.27 (m, 2H) CH_2N; 3.10 (m, 2H) CH_2SO_2; 2.76 (m, 1H) and 2.40 (m, 1H) H-2' and H-2''; 1.86 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$+DMSO-d_6):δ 163.5, C-4; 149.8, C-2; 138.1, phenyl; 135.3, C-6; 127.6, 127.4, 126.4, phenyl; 109.7, C-5; 84.1, C-1'; 77.9, C-4'; 61.6, C-5'; 59.9, C-3'; 52.2, SO_2CH_2; 50.9, benzyl CH_2; 40.8, CH_2N; 32.4, C-2'; 11.6, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{19}H_{25}N_3O_6S$: 424.1543, found 424.1601.

Synthesis of 3'-deoxy-3'-S-(2-N-morpholinoethylsulphonyl)- 5'-O-tritylthymidine 19c:

A mixture of compound **14** (1mmol) and morpholine (5mmol) in dichloromethane (20ml) was stirred at ambient temperature for 10m. After removing dichloromethane under reduced pressure the oily residue was dissolved in ethylacetate and washed with water. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a basic alumina column.

Yield: 85%

m.p: 98-9°C

^{1}H-NMR: ($CDCl_3$):δ 7.65 (d, 1H) H-6; 7.41-7.22 (m, 15H) trityl; 6.27 (t, 1H) H-1'; 4.74 (m, 1H) H-4'; 4.25 (m, 1H) H-3'; 3.77 (m, 1H) and 3.45 (m, 1H) H-5'and H-5''; 3.60 (t, 4H) CH_2OCH_2; 3.29 (m, 1H) and 2.95 (m, 3H) $SO_2CH_2CH_2N$; 2.77 (m, 1H) H-2'or H-2''; 2.45 (m, 5H) H-2'or H-2''and CH_2NCH_2; 1.50 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.4, C-4; 150.5, C-2; 143.4, trityl; 135.5, C-6; 128.7, 128.3, 127.8, trityl; 111.5, C-5; 87.7, trityl; 85.3, C-1'; 76.9, C-4'; 66.7, CH_2OCH_2; 64.6, C-5'; 61.8, C-3'; 53.6, CH_2NCH_2; 51.8, CH_2SO_2; 49.3, CH_2N; 34.3, C-2'; 12.1, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{35}H_{39}N_3O_7S$: 646.2589, found 646.2640.

Synthesis of 3'-deoxy-3'-S-(2-N-morpholinoethylsulphonyl)thymidine 20c:

Compound **19c** (0.39mmol) was dissolved in a mixture of water and methanol (1:4) and was applied on an ion-exchange column (IR 120H$^+$, 15ml settled volume). The column was first eluted with methanol to remove tritanol followed by 3% aqueous ammonia solution. The fractions containing the title compound were pooled together and evaporated to dryness.

Yield: 74%

m.p: hygroscopic

^{1}H-NMR: (D_2O):δ 7.67 (s, 1H) H-6; 6.17 (t, 1H) H-1'; 4.61 (m, 1H) H-4'; 4.26 (m, 1H) H-3'; 3.90 (m, 2H) H-5'and H-5''; 3.73 (m, 4H) CH_2OCH_2; 3.52 (m, 2H) CH_2N; 3.16 (m, 1H) H-2'or H-2''; 2.91 (m, 3H) CH_2SO_2, H-2'or H-2''; 2.60 (m, 4H) CH_2NCH_2; 1.86 (s, 3H) CH_3.

^{13}C-NMR: (D_2O):δ 167.1, C-4; 152.2, C-2; 138.1, C-6; 112.2, C-5; 86.3, C-1'; 79.1, C-4'; 67.0, CH_2OCH_2; 62.9, C-5'; 61.5, C-3'; 53.1, CH_2NCH_2; 50.3, CH_2SO_2; 49.1, CH_2N; 33.1, C-2'; 12.4, CH_3.

Synthesis of 3'-deoxy-3'-S-(2-N-imidazolylethylsulphonyl)- 5'-O-benzoylthymidine 21d:

A mixture of compound **15** (0.5mmol) and imidazole (5mmol) in methanol (10ml) was stirred at ambient temperature. After 20h methanol was removed under reduced pressure and the product mixture was triturated with ether to remove excess imidazole. The residue was dissolved in pyridine (10ml) and benzoyl chloride (2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2.5h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was partitioned with ethyl acetate. The organic layer was separated and evaporated to dryness under reduced pressure. The brown residue was purified by chromatography on a silica gel column.

Yield: 65%

m.p: 104-7°C

^{1}H-NMR: ($CDCl_3$):δ 8.01-6.99 (m, 9H) H-6, phenyl and imidazole; 5.98 (t, 1H) H-1'; 4.62 (m, 5H) H-4', H-5', H-5"and CH_2N; 3.60 (m, 3H) H-3' and CH_2SO_2; 2.88 (m, 1H) and 2.39 (m, 1H) H-2' and H-2"; 1.63 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$+DMSO-d_6):δ 165.7, benzoyl CO; 163.9, C-4; 150.3, C-2; 137.4, C-6; 135.0, 133.4, 129.3, 128.9, 128.4, 119.1, phenyl and imidazole; 110.9, C-5; 85.6, C-1'; 75.4, C-4'; 64.8, C-5'; 61.4, C-3'; 52.5, CH_2SO_2; 40.1 CH_2N; 32.9 C-2'; 11.9, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{22}H_{24}N_4O_7S$: 489.1445, found 489.1475.

Synthesis of 3'-deoxy-3'-S-(2-dimethylmalonateylethylsulphonyl)-5'-O-tritylthymidine 22e:

Dimethyl malonate (12mmol) was added dropwise to a stirred suspension of sodium hydride (5mmol) in THF (15ml) at 0°C. After the addition the reaction mixture was allowed to warm up to ambient temperature and the mixture was stirred for 0.5h. A solution of compound **14** (0.57mmol) in THF (10ml) was added dropwise and the mixture was stirred at the ambient temperature for 20h. THF was removed under reduced pressure. The oily material was dissolved in ethyl acetate and the ethyl acetate layer was washed thoroughly with saturated

aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column.

Yield: 66%

m.p: 79-80°C

^{1}H-NMR: ($CDCl_3$):δ 7.59 (d, 1.2 Hz, 1H) H-6; 7.44-7.24 (m, 15H) trityl; 6.25 (t, 1H) H-1'; 4.62 (m, 1H) H-4'; 3.96 (m, 1H) H-3'; 3.76 (s, 3H) and 3.74 (s, 3H) 2xOCH_3; 3.75 (m, 1H), 3.60 (m, 2H) and 3.40 (m, 1H) H-5', H-5'' and malonate CH; 3.07 (t, 2H) CH_2SO_2; 2.98 (m, 1H) and 2.55 (m, 1H) H-2' and H-2''; 2.35 (m, 2H) CH_2CH; 1.56 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 168.7, 2xmalonate CO; 164.2, C-4; 150.4, C-2; 143.3, trityl; 135.5, C-6; 128.7, 128.2, 127.7, trityl; 111.5, C-5; 87.7, trityl; 85.4, C-1'; 77.6, C-4'; 64.1, C-5'; 60.2, C-3'; 53.1, 2xOCH_3; 49.4, CH_2SO_2 and malonate CH; 33.8, C-2'; 21.1, CH_2CH; 12.1, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{36}H_{38}N_2O_{10}S$: 691.2327, found 691.2295.

Synthesis of 3'-deoxy-3'-S- (2-dimethylmalonateylethylsulphonyl)-5'-O-benzoylthymidine 23e:

A solution of compound **22e** (0.3mmol) in aqueous acetic acid (80%, 10ml) was heated at 65°C. After 2h, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (10ml) and a solution of benzoyl chloride (1.2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was partitioned with ethyl acetate. The organic layer were pooled together and evaporated to dryness. Residual pyridine was coevaporated with toluene. The solid residue thus obtained was purified by chromatography on a silica gel column.

Yield: 82%

m.p: 71-3°C

^{1}H-NMR: ($CDCl_3$):δ 8.05-7.18 (m, 6H) H-6 and phenyl; 6.06 (t, 1H) H-1'; 4.85 (m, 2H) and 4.61 (m, 1H) H-4', H-5' and H-5''; 4.10 (m, 1H) H-3'; 3.76 (s, 3H) and 3.75 (s, 3H) 2xOCH_3; 3.64 (t, 1H) malonate CH; 3.25 (m, 2H) CH_2SO_2; 2.98 (m, 1H) and 2.59 (m, 1H) H-2' and H-2''; 2.44 (m, 2H) CH_2CH; 1.68 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 168.8, malonate CO; 166.1, benzoyl CO; 164.2, C-4; 150.4, C-2; 135.9, C-6; 133.7, 129.7, 129.4, 128.7 phenyl; 111.3, C-5; 86.9, C-1'; 76.5, C-4'; 65.1, C-5'; 60.4, C-3'; 53.0, 2xOCH_3; 49.7, CH_2SO_2; 49.4, malonate CH; 33.6, C-2'; 21.1, CH_2CH; 12.1, CH_3.

MS (FAB^+): $(M+H)^+$ calc. for $C_{24}H_{27}N_2O_{11}S$: 553.1493, found 553.1499.

Synthesis of 3'-deoxy- 3'-S-(2-N-N'-acetyl- 1,4,10,13-tetraoxa-7,16-diazacyclooctadecanyl ethyl sulphonyl)-5'-O-tritylthymidine 24f:

A solution of compound **14** (0.5mmol) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (2mmol) in dichloromethane (15ml) was stirred at room temperature. After 2days, dichloromethane was removed under reduced pressure and the solid residue was purified on a silica gel column to remove excess crown ether. The product was dissolved in pyridine (15ml) and acetic anhydride (2mmol) was added dropwise. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the mixture was partitioned with ethylacetate (3x20ml). The organic layers were pooled together and evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column.

Yield: 35%

m.p: 78-80°C

^{1}H-NMR: ($CDCl_3$):δ 7.59 (d, 1H) H-6; 7.43-7.29 (m, 15H) trityl; 6.27 (t, 1H) H-1'; 4.69 (m, 1H)

H-4'; 4.06 (m, 1H) H-3'; 3.75-2.40 (m, 32H) crown ether, $SO_2CH_2CH_2N$, H-5', H-5'', H-2', H-2''; 2.09 (s, 3H) acetyl CH_3; 1.47 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$+DMSO-d_6):δ 170.6 acetyl CO; 163.9, C-4; 150.2, C-2; 143.0, trityl; 134.9, C-6; 128.4, 127.8, 127.3, trityl; 111.0, C-5; 87.2, trityl; 84.9, C-1'; 76.6, C-4'; 70.6, 70.2, 69.6, 69.4, crown ether CH_2; 64.4, C-5'; 61.3, C-3'; 53.7, 49.9, 49.5, 47.8, 46.6 crown ether CH_2 and $SO_2CH_2CH_2N$; 33.5, C-2'; 21.3, acetyl CH_3; 11.7, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{45}H_{58}N_4O_{11}S$: 863.3903, found 863.3947.

Synthesis of 3'-deoxy-3'-S-(2-S-thiophenylethylsulphonyl)- 5'-O-tritylthymidine 25g:

To a stirred solution of thiophenol (2.5mmol) and tetramethylguanidine (2mmol) in dichloromethane (10ml) compound **14** (0.5mmol) was added. After 0.5h at ambient temperature, the mixture was poured into water. The organic material from the aqueous mixture was extracted with dichloromethane. The dichloromethane solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on a silica gel column.

Yield: 82%

m.p: 95-6°C

^{1}H-NMR: ($CDCl_3$):δ 7.58 (d, 1.0 Hz, 1H) H-6; 7.44-7.22 (m, 20H) trityl and phenyl; 6.22 (t, 1H) H-1'; 4.60 (m, 1H) H-4'; 3.96 (m, 1H) H-3'; 3.74 (m, 1H) H-5' 3.40-3.07 and 3.11 (m, 5H) H-5'or H-5''and $SCH_2CH_2SO_2$; 2.86 (m, 1H) and 2.38 (m, 1H) H-2' and H-2''; 1.55 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 164.1, C-4; 150.4, C-2; 143.3, trityl; 135.5, C-6; 133.5, 130.5, 129.6, 128.7, 128.3, 127.7, 127.6, trityl and phenyl; 111.6, C-5; 87.8, trityl; 85.5, C-1'; 77.7, C-4'; 64.1, C-5'; 61.0, C-3'; 51.9, CH_2SO_2; 33.9, C-2'; 25.9, CH_2S; 12.1, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{37}H_{36}N_2O_6S_2$: 669.2095, found 669.2129.

Synthesis of 3'-deoxy-3'-S-(2-S-thiophenylethylsulphonyl)- 5'-O-benzoylthymidine 26g:

A solution of compound **25g** (0.4mmol) in aqueous acetic acid (80%, 15ml) was heated at 100°C. After 15m, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (15ml) and benzoyl chloride (1.6mmol) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed thoroughly with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column.

Yield: 82%

m.p: 73-5°C

^{1}H-NMR: ($CDCl_3$):δ 8.03 and 7.66-7.15 (m, 11H) H-6 and 2xphenyl; 6.02 (t, 1H) H-1'; 4.83 (m, 2H) and 4.58 (m, 1H) H-4', H-5' and H-5''; 4.10 (m, 1H) H-3'; 3.32 (m, 4H) $SO_2CH_2CH_2S$; 2.91 (m, 1H) and 2.49 (m, 1H) H-2' and H-2''; 1.69 (s, 3H) CH_3.

^{13}C-NMR: ($CDCl_3$):δ 166.1, benzoyl CO; 164.2, C-4; 150.4, C-2; 135.9, C-6; 133.7, 133.5, 130.4, 129.7, 129.5, 129.3, 128.8, 127.5, 2xphenyl; 111.2, C-5; 87.1, C-1'; 76.6, C-4'; 65.1, C-5'; 61.1, C-3'; 52.3, CH_2SO_2; 33.8, C-2'; 25.8, CH_2S; 12.3, CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{25}H_{26}N_2O_7S_2$: 531.1261, found 531.1298.

Synthesis of 3'-deoxy-5'-O-trityl-3'-[S-{1-(thymine-1-yl)-1,2,5-trideoxy-3-O-trityl-β-D-erythropentofuranos-5-yl}-N-(methyl)-ethylsulphonyl]thymidine 29:

A solution of 3'-O-trityl-5'-O-mesylthymidine **27** (1.12g, 2mmol) in 40% aqueous solution of methylamine (6ml) was stirred at room temperature for 38 hours then 100°C for 1.5h. Excess methylamine was removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The ethyl acetate part was washed with water and dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness. The solid residue was purified over silica gel to give **28** (0.56g, 56%). A solution of compound **28** (0.5g, 1mmol) and compound **14** (0.28g, 0.5mmol) 1n dichloromethane (15ml) was stirred at room temperature for 15h. Dichloromethane was evaporated to dryness and the residue was purified over basic alumina to give compound **29** .

Yield: 76%

^{1}H-NMR: ($CDCl_3$):δ 7.53-7.21 (m, 31H); 7.00 (s, 1H); 6.14 (t, 1H); 5.99 (t, 1H); 4.64 (m, 1H); 4.02 (m, 3H); 3.69 (dd, 1H); 3.38 (dd, 1H); 3.06-2.77 (m, 5H); 2.12 (s, 4H); 1.81 (s, 5H); 1.53 (s, 3H).

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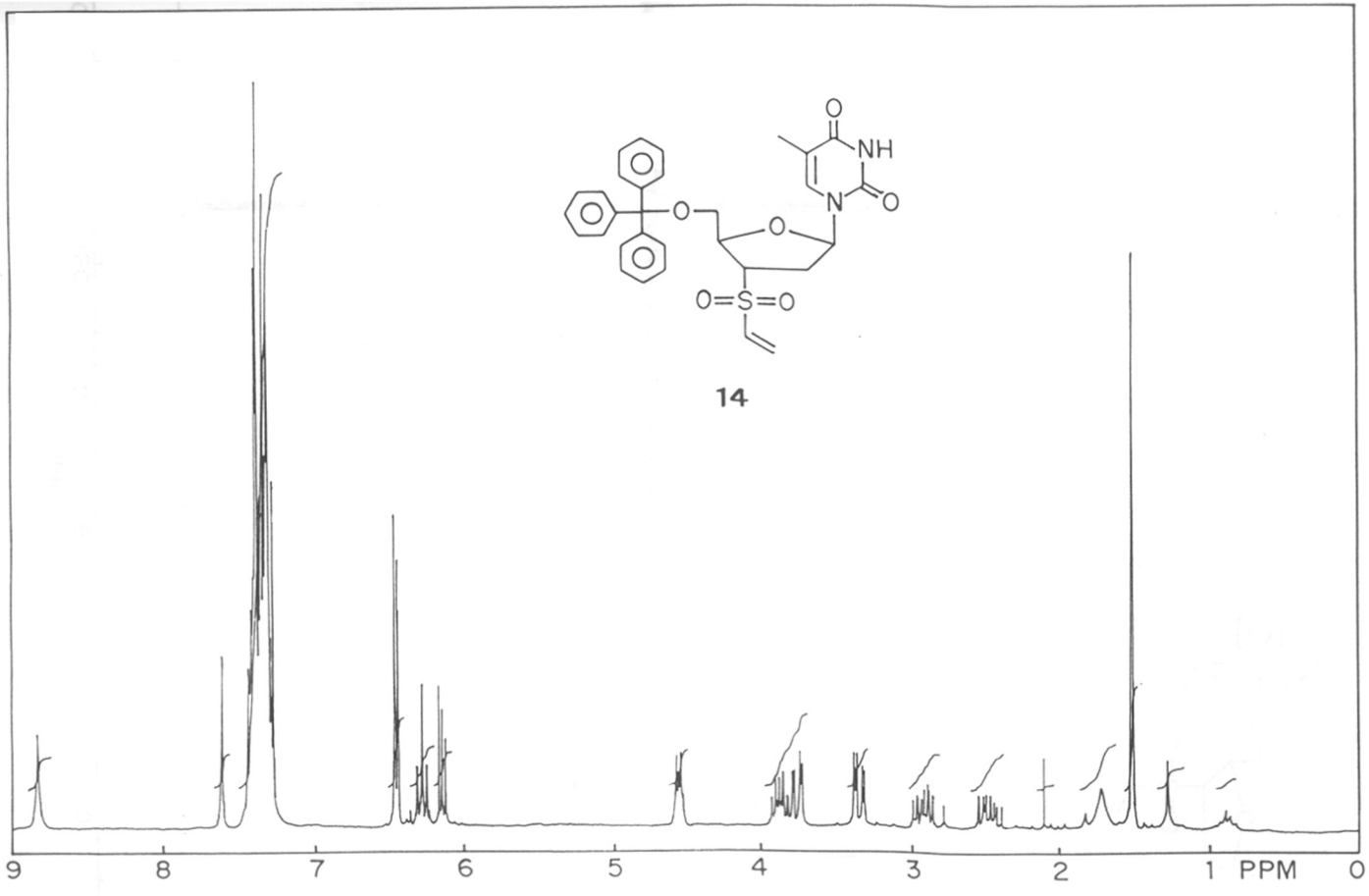

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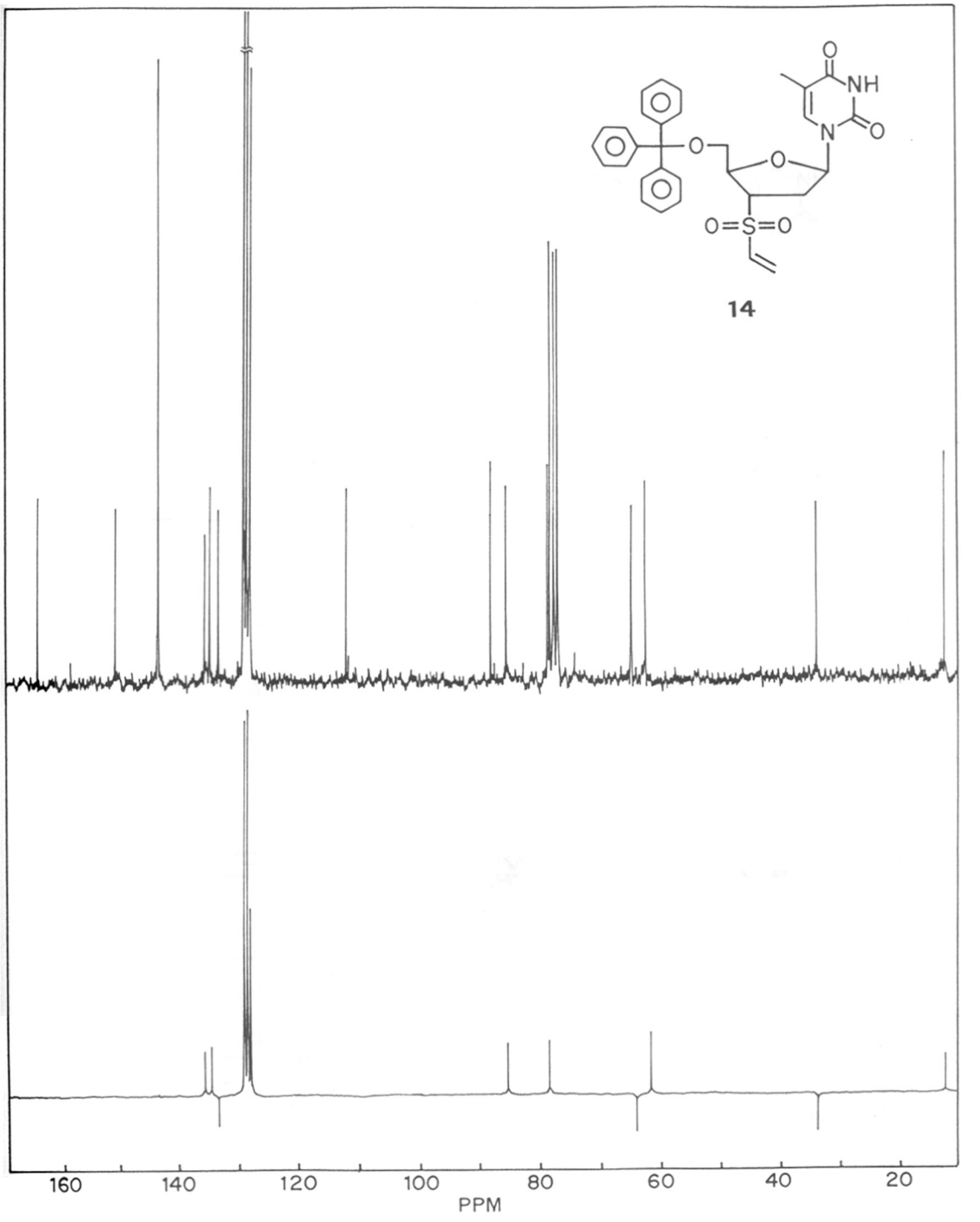

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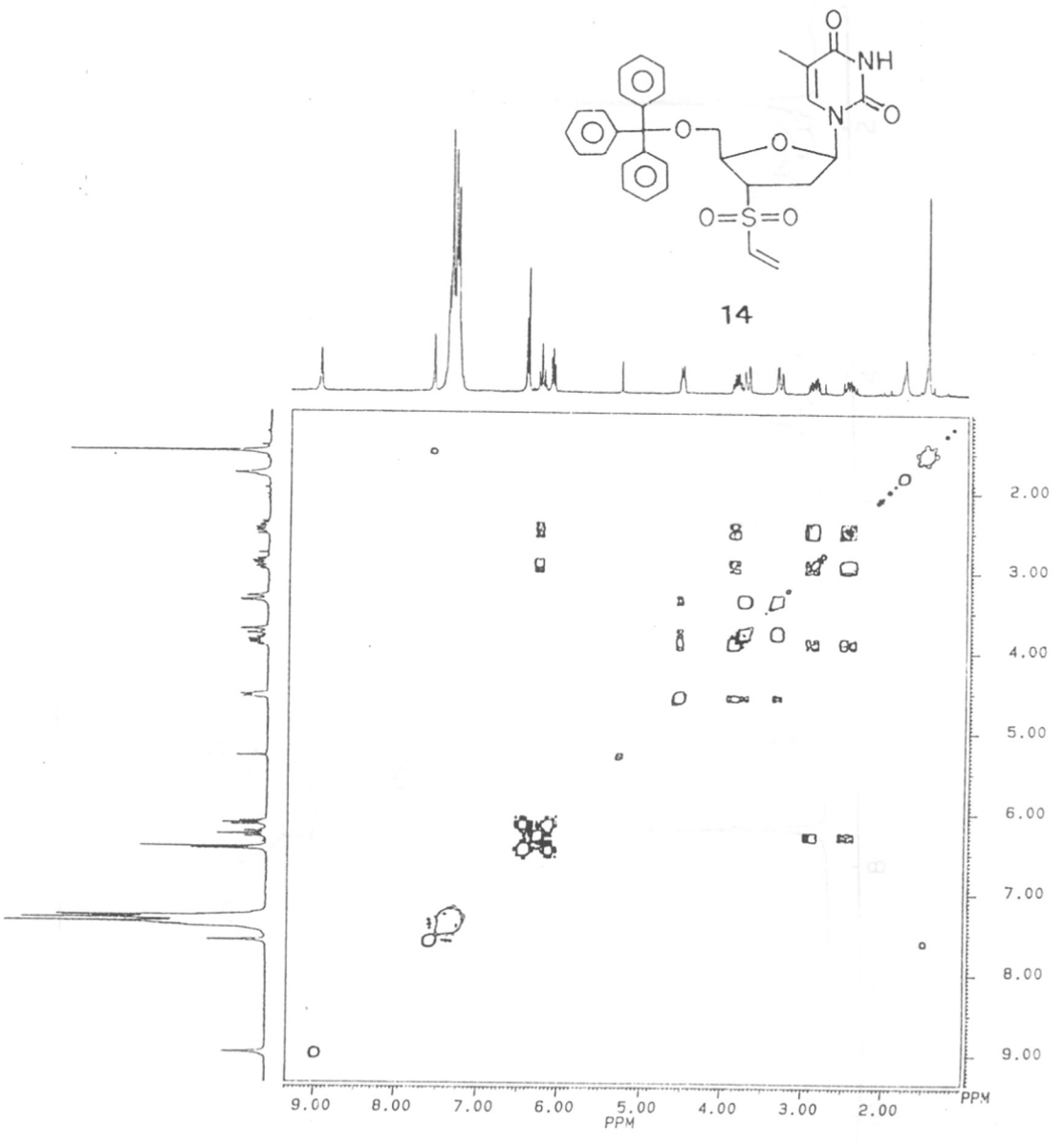
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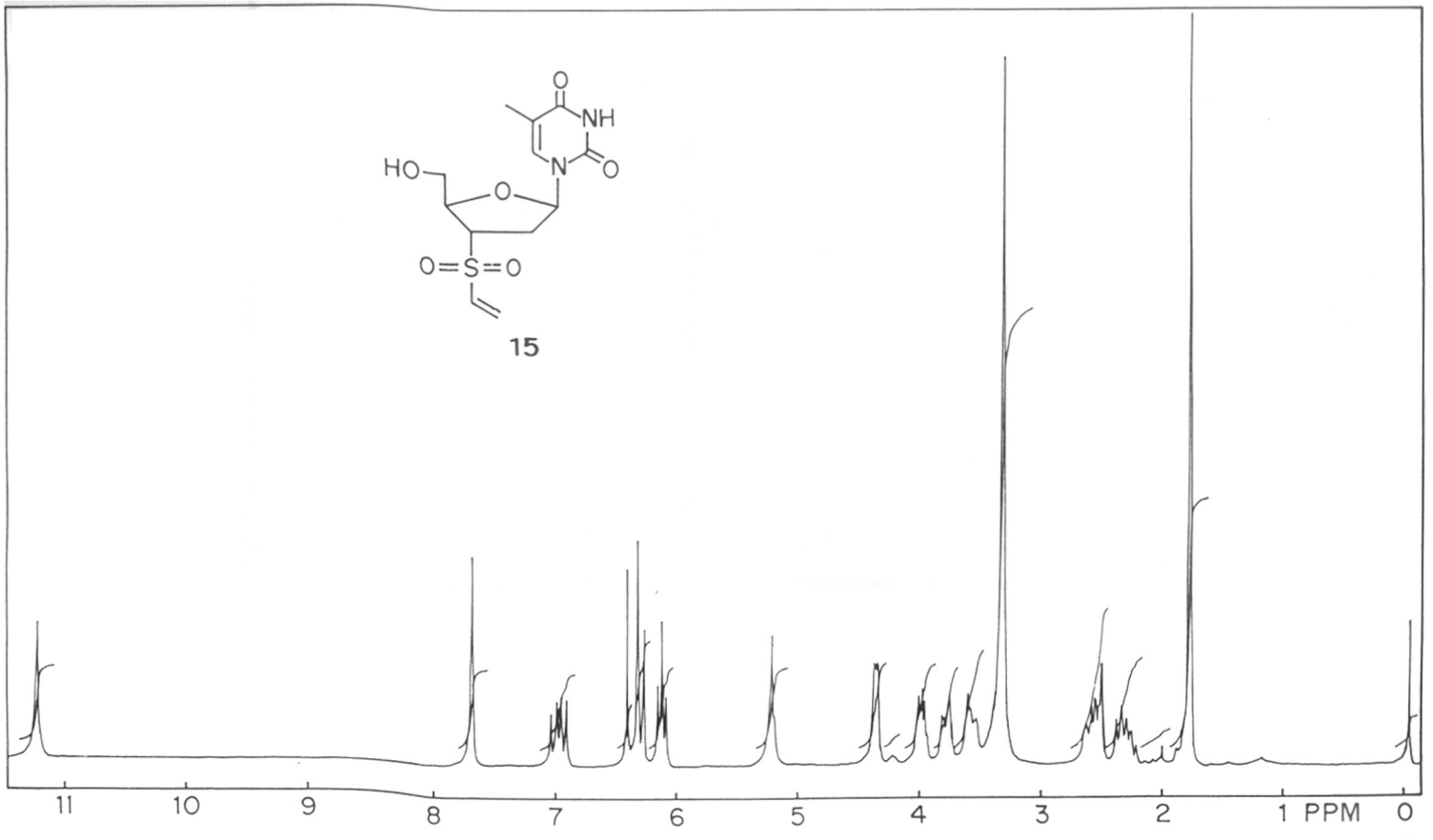

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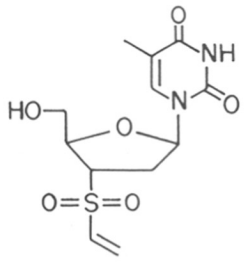

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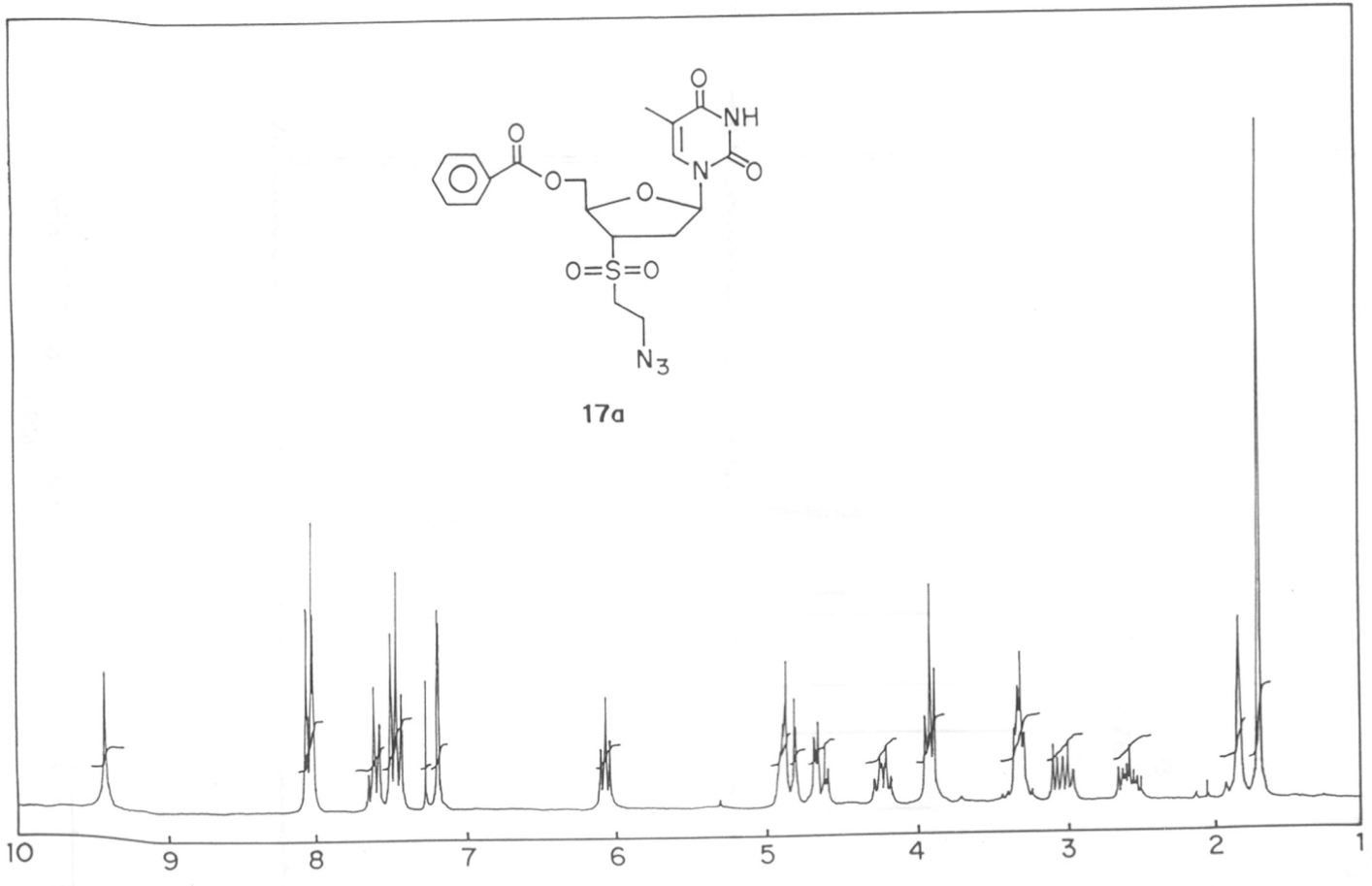

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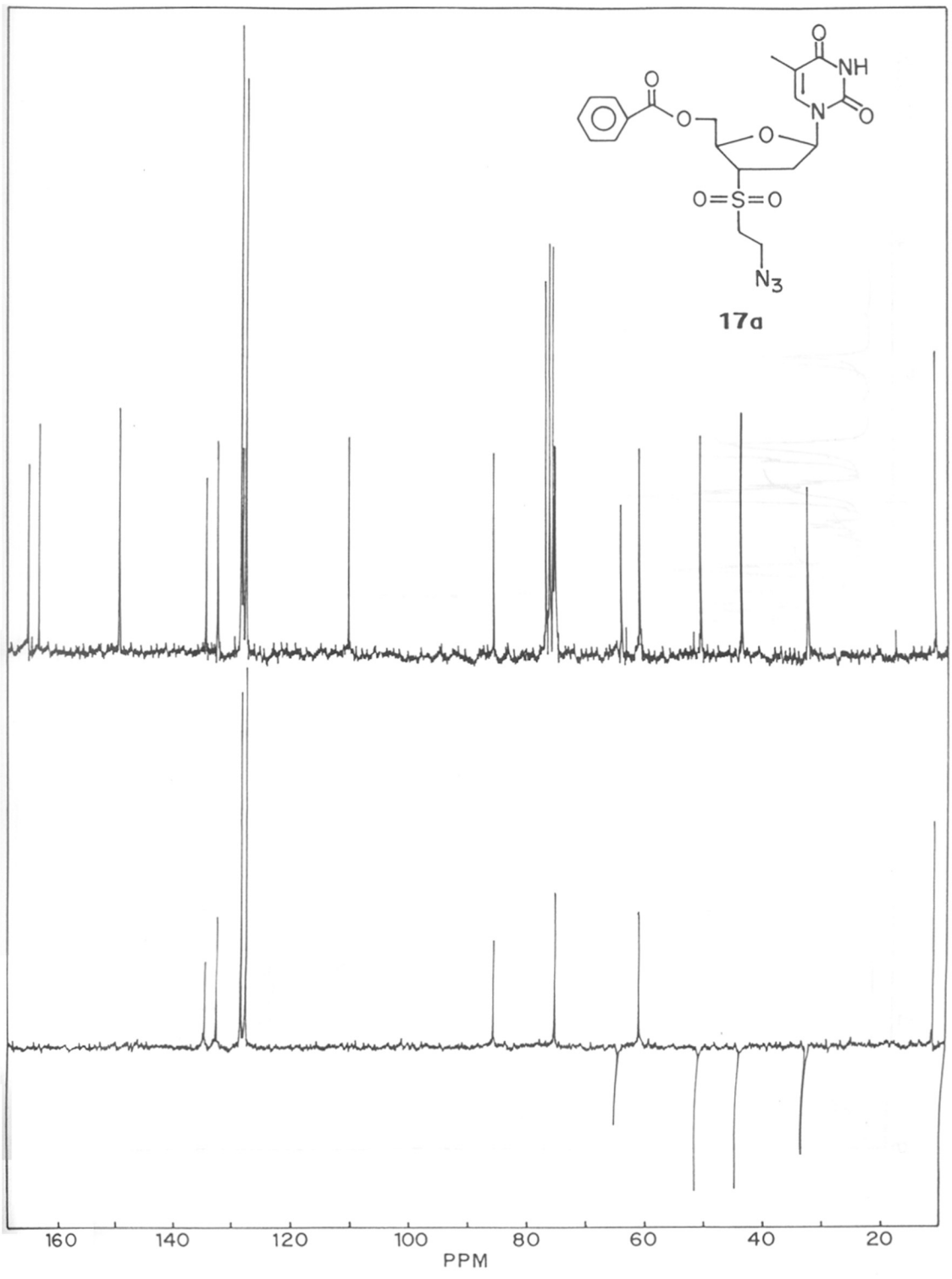

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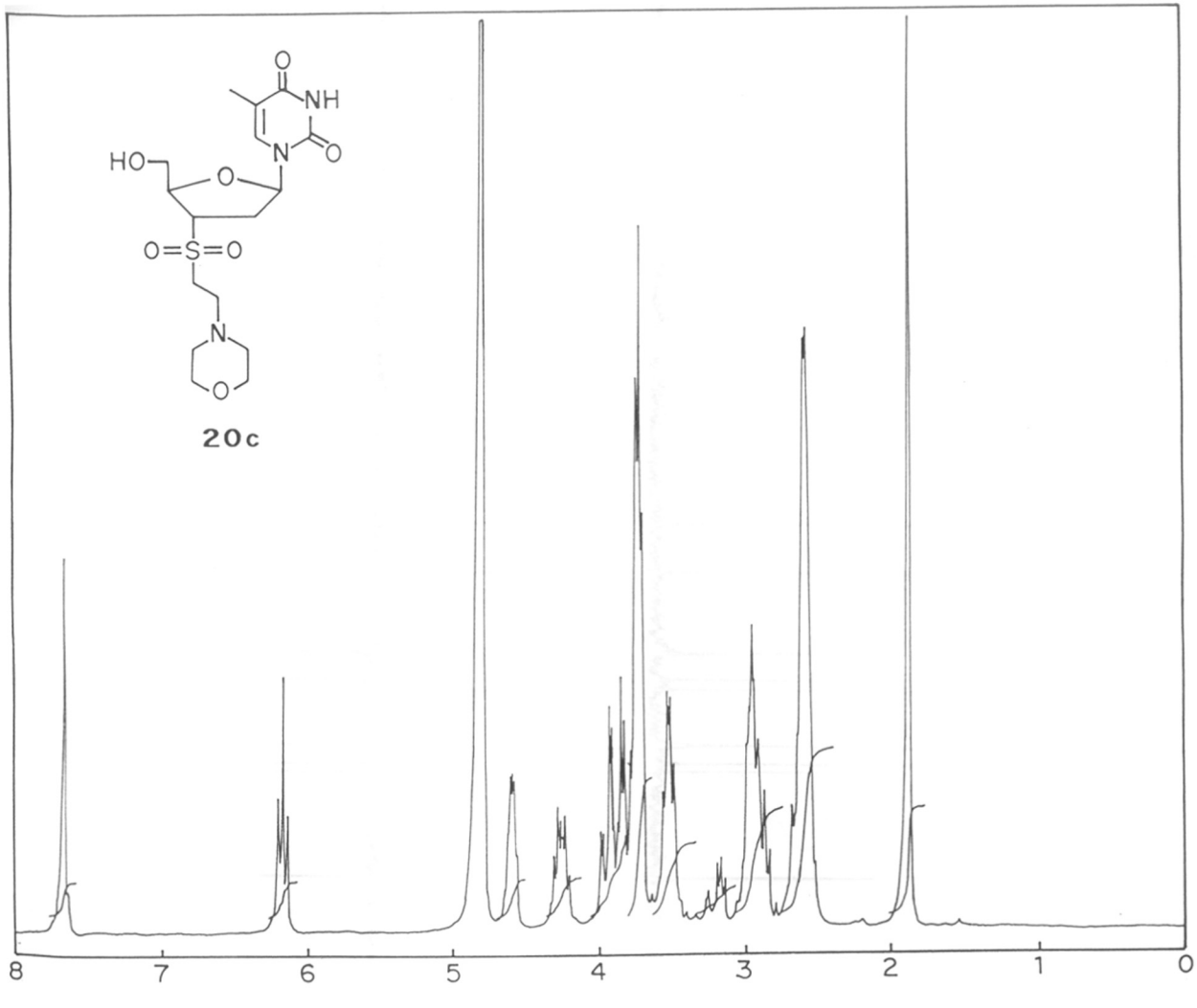

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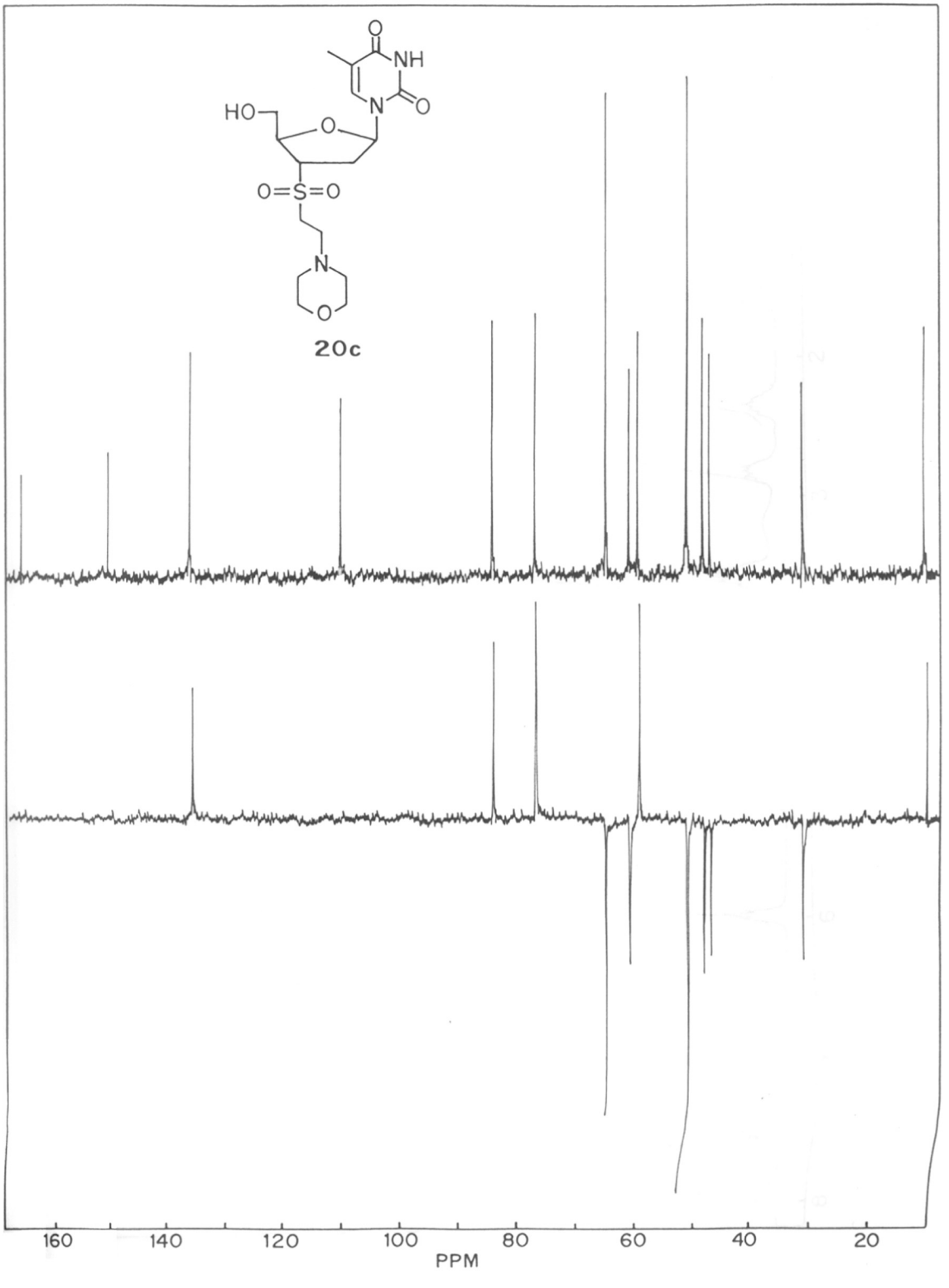

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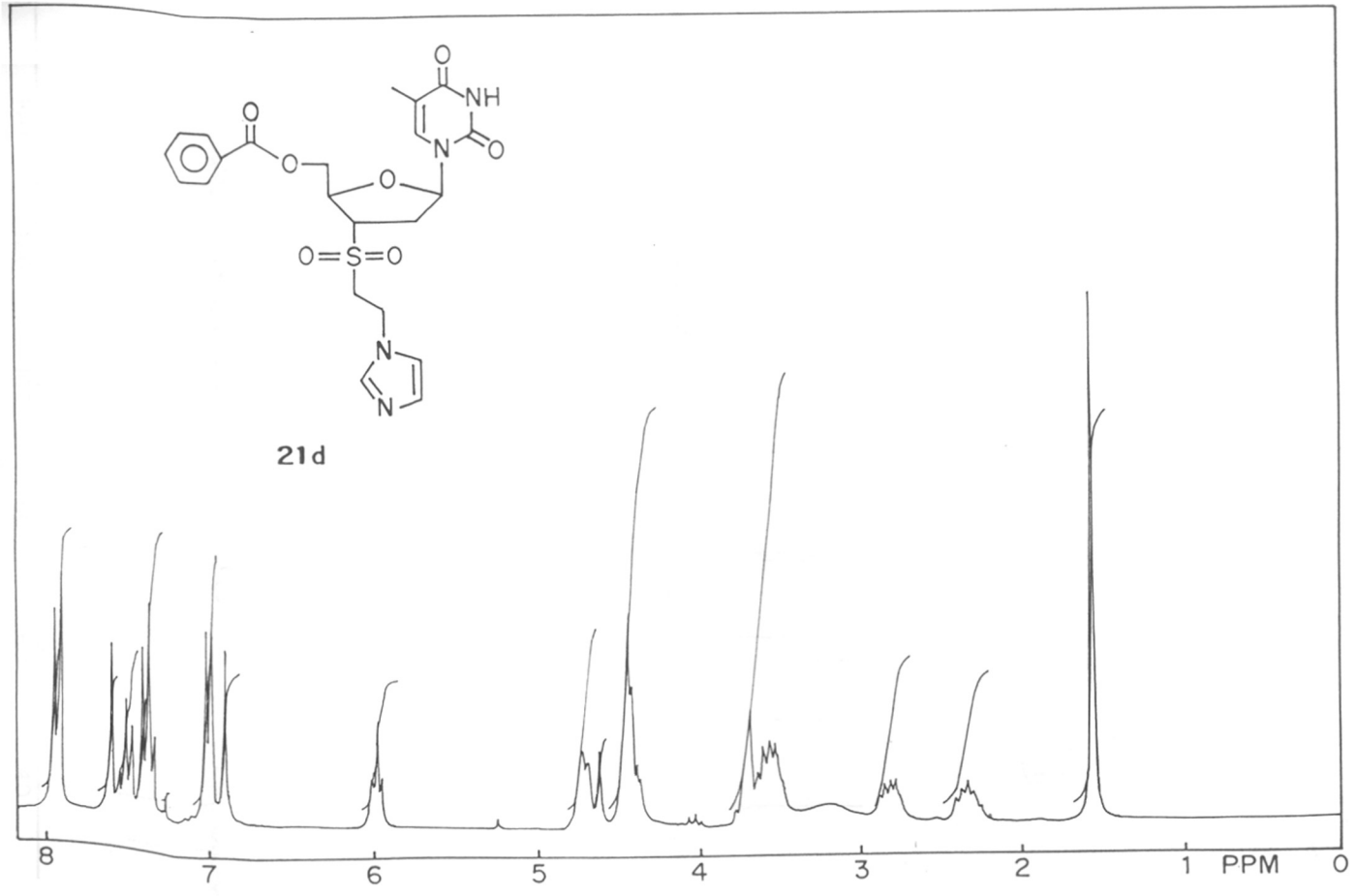

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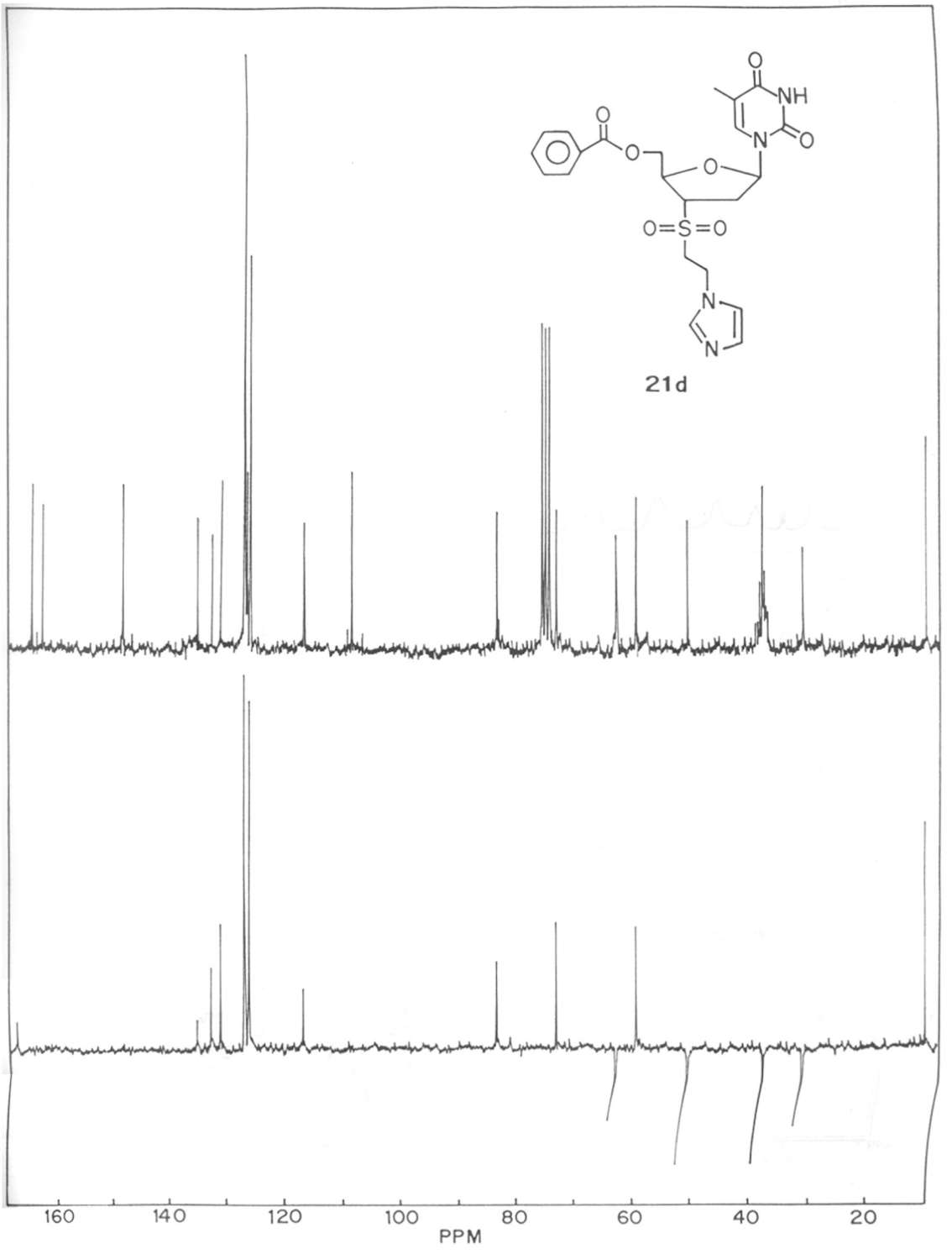

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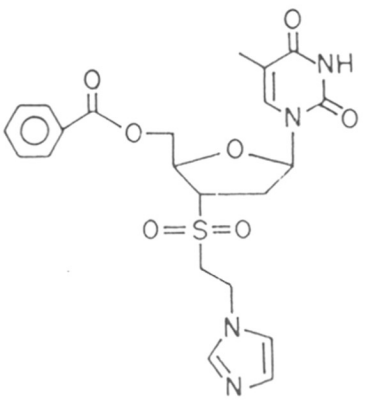
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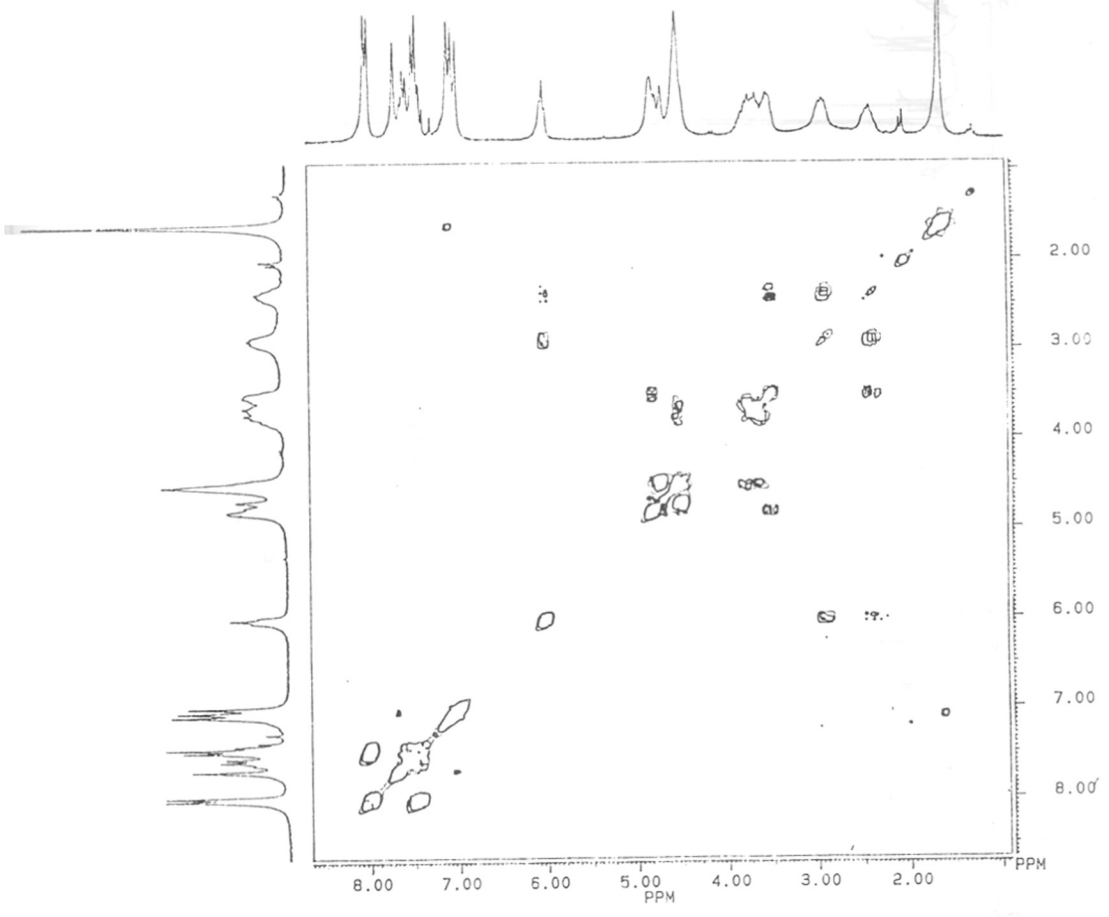
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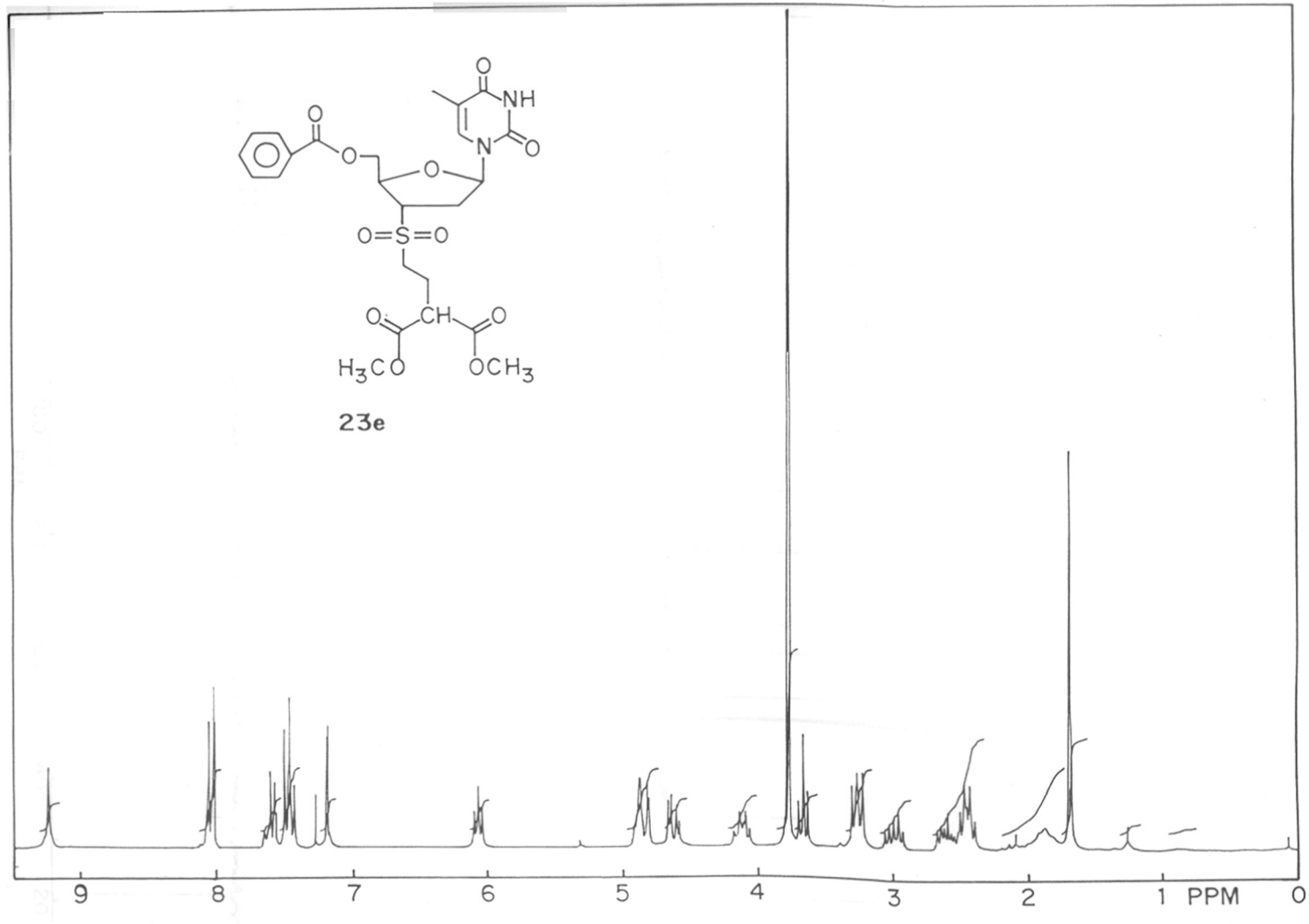

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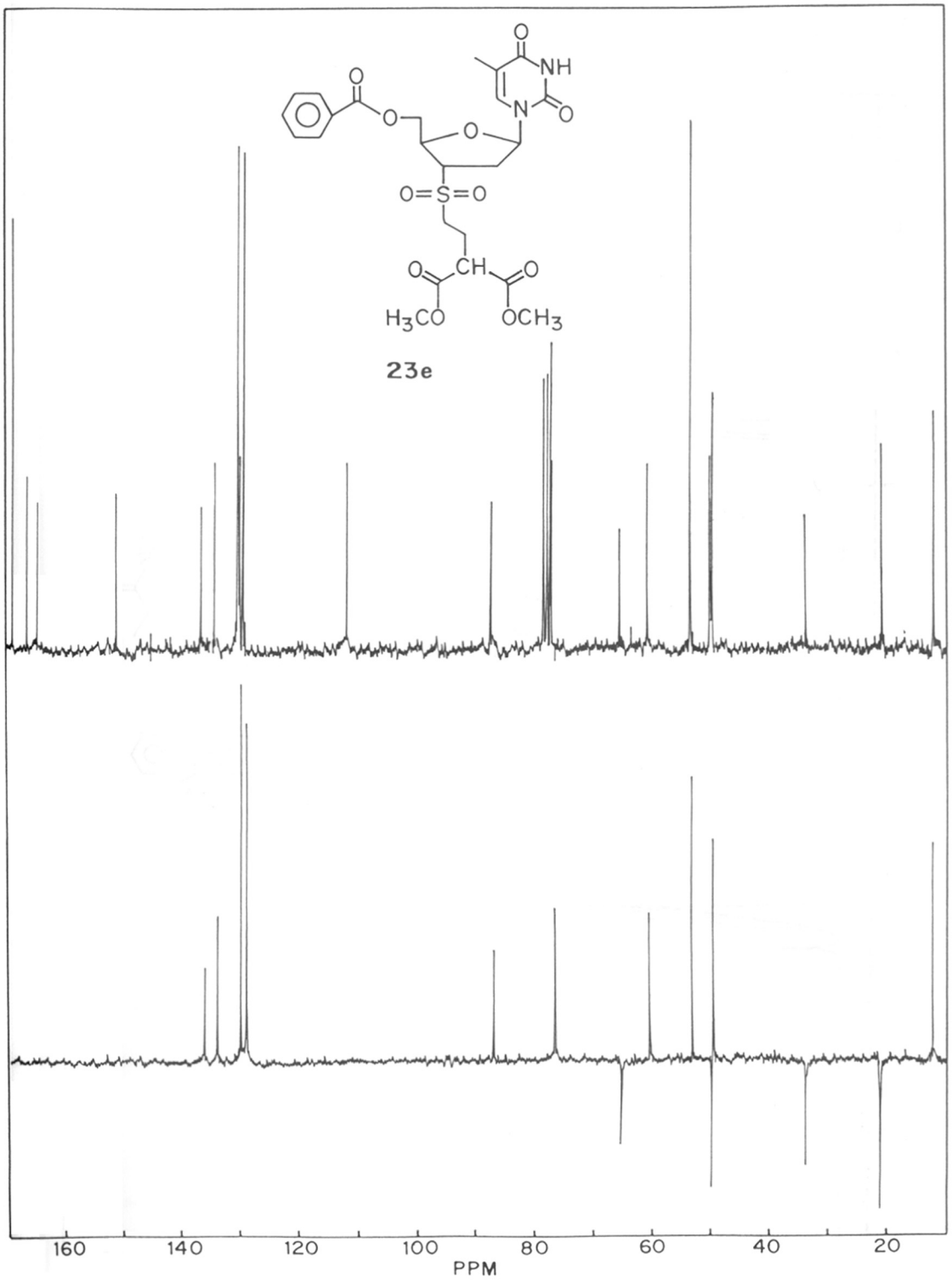

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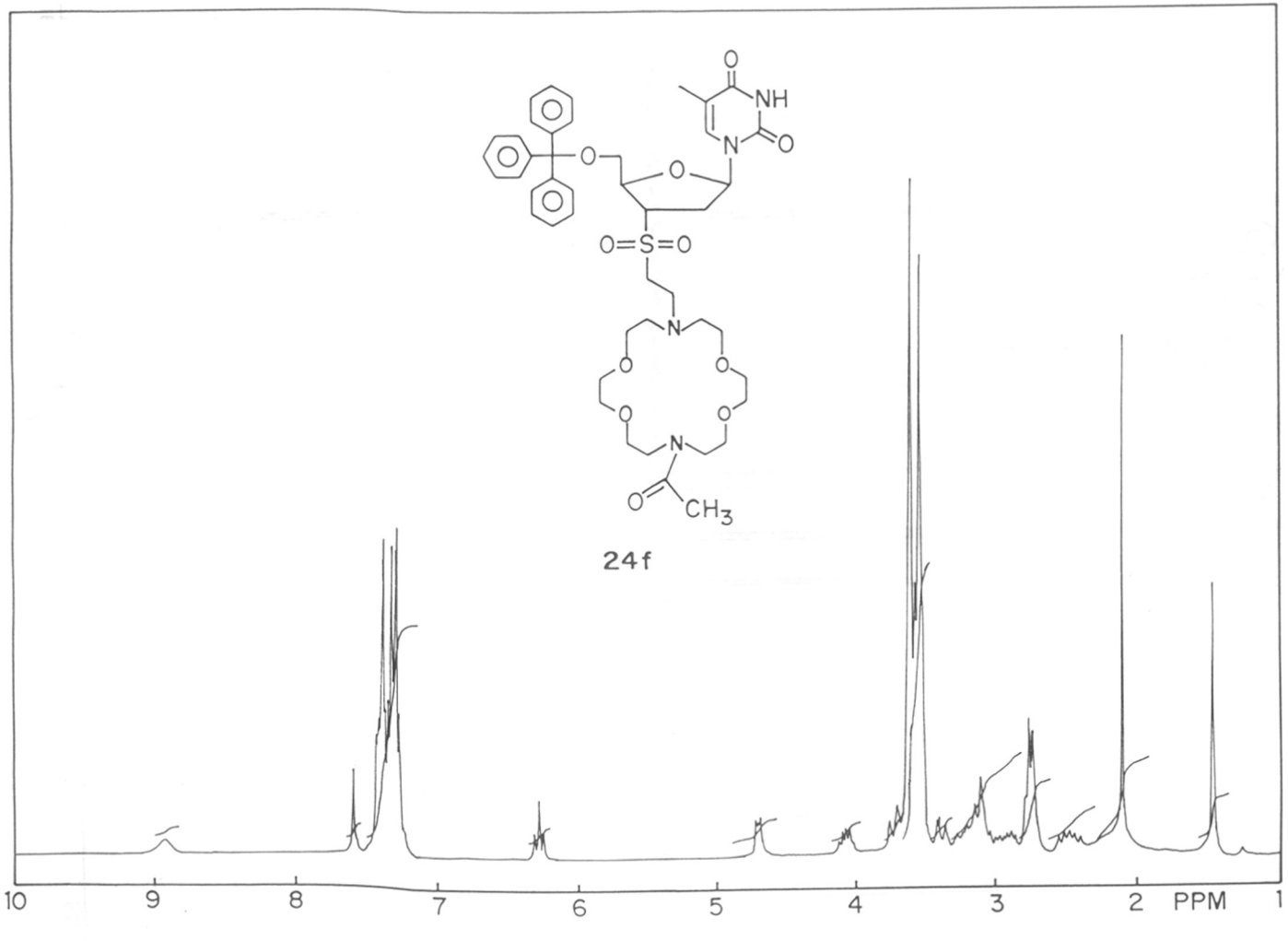

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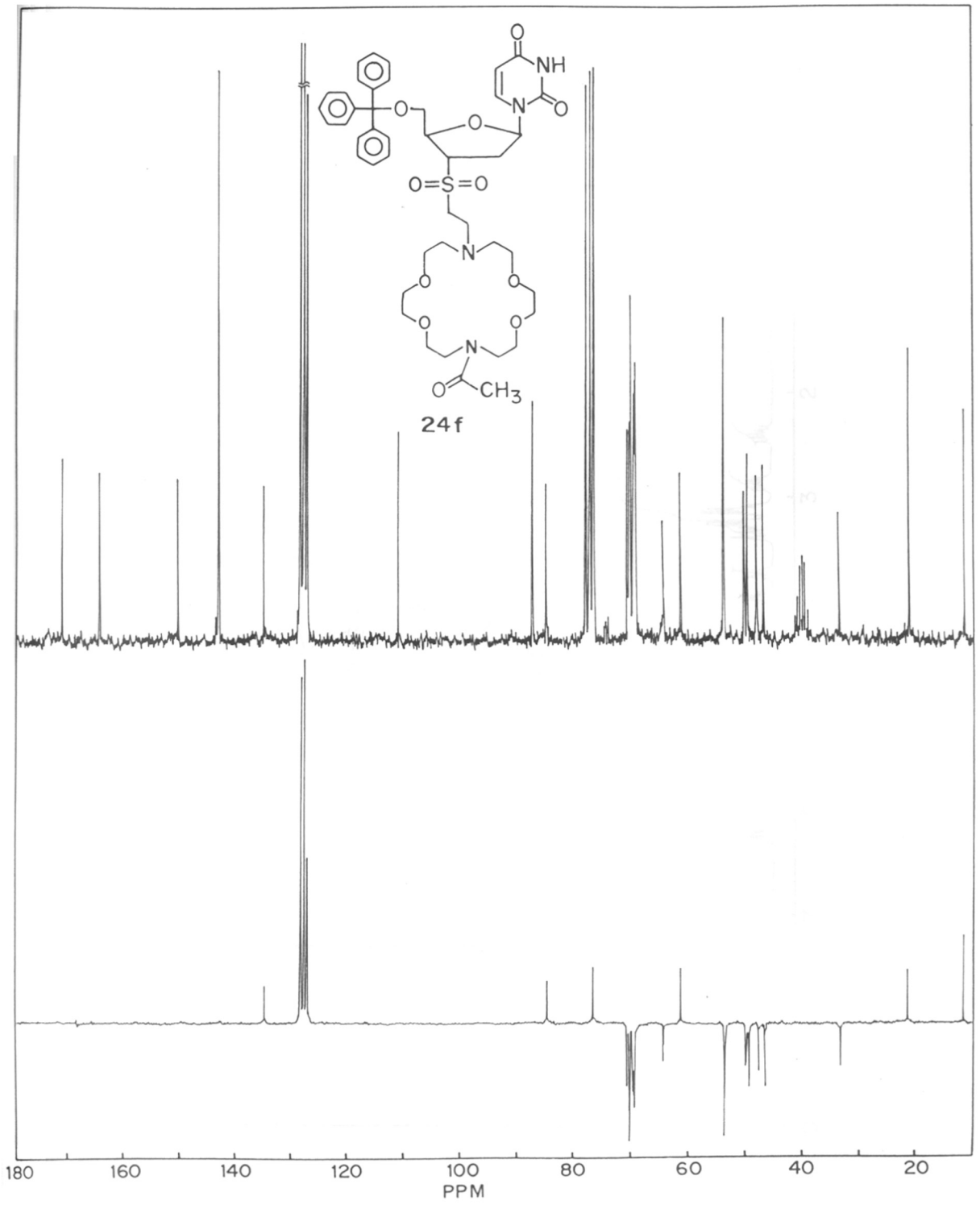

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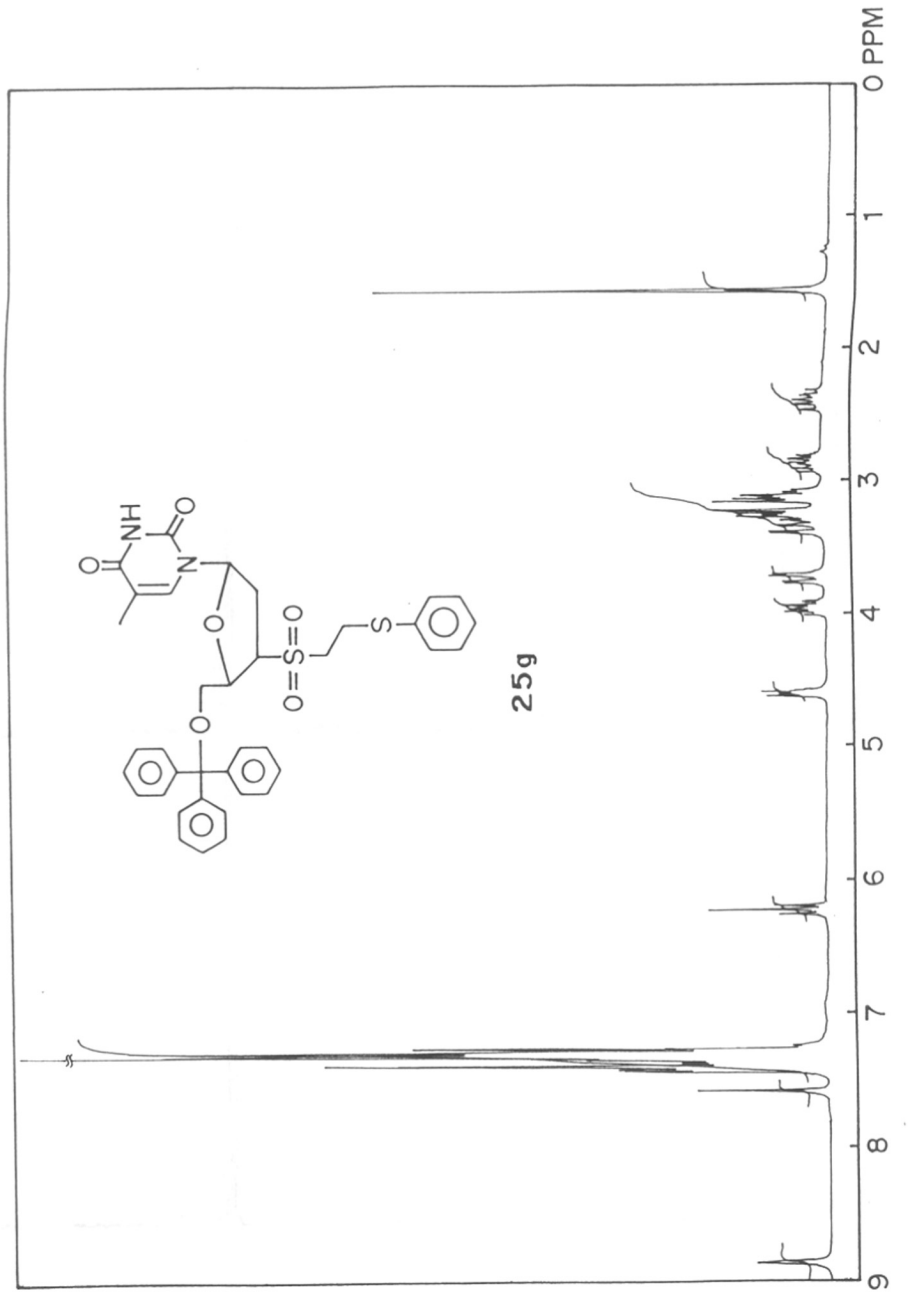
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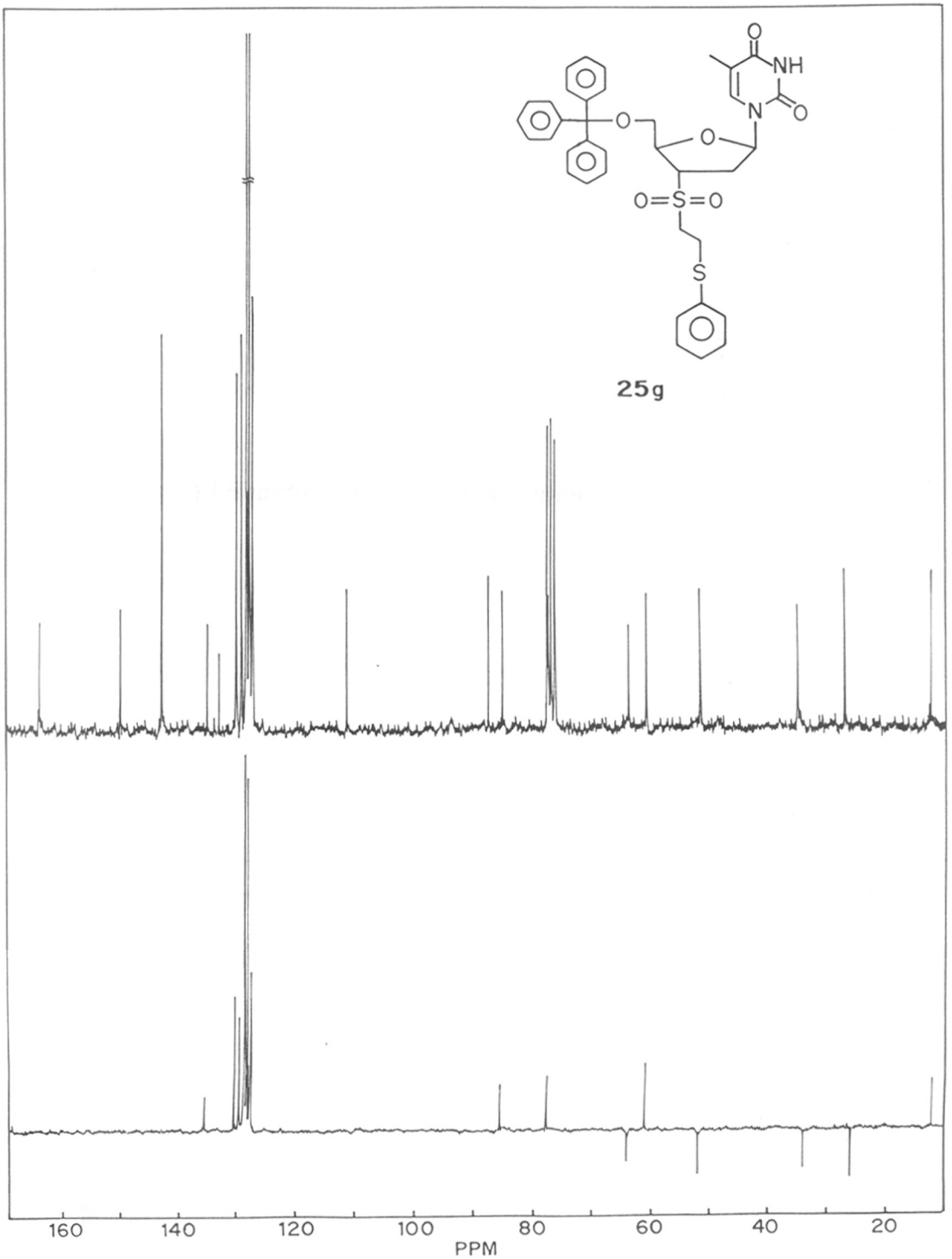


25g

CHAPTER-IV

Synthesis and Reactivities of Sugar Modified Bisvinylsulphonyluridine

4.1 Introduction:

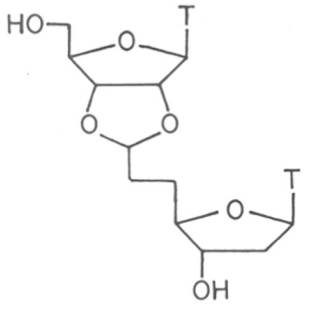
In the previous chapter (Chapter-III) we have described the synthesis of a "reactive" nucleoside, 3'-deoxy-3'-S-(vinylsulphonyl)thymidine and studied its reactivities towards various nucleophiles. In continuation of our interest in the area of nucleosides modified with reactive functionalities, we decided to study the behavior of a sugar modified nucleoside carrying a *bis*vinylsulphone moiety, which was expected to generate bicyclic nucleosides when reacted with appropriate nucleophiles. Synthesis of such compounds are of immense importance as various sugar modified polycyclic nucleosides have been synthesised in recent time, either to control the conformational mobilities of the corresponding nucleotides incorporated in DNA[1-5] (**Figure-4.1**) or to use the modified nucleosides as reverse transcriptase inhibitors[6-14] (**Figure-4.2**); naturally occurring modified nucleosides such as griseolic acids (**Figure-4.3**) containing bicyclic system are known nucleotide-phosphodiesterase inhibitors[15]; herbicidines and aureonucleomycin (**Figure-4.3**) are the unusual nucleosides having furano-pyrano-pyran skeletons[16]. Moreover, by virtue of the facts that vinylsulphone was reported[17] to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase and vinyl sulphone containing dipeptides were shown[18] to be efficient cysteine protease inhibitors (discussed in Chapter-III, **Scheme-3.3**), development of a methodology for the synthesis of vinylsulphone modified nucleoside will be of immense importance.

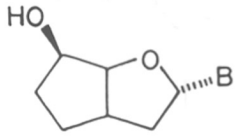
Alkylating agents such as nitrogen mustards, can undergo SN^1 or SN^2-type reactions, depending on the relative rates of the aziridinium ion formation and the nucleophilic attack on the aziridinium ion[19] (**Scheme-4.1**). The DNA undergoes intrastrand and interstrand *cross-linking*[20,21] with this bifunctional alkylating agent (**Figure-4.4**). In the previous chapter (Chapter-III) we have described that unlike nitrogen mustards, the 3'-deoxy-3'-S-(vinylsulphonyl)thymidine would react with only one nucleophile at a time. But the *bis*vinylsulphone functionality like nitrogen mustard, having two electrophilic sites can alkylate two nucleophiles at a time by Michael addition reaction.

4.2 Present Work:

Synthesis of 5'-O-trityl-2',3'-dideoxy-2'-ene-3'-S-(1-vinylsulphonyl) uridine 6: 5'-O-Trityl-2',3'-O-anhydro-*lyxo*uridine **1**[22] was reacted with mercaptoethanol in presence of TMG

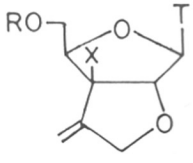
Figure-4·1

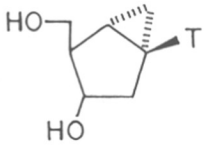


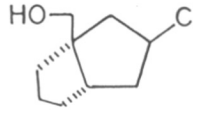


B = T, C, Ad, Gua

Figure-4·2

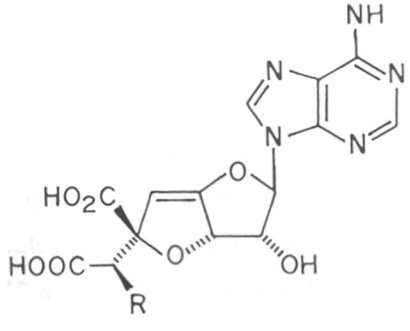




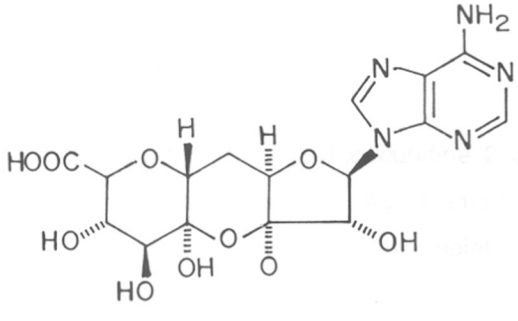


X = CH_2OH , CH_2CH_2CN

Figure-4·3



Griseolic acid



Aureonuclemycin

Scheme - 4·1

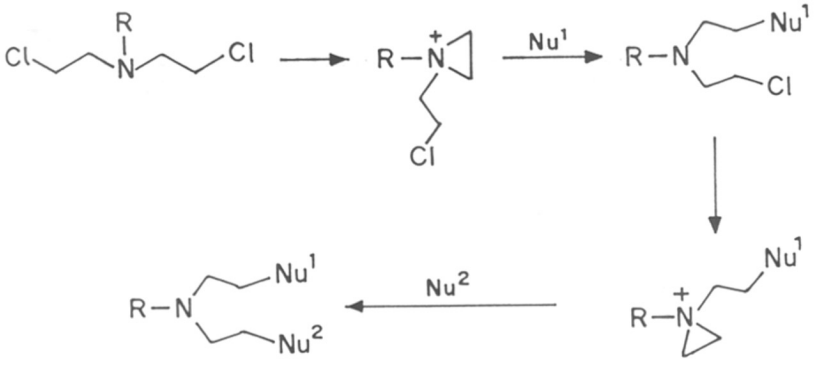
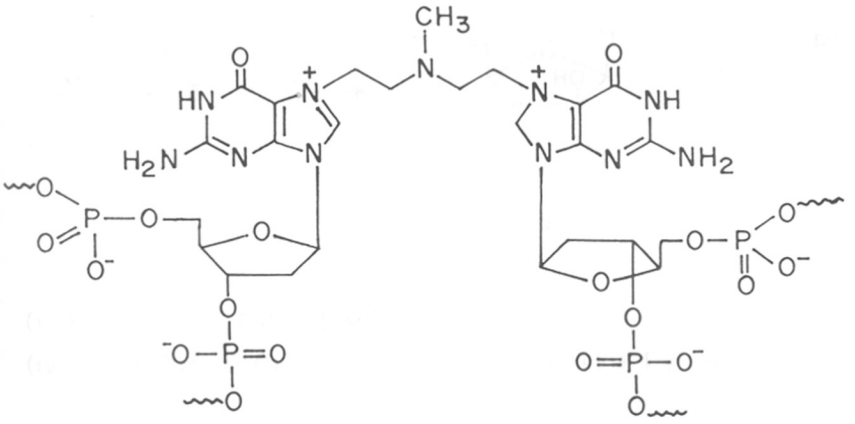
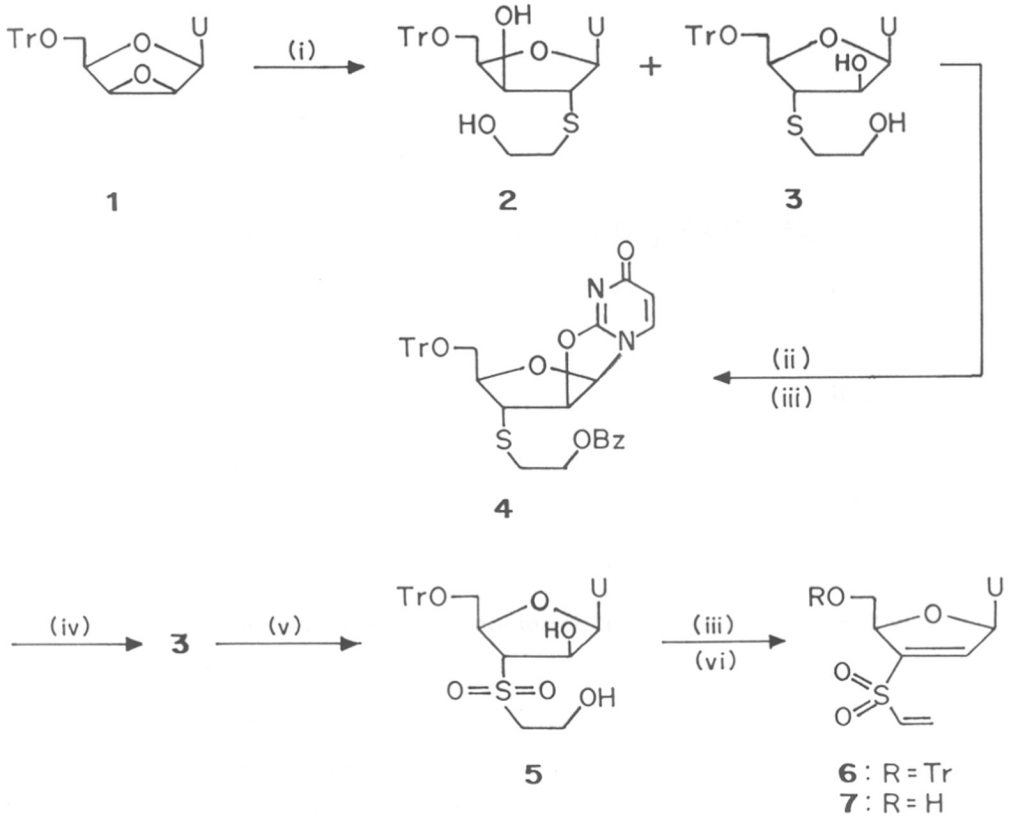


Figure - 4·4



to generate a mixture of 2'-deoxy-2'-S-(2-hydroxyethylthio)-5'-O-trityl-*xylo*uridine **2** and 3'-deoxy-3'-S-(2-hydroxyethylthio)-5'-O-trityl-*ara*uridine **3** (**Scheme-4.2**). As all efforts to separate the isomers failed, the primary hydroxyl group of the hydroxyethylthio moieties of **2** and **3** were benzoylated selectively at 0°C. After work-up, 2'(3')-hydroxyl groups of the crude benzoylated products were mesylated at 0°C. The resulting mesylated products were heated at 100°C in pyridine; intramolecular 2',3'-epithiiranium ion formation followed by the attack of C-2 oxygen at the C-2' center resulted in the formation of 2,2'-O-anhydro-3'-deoxy-3'-S-(mercaptoethylbenzoate)-5'-O-trityluridine **4** in 50% overall yield in four steps. Compound **4** was debenzoylated and the 2,2'-O-anhydro bridge was hydrolysed by aqueous NaOH

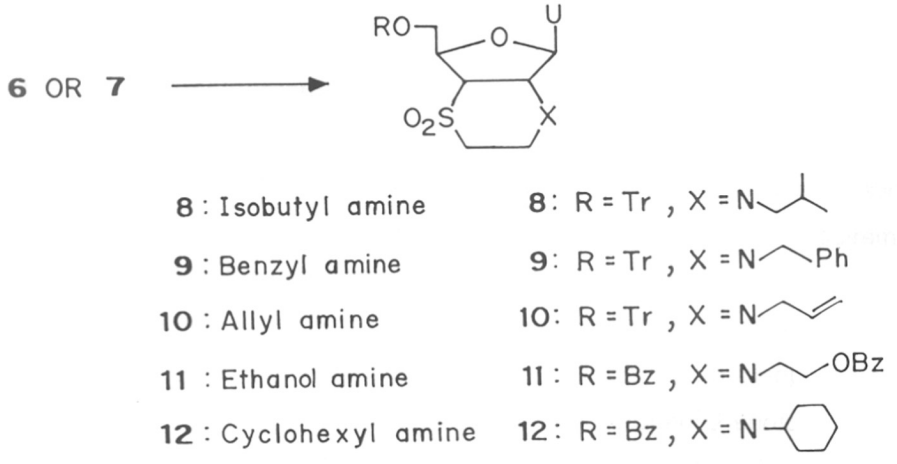
Scheme-4·2



(i) HS⌒OH , TMG , DMF, 70°C **(ii) (a) Bzcl, Py, 0°C, (b) Mscl, Py, 0°C, (iii) Py, 100°C**
(iv) IN NaOH , EtOH (v) MMPP, MeOH (vi) Py , 40°C

treatment to produce **3** in 96% yield. Oxidation of **3** produced 3'-deoxy-3'-S-(2-hydroxyethylsulphonyl)-5'-O-trityl-*ara*uridine **5** in 86% yield. Both the hydroxyl groups of **5** were mesylated and the crude product obtained after work-up was heated at 40°C in pyridine; elimination of the mesyl groups produced the desired *bis*vinylsulphonyl uridine **6** in 86% yield (**Scheme-4.2**). Detritylation of compound **6** with 80% aqueous acetic acid did produce compound **7**; however, it was contaminated with unidentified and inseparable impurities. Therefore, after removing tritanol by triturating the detritylating mixture of **7** with ether, crude **7** was treated directly with nucleophiles. The products were isolated as the corresponding benzoylated derivatives (**Scheme-4.3**).

Scheme - 4.3



Reactions of compounds 6 and 7 with nucleophiles: Compounds **6** or **7** were reacted with six primary amines in methanol. All amines except allylamine were slow to react (around 2 days at room temperature) but all produced bicyclic derivatives **8-12** in high yields in stereoselective fashion (**Scheme-4.3**). Interestingly, selection of solvent was important for these reactions. For example, when **6** was reacted with *iso*butylamine in *chloroform*, no cyclised product was obtained. One equivalent of morpholine reacted selectively with the exocyclic vinylsulphone functionality of **6** to produce **13** in 92% yield (**Scheme-4.4**). Compound **7** similarly reacted with *p*-anisidine to produce a single product. Attempted cyclisation of this compound at elevated temperature was unsuccessful. Therefore, the product was isolated as its dibenzoyl derivative **14**. Dimethyl malonate in presence of sodium hydride reacted with **6** to produce **15** in 86% yield (**Scheme-4.4**). All the reactions presented in **Scheme 4.4** demonstrated that the exocyclic vinylsulphone group of **6** or **7** was more reactive than the endocyclic one.

To demonstrate the usefulness of a compound like **13** in the generation of a vast number and wide variety of potential reverse transcriptase inhibitors[6-14], **13** was reacted with isobutylamine in chloroform. The reaction was slow but only one product **16** was obtained in 72% yield. The same reaction when performed in methanol, produced a mixture of **16** and

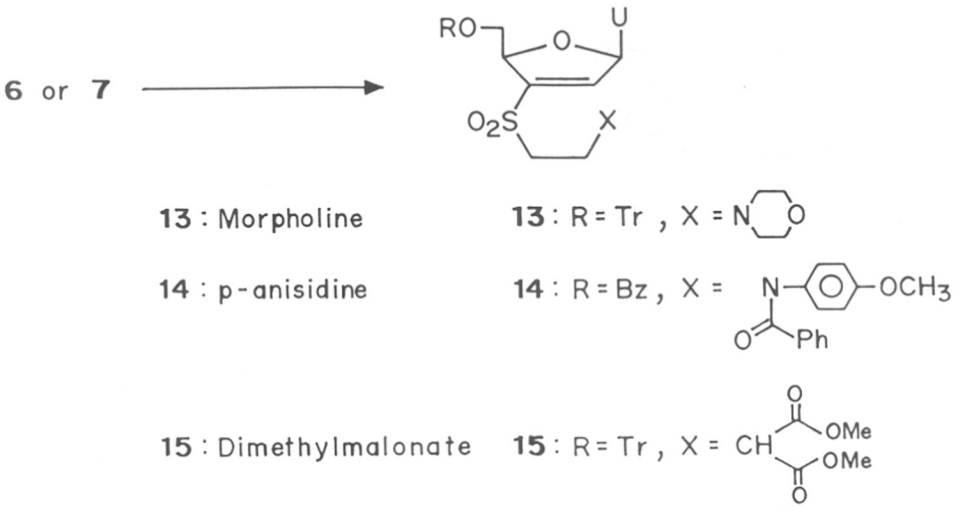
17 in a ratio 4:1 (**Scheme 4.5**). Compound **15** on treatment with excess sodium hydride in dioxane produced an inseparable mixture of cyclised products **18*cis*** and **18*trans*** (**Scheme 4.5**).

4.3 Structural Assignment:

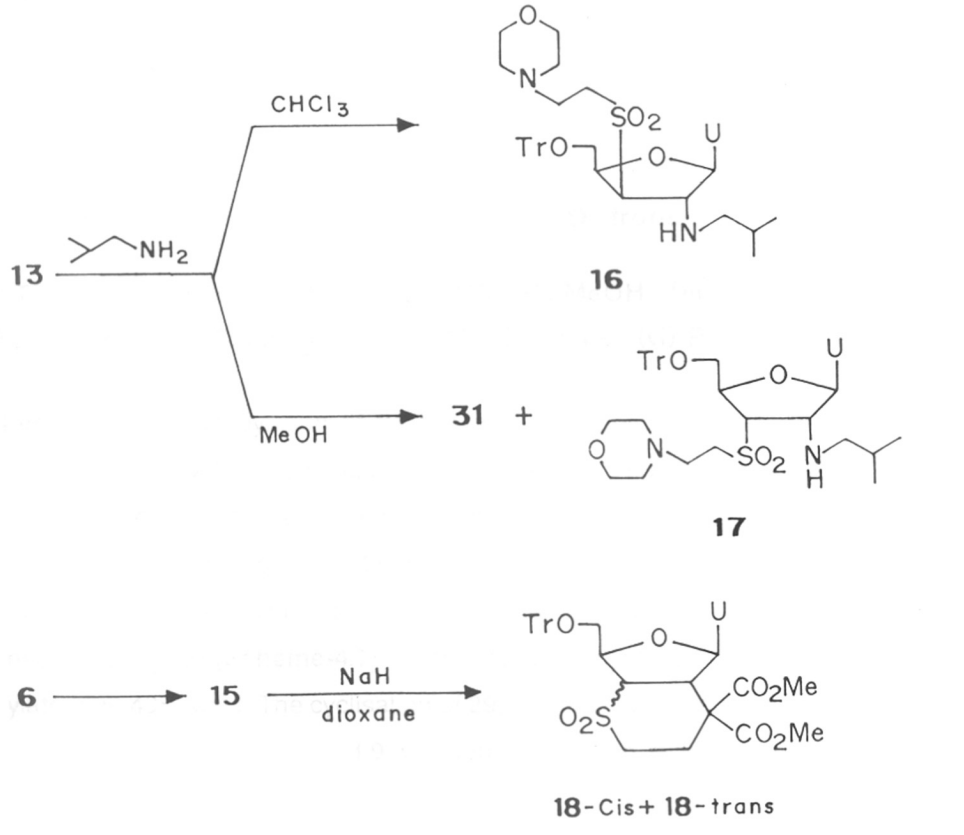
In order to establish the structures of **8-12** unambiguously, we decided to synthesise some of these compounds through different routes. The most important requirement of such a synthesis would be the regio- and stereospecific construction of C-2'-N- and C-3'-S- bonds. We assumed that in case of any of the compounds **8-12**, the C-2'-N- bond was α to the plane of the furan ring because it was demonstrated earlier[23] that nucleophiles attacked C-2' of 1-(5-O-trityl-2,3-dideoxy-3-toluenesulphonyl-β-D-glyceropent-2-enofuranosyl)uracil (and adenosine) exclusively from the α-side due to the presence of a bulky heterocycle at the C-1' position in β configuration. It was also known that intermolecular Michael type addition of thiophenol to 1-*p*-tolylsulphonyl cyclopentene[24] or benzylamine to nucleosides containing endocyclic vinylsulphone functionalities exclusively produced the *trans* product due to steric strain. Compound **21**, with only one vinylsulphone group available for reaction was, therefore, selected as the key starting material for producing C-2'-N- α and C-3'-S- β linkages. Synthesis of **21** began with the selective protection of the primary hydroxyl group of **3** with TBDMS to produce **19** in 93% yield. Compound **19** was oxidised to **20**. Compound **21** was obtained by mesylating **20** and heating the reaction mixture at 40°C. On reaction with benzylamine in dichloromethane, **21** generated **22** exclusively in 79% yield. Deprotection of **22** produced **23**. All attempts to cyclise **23** failed (**Scheme 4.6**). However, **23** was needed for cross-checking the structure of **29** (See later).

With the failure of the cyclisation reaction of **23**, we turned our attention to the synthesis of **29**. We expected that by having both C-2'-N- and C-3'-S- bonds in α configuration, cyclisation of **29** would be easier than that of **23**. For the synthesis of **29** we started with the anhydro derivative **4** as it was having the desired configurations at both the C-2' and C-3' positions. C-3'-S linkage was already α due to the opening of 2',3'-O-anhydro *lyxo*uridine **1** by mercaptoethanol from the α face. 2,2'-O-Anhydro linkage, on the other hand, would allow a nucleophile, such as azide to attack the C-2' position exclusively from the α side. Compound **24** was thus obtained by the azidolysis of **4** at elevated temperature in 70% yield

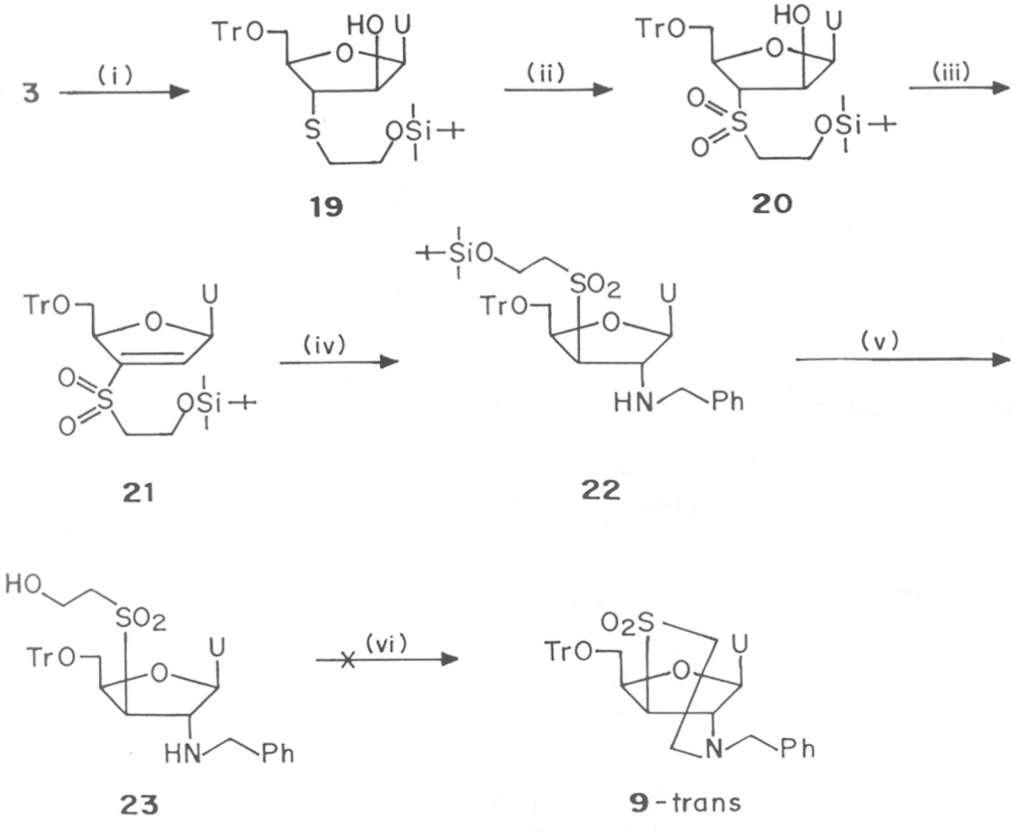
Scheme-4·4



Scheme-4·5



Scheme - 4·6

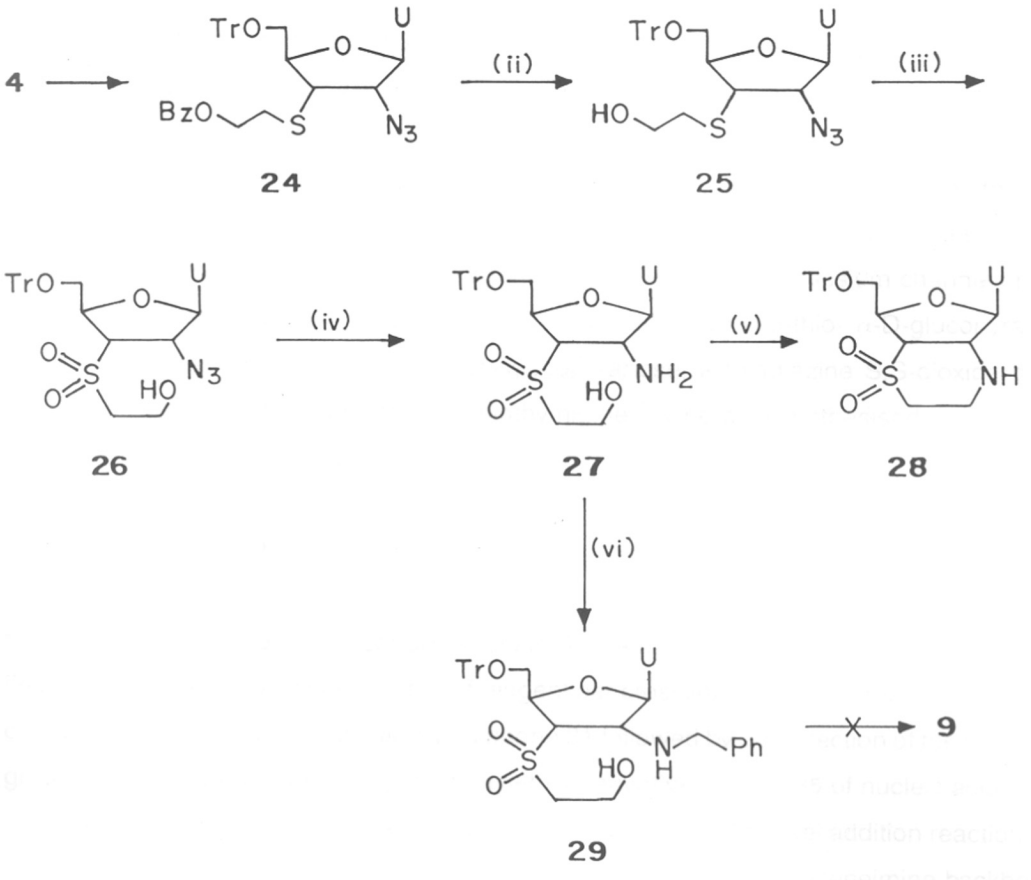


(i) TBDMS, Tmidazole, DHF (ii) MMPP, MeOH (iii) MsCl, Py, 0°C
(iv) Benzylamine, CH_2Cl_2 (v) TBAF, Dioxane (vi) Ph_3P, DIAD

(**Scheme-4.7**). Debenzoylation of **24** produced **25**. Compound **25** was oxidised to the sulphone derivative **26** in high yield. The presence of azido group in **24**, **25** and **26** was confirmed by the appearance of sharp peaks at 2130, 2140 and 2125 cm^{-1} respectively in the IR spectra. The azido group of **26** was reduced and the crude amino derivative **27** was cyclised under Mitsonubo conditions[25]. The required S, S-dioxide thiazine derivative **28** was obtained in 80% yield (**Scheme-4.7**). In an attempt to synthesise **9** (or its isomer), **27** was benzylated[26] in 40% yield. The cyclisation of **29**, like the cyclisation of its isomer **23** was also unsuccessful. However, compound **9** was debenzylated in 75% yield by reacting it with 4%

formic acid and Pd/C in refluxing methanol[27]. The debenzylated product of **9** was identical to the thiazine derivative **28**. Furthermore, **28** on treatment with allyl bromide in presence of silver oxide was allylated to produce previously synthesised allyl derivative **10** (**Scheme-4.8**).

Scheme - 4·7



(i) LiN_3, DMF, 140°C (ii) IN NaOH, EtOH (iii) MMPP, MeOH
(iv) H_2, Pd/C (v) Ph_3P, DIAD, CH_2Cl_2 (vi) PhCHO, $NaBH_4$

Scheme - 4·8

(i) 4% HCOOH, MeOH, reflux (ii) Allyl bromide, Ag_2O, DMF

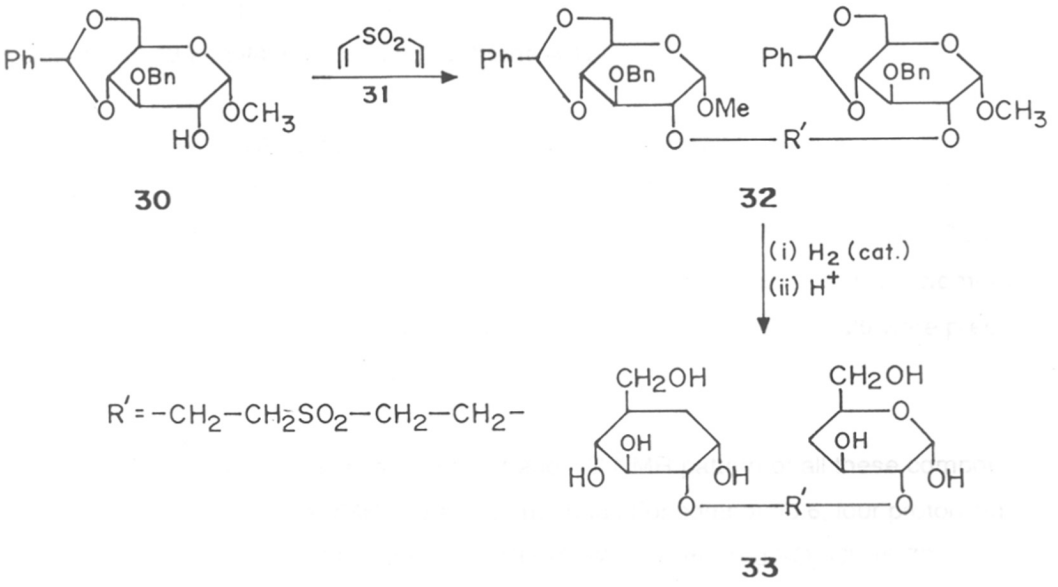
These experiments proved unambiguously that the bicyclic derivatives **8-12** were *cis*-fused.

4.4 Discussion:

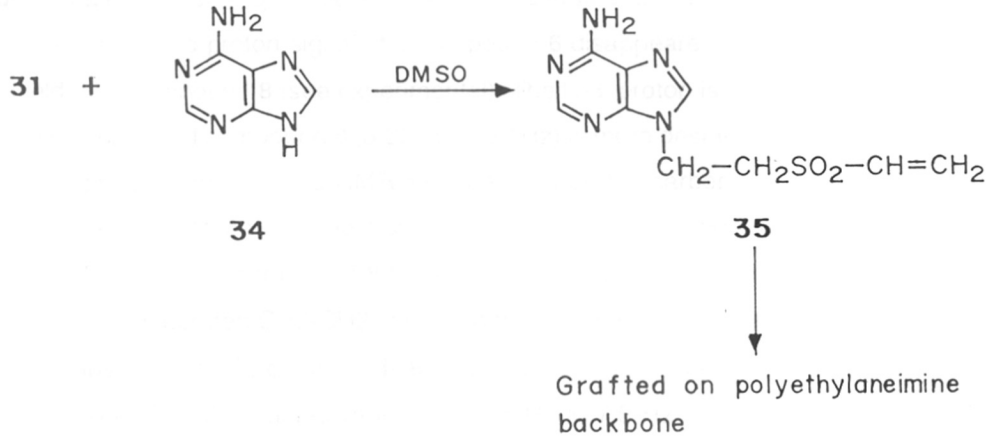
Sulphones have been employed in varieties of synthetic methodologies for the preparation of vast array of compounds[28]. Although, in most of the synthetic strategies, the sulphone functionality is disposed off at the end of the synthesis, there are several reports on the synthesis of useful heterocycles containing sulphone functionality as part of the ring where the sulphone functionality was retained at the end of the synthesis. For example, several modified β-lactams[29,30], antiflogists and photosensitizers[31], electron transport materials in xerography[32], several derivatives of known pesticide oxycarboxine[33], analogues[34] of diazoxide, a well known antihypertensive agent and ATP-sensitive potassium channel opener were synthesised. Moreover, 1-O-acetyl-2,3,4,6-tetra-O-methyl-5-thio- α-D-glucopyranose S,S,-dioxide[35], an analogue of 1-O-acetylglucopyranose, a thiadiazine S,S-dioxide diacyclonucleoside[36] and the sulphone of 4'-thiothymidine[37] were also synthesised to study their biological or biophysical properties.

One of the strategies for the synthesis of sulphone containing heterocycles would be to use *bis*vinylsulphone or its derivatives as starting materials. *Bis*vinylsulphone had been used in the past as crosslinkers[38] for cotton cellulose Authentic, simple crosslinked derivatives of D-glucose **33** having only one residue of reagent per crosslink were prepared by the reaction of protected D-glucose **30** with *bis*vinylsulphone **31** followed by deprotection of the protecting groups of **32** (**Scheme-4.9**). Vinylsulphonylethyl derivatives (VSE) **35** of nucleic acid bases adenine , thymine, cytosine have been prepared *via* a simple Michael addition reaction with divinyl sulphone **31**. The VSE derivatives were grafted on a polyethyleneimine backbone[39] (**Scheme-4.10**). Although there are few other reports on the use of *bis*vinylsulphone in various other areas[40-45], it has only recently been used for the synthesis of 2,3,5,6-tetrahydro-4H-1,4-thiazine-1,1-dioxides **37** by the reaction of **31** with primary amines[46,47] (**Eqn.-1, Scheme-4.11**). Reactions of **31** with secondary amines give disubstituted products **38** (**Eqn.-2, Scheme-4.11**). Similarly, reaction of *bis*-(hydroxymethyl) phenyl phosphine **40** with distyryl sulphone **39** proceeds stereoselectively to give only one of the two possible stereoisomers of 3,4,5-triphenyl-1,4-thiaphosphorinane 1,1-dioxides **41a-b**[48] (**Eqn.-3, Scheme-4.11**). Synthesis of 1,4-dithiane 1,1,4,4-tetroxide and seven membered cyclic

Scheme-4·9



Scheme-4·10



peroxides[49] have also been reported from *bis*vinylsulphone. However, *bis*vinylsulphone was used more extensively as the source of electron deficient double bonds in cycloaddition reactions to generate various cyclic compounds[50-55]. Tandem cycloaddition reactions between

simple sugar aldoximes **12** and *bis*vinylsulphone **31** have been shown to occur regiospecifically and with high diastereoselectivity in the cycloaddition step to afford homochiral cycloadducts **43** and **44** in good yield (**Scheme-4.12**).

In this chapter we have described the synthesis of *bis*vinylsulphones **6** and **7** and their reactivities with various nucleophiles. Treatment of **6** or **7** with primary amines afforded the 2',3'-(4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxide) derivatives of uridine **8-12** (**Scheme-4.3**). The same kind of cyclic derivative **28** was prepared from some other route (**Scheme-4.7**). 2',3'-Disubstituted *xylo*-derivatives **16** and **23** and *ribo*-derivative **17** and **29** were prepared either from compound **6** or following different method.

There are appreciable differences in both ^{1}H and ^{13}C NMR pattern of all these compounds. So it is worth discussing the NMR of these compounds.For compound **6**, four proton signals of H-1' (7.15 ppm, m) , H-2' (6.80 ppm, bs), $=CH_2$ (6.52-6.23, m) and SO_2-CH (5.78, d, 9.2Hz) are appearing at downfield region, whereas H-5 proton is upfield (4.65 ppm, 8.1Hz). As expected, the H-3' proton signal is absent. In the ^{13}C spectra also, there are four signals at 141.2 ppm (C-2'), 146.1 (C-3'), 131.4 ($=CH_2$) and 136.8 (=CH) corresponding to the unsaturated carbons. But in case of the cyclic compounds (for example compound **8**) all the above mentioned proton signals for compound **6** disappeared and these protons are more shielded in compound **8** (see experimental). The H-3' proton is also appearing at 3.81 ppm. The H-5 proton of compound **8** (5.22 ppm, 8.1Hz) is more deshielded than that of compound **6**. Like proton signals, in ^{13}C-NMR also the unsaturated carbon signals of compound **6** are disappearing and those are more shielded in case of compound **8** (see experimental). In the ^{13}C-NMR spectra of compound **8** there are two extra CH_2 signals which also supports the presence of saturated CH2-CH2 linkage in the structure of compound **8.** The H-1' signals of all N-substituted cyclic compounds **8-12** are appearing in the region 6.13 ppm to 6.37 ppm as doublets. The $J_{1',2'}$ values varies from 3.1 Hz to 7.5 Hz. Whereas, for the unsubstituted cyclic derivative **28**, the H-1' proton signal is appearing more upfield (5.66ppm) than other cyclic compounds as a singlet. These coupling constant values clearly indicates that N-substitution influences the conformation of the furanose ring. As reported in the literature[23], owing to the *xylo*-orientation of the sulphonyl groups, H-5 proton of *trans*- products **16** and **23** were more downfield (5.68ppm for **16** and 5.63 ppm for **23**) than the corresponding *cis*-compounds **17** and **29** (5.28 ppm for **17** and 5.38 ppm for **29**). In the *cis*-products (*ribo*), H-1'

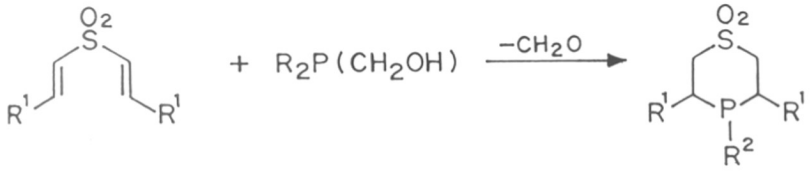
Scheme-4·11

31 + H_2N-R → **37** Eqn.1

36

R = alkyl groups

31 + Secondary amines → **38** Eqn.2

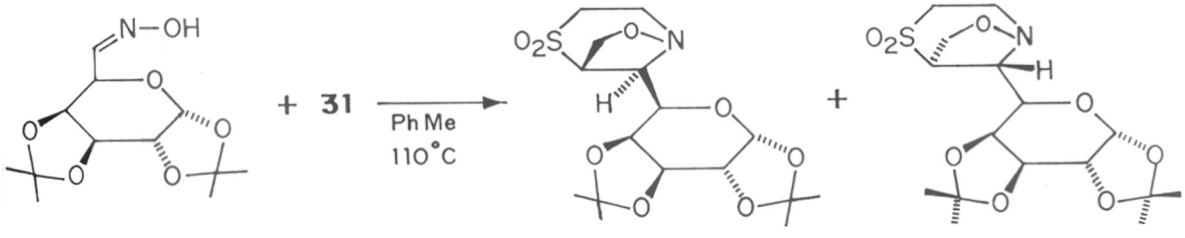


39 + $R_2P(CH_2OH)$ $\xrightarrow{-CH_2O}$ **41a-b** Eqn.3

40

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

Scheme-4·12



42 + **31** $\xrightarrow[110°C]{PhMe}$ **43** + **44**

are always more deshielded (6.12 ppm for **17** and 6.14 ppm for **29**) than the corresponding *trans*-products (5.82 ppm for **16** and 5.97 ppm for **23**). The $J_{1',2'}$ of the *trans*-products (4.5 Hz for **16** and 4.3 Hz for **23**) were smaller than the corresponding coupling constants in the *cis*-products (6.8 Hz for **17** and 6.5 Hz for **29**). The H-1' and H-5 signals of cyclic derivatives **8-12** are also comparable to those of non cyclic *ribo*- derivatives **17** and **29**.

4.5 Conclusion:

We have reported the synthesis of a highly reactive modified nucleoside **6** (and **7**). We have demonstrated that **6** or **7** has the potential to generate varieties of modified nucleosides including a new class of bicyclic thiazine S,S,-dioxide derivatives **8-12**. To the best of our knowledge this group of bicylic thiazine derivatives are the first of its kind in literature.

4.6 Experimental:

Melting points were uncorrected. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merck 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, 60-100 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 or solvent chloroform-d as internal standards. ^{13}C-NMR (75 MHz) spectra were also recorded on Bruker MSL300 NMR spectrometer. All mass spectrometric experiments were carried out on a VG Analytical 70-250-SE normal geometry double focussing mass spectrometer. Accurate mass measurements were carried out at 10 000 resolution using mixtures of polyethylene glycols as mass caliberants.

Synthesis of 1-[5-O-trityl-2,2-O-anhydro-3-deoxy-3-S-(2-O-benzoyl ethyl)-β-D-*arabino*furanosyl] uracil 4:

In a solution of marcaptoethanol (3.9 gm., 50 mmol) in DMF (25 ml), tetramethyl guanidine (2.3 g, 20 mmol) was added and the mixture was heated at 70°c for 10 min. To this mixture, epoxide **1** (4.68 g, 10 mmol) was added and the reaction mixture was heated at 70°C for 2h. It was then cooled to room temperature and poured into saturated sodium bicarbonate solution with vigorous stirring. The mixture was filtered and the residue was washed with water and dissolved in ethyl acetate. The ethylacetate part was kept over anhydrous sodiumsulphate and filtered. The filtrate was evaporated to dryness and the solid residue was purified over silica gel. This mixture of isomers **2** and **3** (8.5 mmol) was taken in 40 ml pyridine and benzoyl chloride (1.4g, 9.5 mmol) in 20 ml pyridine was added dropwise at 0°C for a period of 1h. After consumption of the starting material (TLC) the reaction mixture was poured into saturated sodium bicarbonate solution with stirring. The residue was filtered, washed with water and dissolved in ethylacetate. The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness. The crude monobenzoylated product was dissolved in pyridine (40 ml) and mesylchloride (2.86g,25 mmol) in pyridine (10ml) was added dropwise at 0°C. After the addition the reaction mixture was kept at 4°C overnight. The reaction mixture was then poured into saturated sodium bicarbonate solution. The residue

was filtered, washed with water, dried and dissolved in ethylacetate. The ethylacetate part was dried over sodiumsulphate and filtered. The filtrate was evaporated to dryness. The solid residue was then dissolved in anhydrous pyridine(75ml) and heated at 100°C for 26h. The reaction mixture was cooled to room temperature and poured into saturated sodium bicarbonate solution. It was filtered and the residue was washed with water, dried and dissolved in ethylacetate. The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness. The brown residue was purified over silica gel column to give compound **4**.

Yield: 50% from epoxide).

mp: 74-76°C.

^{1}H NMR($CDCl_3$):δ 8.02 (m, 2H) and 7.61-7.19 (m, 19H) aromatic and H-6; 6.15 (d, 5.8Hz, 1H) H-1'; 5.98 (d, 7.6Hz, 1H) H-5; 5.31 (m, 1H) H-2'; 4.50 (t, 2H) CH_2-OBz; 4.26 (q, 1H) H-4'; 3.71 (m, 1H) H-3'; 3.11 (d, 5.6Hz, 2H) H-5', H-5"; 3.02 (m, 2H) -S-CH_2.

^{13}C NMR ($CDCl_3$):δ 171.6, C-4; 166.2, ester CO; 159.2, C-2; 143.2, trityl; 134.8, C-6; 133.3, 129.7, 128.6, 128.4, 128.1, 127.4, aromatic; 110.3, C-5; 90.5, C-1'; 88.9, C-2'; 87.1, trityl; 86.2, C-4'; 63.3, C-5' and -CH_2-OBz; 49.4, C-3'; 31.0, -S-CH_2.

MS (FAB$^+$): M^+ calc. for $C_{37}H_{32}N_2O_6S$: 632.1981, found 632.1946.

Synthesis of 1-[5-O-trityl-3-deoxy-3-S-(2-hydroxy ethyl)-β-D-*arabino*furanosyl] uracil 3:

To a solution of compound **4** (3.16g, 5mmol) in ethanol (40ml) and water (10ml), 1(N) sodium hydroxide (15ml) was added. The reaction mixture was stirred at room temperature for 2h. And then neutralised with 1(N) hydrochloric acid under cold condition. The residue, thus obtained was filtered, washed with water, dried and dissolved in ethylacetate. The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the white residue was purified over silica gel column to give compound **3**.

Yield: 96%

mp: 99-100°C

^{1}H NMR($CDCl_3$):δ 8.18 (d, 8.2Hz, 1H) H-6; 7.46-7.25 (m, 15H) trityl; 6.15 (d, 5.9Hz, 1H) H-1'; 5.33 (d, 8.1Hz, 1H) H-5; 4.55 (t, 1H) H-2'; 3.84-3.39 (m, 7H) H-3', H-4', H-5' H-5" and CH^2-OH; 2.77 (m, 2H) -S-CH_2.

^{13}C NMR($CDCl_3$):δ 164.6, C-4; 151.6, C-2; 143.4, trityl; 142.1, C-6; 129.0, 128.2, 127.6, trityl; 101.8, C-5; 87.7, trityl; 85.0, C-1'; 81.5, C-4'; 78.2, C-2'; 62.1/61.6, C-5'/-CH_2-OH; 47.7, C-3'; 34.8, -S-CH_2.

MS (FAB$^+$): M^+ calc. for $C_{30}H_{30}N_2O_6S$: 546.1825, found 546.1778.

Synthesis of 1-[5-O-trityl-3-deoxy-3-S-(2-hydroxy ethyl sulphonyl)-β-D-*arabino*furanosyl] uracil 5:

To a solution of compound **3** (1.63g, 3mmol) in methanol (30ml) ,magnesium monoperoxyphthalate (4.5g, 9mmol) was added and the reaction mixture was stirred at room temperature for 4-5h. The white residue was filtered off and washed with methanol. The filtrate was evaporated to dryness under reduced pressure. The residue was triturated with saturated sodium bicarbonate solution and filtered. The residue was washed with sodium bicarbonate followed by water and dried. The solid mass was dissolved in ethylacetate, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the white residue was purified over silica gel column to give compound **5**.

Yield: 86%

mp: 154-155°C

^{1}H NMR($CDCl_3$+DMSO-d_6):δ 7.58 (d, 8.1Hz, 1H) H-6; 7.27-7.03 (m, 15H) trityl; 5.91 (d, 5.4Hz, 1H) H-1'; 5.74 (d, 1H, -OH); 5.03 (d, 8.1Hz, 1H) H-5; 4.63 (m, 2H) H-4', -OH; 4.30 (m, 1H) H-2'; 4.06 (m, 1H) H-3'; 3.84 (m, 2H) -CH_2OH; 3.45-2.94 (m, 4H) H5', H-5", -SO_2-CH_2.

^{13}C NMR($CDCl_3$+DMSO-d_6):δ 162.5, C-4; 149.4, C-2; 142.3, trityl; 140.7, C-6; 127.4, 126.7, 126.0, trityl; 99.3, C-5; 85.7, trityl; 84.1, C-1'; 73.2, C-4'; 70.1/66.8, C-2'/C-3'; 62.8, C-4'; 54.2, $-CH_2$-OH; 54.1, $-SO_2-CH_2$.

MS (FAB^+): M^+ calc. for $C_{30}H_{30}N_2O_8S$: 578.1723, found 578.1672.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-3-S-(vinylsulphonyl) -β-D-glyceropent-2-enofuranosyl] uracil 6:

Compound **5** (1.15g, 2mmol) was dissolved in pyridine (20ml) and mesylchloride (1.4g, 12mmol) in 5ml pyridine was added dropwise at 0°C. After the addition the reaction mixture was kept at +4°C overnight. It was then poured into saturated sodium bicarbonate solution (50ml) and extracted with dichloromethane (3x20ml). The dichloromethane part was evaporated to dryness under reduced pressure and the residue was coevaporated with toluene. The brown coloured residue was partitioned between ethylacetate (80ml) and water (70ml). The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous pyridine (30ml) and heated at 40°C for 1.5h. The solution was poured into saturated sodium bicarbonate solution (100ml) and extracted with dichloromethane (3x25ml). The dichloromethane part was evaporated and the residual pyridine was coevaporated with toluene under reduced pressure. The residue was purified over silica gel to give compound **6**.

Yield: 86%

mp:195-198°C

^{1}H NMR($CDCl_3$):δ 9.10 (bs, 1H) NH; 7.90 (d, 8.0Hz, 1H) H-6; 7.68-7.24 (m, 15H) trityl; 7.15 (m, 1H) H-1'; 6.80 (bs, 1H) H-2'; 6.52-6.23 (m, 2H) $=CH_2$; 5.78 (d, 9.2Hz, 1H) $-SO_2$-CH; 5.16 (m, 1H) H-4'; 4.65 (d, 8.1Hz, 1H) H-5; 3.83 (m, 1H), 3.66 (m, 1H) H-5', H-5".

^{13}C NMR($CDCl_3$+DMSO-d_6):δ 163.4, C-4; 150.8, C-2; 146.1, C-3'; 142.9, trityl; 141.2, C-2'; 138.5, C-6; 136.8, $-SO_2$-CH; 131.4, $=CH_2$; 129.1, 128.1, 127.6, trityl; 102.3, C-5; 88.1/87.7,

C-1'/trityl; 83.7, C-4'; 63.3, C-5'.

MS (FAB$^+$): M$^+$ calc. for $C_{30}H_{26}N_2O_6S$: 542.1512, found 542.1467.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-(isobutyl)-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxides-β-D-*ribo*furanosyl] uracil 8:

A mixture of compound **6** (0.271g, 0.5mmol) and isobutylamine (0.037g, 0.5mmol) in methanol (20ml) was stirred at room temperature for three days. Methanol was removed under reduced pressure. The residue was purified over silica gel column to give compound **8.**

Yield: 83%

M.P: 134-138°C

^{1}H NMR($CDCl_3$):δ 7.86 (d, 8.2Hz, 1H) H-6; 7.37-7.27 (m, 15H) trityl; 6.31 (d, 6.1Hz, 1H) H-1'; 5.22 (d, 8.1Hz, 1H) H-5; 4.80 (m, 1H) H-4'; 3.81 (t, 1H) H-3'; 3.64 (m, 4H) H-5', H-5", -SO2-CH_2-; 3.10 (m, 3H) -N-CH_2-, H-2'; 2.73 (m, 1H), 2.28 (m, 1H) isobutyl-CH_2-; 1.65 (m, 1H) isobutyl-CH; 0.87 (2xs, 6H) 2x-CH_3

^{13}C NMR($CDCl_3$):δ 163.6, C-4; 150.6, C-2; 142.9, trityl; 139.6, C-6; 128.7, 128.3, 127.8, trityl; 102.6, C-5; 88.4, trityl; 83.3, C-1'; 75.4, C-4'; 69.2, C-3'; 64.3, C-5'; 62.5, -SO_2-CH_2-; 58.5, C-2'; 47.7, 47.2, -CH_2-N-CH_2-; 27.3, isobutyl-CH; 20.3, 20.2, 2x-CH_3.

MS (FAB$^+$): (M+H)$^+$ calc. for $C_{34}H_{37}N_3O_6S$: 616.2481, found 616.2432.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-(benzyl)-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxides-β-D-*ribo*furanosyl] uracil 9:

A mixture of compound **6** (0.271g, 0.5mmol) and benzylamine (0.054g, 0.5mmol) in methanol (20ml) was stirred at room temperature for 40h. Methanol was removed under reduced pressure and the residue was purified over basic alumina column to give compound **9**.

Yield: 83%

mp: 143-144°C

^{1}H NMR($CDCl_3$):δ 9.21 (bs, 1H) NH; 7.81 (d, 8.2Hz, 1H) H-6; 7.43-7.22 (m, 20H) aromatic, 6.31 (d, 4.5Hz, 1H) H-1'; 5.13 (d, 8.2Hz, 1H) H-5; 4.82 (m, 1H) H-4'; 4.30 (d, 14.4Hz, 1H) one of benzyl -CH_2-; 3.79-3.52 (m, 6H) H-3', H-5', H-5", -SO_2-CH_2- and one of benzyl -CH_2; 3.20-3.09 (m, 3H) H-2', -N-CH_2-.

^{13}C NMR($CDCl_3$):δ 163.7, C-4; 150.6, C-2; 142.9, trityl; 139.5, C-6; 137.6, 128.9, 128.8, 128.3, 128.2, 127.9, 127.7, aromatic; 102.6, C-5; 88.3, trityl; 84.4, C-1'; 76.4,C-4'; 68.7, C-3'; 63.5, C-5'; 58.4, -SO_2-CH_2- and C-2'; 47.7, -CH_2-N-CH_2-.

MS (FAB$^+$): M^+ calc. for $C_{37}H_{35}N_3O_6S$: 649.2247, found 649.2189.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-(allyl)-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxides-β-D-*ribo*furanosyl] uracil 10:

A mixture of compound **6** (0.271g, 0.5mmol) and allylamine (0.029g, 0.5mmol) in methanol (10ml) was stirred at room temperature for 22h. Methanol was removed under reduced pressure and the residue was purified over basic alumina column to give compound **10**.

Yield: 73%

mp: 135-137°C

^{1}H NMR($CDCl_3$):δ 9.23 (bs, 1H) NH; 7.94(d, 8.2Hz, 1H) H-6; 7.43-7.27 (m, 15H) trityl; 6.27 (d, 4.8Hz, 1H) H-1'; 5.76 (m, 1H) =CH; 5.21 (m, 3H) =CH_2, H-5; 4.76 (m, 1H) H-4'; 3.85-3.49 (m, 6H) H-2', H-3', H-5', H-5", -SO_2-CH_2- and 3.13 (m, 4H) -CH_2-N-CH_2-.

^{13}C NMR($CDCl_3$):δ 163.7, C-4; 150.5, C-2; 142.9, trityl; 139.9, C-6; 134.2, =CH; 128.8, 128.3, 127.7, trityl; 118.8, =CH_2; 102.6, C-5; 88.3, trityl; 83.9, C-1'; 76.1, C-4'; 68.2, C-3'; 63.6, C-5'; 58.8, C-2'; 57.3, -SO_2-CH_2-; 47.9, 47.3, -CH_2-N-CH_2-.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{33}H_{33}N_3O_6S$: 599.2090, found 599.2081.

Synthesis of 1-[5-O-benzoyl-2,3-dideoxy-2-N-(2-O-benzoyl ethyl)-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxides-β-D-*ribo*furanosyl] uracil 11:

A solution of compound **6** (0.4g, 0.73mmol) in 80% aqueous acetic acid (50ml) was heated at 75°C for 45 mins. Acetic acid was evaporated under reduced pressure and was co-evaporated with ethanol.The residue was triturated with ether. The detritylated product was taken in methanol (15ml) and ethanolamine (0.044g, 0.73mmol) was added. The suspension was stirred at room temperature for 42h. Methanol was removed under reduced pressure. The residue was dissolved in anhydrous pyridine (15ml) and benzoyl chloride (0.75g, 5mmol) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 2h. The pyridine solution was then poured into saturated sodium bicarbonate solution (60ml) and extracted with chloroform (3x20ml). The chloroform part was evaporated to dryness and the residue was coevaporated with toluene. The product was purified over silica gel column to give **11**.

Yield: 56% (for three steps)

mp: 109-111°C

^{1}H NMR($CDCl_3$):δ 8.05 (m, 4H) and 7.68-7.35 (m, 7H) H-6 and aromatic; 6.13 (d, 3.1Hz, 1H) H-1'; 5.40 (dd, 8.2Hz, 1H); 4.85-4.53 (m, 4H); 4.29 (m, 1H); 3.84 (m, 1H) H-2'; 3.63 (m, 3H) H-3'; 3.20 (m, 3H); 2.80 (m, 1H).

^{13}C NMR($CDCl_3$):δ 166.5, C-4, 165.8, ester carbonyl; 163.5, ester carbonyl; 150.5, C-2; 139.0, C-6; 133.8, 133.3, 129.7, 129.6, 129.4, 129.1, 128.7, 128.5, aromatic; 102.7, C-5; 86.1, C-1'; 75.6, C-4'; 68.4, C-3'; 64.0, C-5'; 61.8, CH_2-OBz; 58.6, C-2'; 52.5, SO_2-CH_2; 48.2, CH_2-N-CH_2.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{27}H_{27}N_3O_8S$: 570.1546, found 570.1577.

Synthesis of 1-[5-O-benzoyl-2,3-dideoxy-2-N-(cyclohexyl)-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxides-β-D-*ribo*furanosyl] uracil 12:

A solution of compound **6** (0.3g, 0.55mmol) in 80% aqueous acetic acid (50ml) was heated at 75°C for 45 mins. Acetic acid was evaporated under reduced pressure and was co-evaporated with ethanol.The residue was triturated with ether. The detritylated product was taken in methanol (15ml) and cyclohexylamine (0.055g, 0.55mmol) was added. The suspension was stirred at room temperature for 3 days. Methanol was removed under reduced pressure. The residue was dissolved in pyridine (10ml) and benzoyl chloride (0.42g, 3mmol) in pyridine (10ml) was added dropwise at 0°C. After the addition the reaction mixture was stirred at 0°C for 2h. The pyridine solution was then poured into saturated sodium bicarbonate solution (50ml), stirred for 15m and extracted with chloroform (3x20ml). The combined organic part was evaporated to dryness under reduced pressure and coevaporated with toluene. The crude product was purified over silica gel column to afford compound **12**.

Yield: 58%

mp: 125-127°C

^{1}H NMR($CDCl_3$):δ 8.86 (bs, 1H) NH; 8.05-7.47 (m, 6H) H-6, aromatic; 6.37 (d, 7.5Hz, 1H) H-1'; 5.60 (d, 8.1Hz, 1H) H-5; 5.11 (m, 1H) H-4'; 4.77 (m, 2H) -CH_2-OBz; 3.79 (m, 2H) H-2', H-3'; 3.47 (m, 2H) -SO_2-CH_2; 3.03 (m, 2H) N-CH_2; 2.63 (m, 1H) N-CH; 1.64 (m), 1.05(m) cyclohexyl.

^{13}C NMR($CDCl_3$):δ 165.9, ester carbonyl; 163.5, C-4; 150.5, C-2; 138.9, C-6; 133.9, 129.5, 129.1, 128.8, aromatic; 102.9, C-5; 82.5, C-1'; 73.0, C-4'; 65.8, C-5'; 64.2/62.4, C-2'/C-3'; 58.9, N-CH; 48.3, -SO2-CH_2; 44.7, N-CH_2; 32.8, 31.4, 25.6, 25.4, cyclohexyl.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{24}H_{29}N_3O_7S$: 504.1804, found 504.1796.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-3-S-(2-N-morpholino ethyl sulphonyl) -β-D-glyceropent-2-enofuranosyl] uracil 13:

A mixture of compound **6** (0.4g, 0.74mmol) and morpholine (0.065g, 0.75mmol) in dichloromethane (10ml) was stirred at room temperature for 2h. Dichloromethane was removed under reduced pressure and the residue was purified over silica gel column to give compound **13**.

Yield: 92%

mp: 107-110°C

^{1}H NMR($CDCl_3$):δ 9.25 (bs, 1H) NH; 7.89 (d, 8.2Hz, 1H) H-6; 7.38-7.27 (m, 15H) trityl; 7.10 (m, 1H) H-1'; 6.80 (t, 1H) H-2'; 5.22 (m, 1H) H-4'; 4.86 (d, 8.1Hz, 1H) H-5; 3.76 (d, 2H) H-5', H-5"; 3.62 (t, 4H) $-CH_2-O-CH_2$; 3.27 (m, 2H) SO_2-CH_2; 2.81 (m, 2H) $N-CH_2$; 2.37 (t, 4H) $-CH_2-N-CH_2$.

^{13}C NMR($CDCl_3$):δ 163.4, C-4; 150.7, C-2; 147.0, C-3'; 142.7, trityl; 140.9, C-2'; 138.1, C-6; 128.9, 128.0, 127.6, trityl; 102.9, C-5; 88.2, trityl; 87.7, C-1'; 84.4, C-4'; 66.5, $-CH_2-O-CH_2$; 63.1, C-5'; 53.1, $-CH_2-N-CH_2$; 52.8, SO_2-CH_2; 50.5, $N-CH_2$.

Synthesis of 1-[5-O-benzoyl-2,3-dideoxy-3-S-(2-N-benzoyl-p-methoxyanilino ethyl sulphonyl) -β-D-glyceropent-2-enofuranosyl] uracil 14:

A solution of compound **6** (0.272g, 0.5mmol) in 80% aqueous acetic acid (40ml) was heated at 75°C for 45 mins. Acetic acid was evaporated under reduced pressure and was co-evaporated with ethanol. The residue was triturated with ether. The detritylated product was taken in methanol (15ml) and *p*-methoxyaniline (0.061g, 0.5mmol) was added. The suspension was stirred at room temperature for 20h, then refluxed for 10h. Methanol was removed under reduced pressure, the residue was dissolved in pyridine (10ml) and benzoyl chloride (0.35g, 2.5mmol) in 10ml pyridine was added dropwise at 0°C. After the addition, the reaction mixture was stirred at 0°C for 2h, It was then poured into saturated sodium

bicarbonate solution (50ml), stirred for 15m and extracted with chloroform (3x20ml). The combined chloroform part was evaporated to dryness under reduced pressure and coevaporated with toluene. The residue was purified over silica gel column to give compound **14**.

Yield: 61%

mp: 112-114°C

^{1}H NMR($CDCl_3$):δ 9.20 (bs, 1H) NH; 7.99 (m, 2H) and 7.60-6.70 (m, 15H) H-1', H-2', H-6, aromatic; 5.57 (m, 1H) H-4'; 5.18 (d, 8.1Hz, 1H) H-5; 4.95 (2xd, 1H), 4.65 (2xd, 1H) H-5', H-5"; 4.28 (m, 2H) N-CH_2; 3.75 (s, 3H) -O-CH_3; 3.63 (m, 2H) -SO_2-CH_2.

^{13}C NMR($CDCl_3$):δ 171.0, 165.9, 163.3, 158.6, 150.6, 144.9, 139.9, 139.1, 135.0, 134.8, 133.6, 130.2, 129.5, 128.8, 127.9, 114.8, aromatic, 103.2, C-5; 88.2, C-1'; 82.7, C-4'; 63.9, C-5'; 55.4, O-CH_3; 51.6, SO_2-CH_2; 44.7, N-CH_2.

MS (FAB$^+$): M^+ calc. for $C_{32}H_{29}N_3O_9S$: 631.1625, found 631.1600.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-3-S-(2-dimethylmalonato ethyl sulphonyl) -β-D-glyceropent-2-enofuranosyl] uracil 15:

To a solution of dimethyl malonate (0.53g, 3mmol) in dioxane (15ml) was added sodium hydride (0.06g, 2.0mmol) and the mixture was stirred at room temperature for 0.5h. A solution of compound **6** (0.405g, 0.75mmol dissolved in dioxane (10ml) was then added and stirred for 20m. The reaction mixture was then poured into saturated aqueous ammonium chloride solution (25ml) and extracted with dichloromethane (3x20ml). The combined dichloromethane extract was evaporated under reduced pressure and the crude product was purified over silica gel column to produce **15**.

Yield: 86%

mp: 93-95°C

^{1}H NMR($CDCl_3$):δ 9.22 (bs, 1H) NH; 7.90 (d, 8.0Hz, 1H) H-6; 7.33 (s, 15H) trityl; 7.15 (m, 1H) H-1'; 6.84 (s, 1H) H-2'; 5.18 (m, 1H) H-4'; 4.81 (dd, 8.1Hz, 1H) H-5; 3.75 (s, 6H) 2x-OCH_3; 3.49 (t, 1H) CH of dimethyl malonate; 3.20 (m, 2H) H-5', H-5"; 2.32 (m, 2H) -CH_2-.

^{13}C NMR($CDCl_3$):δ 168.6, ester carbonyl; 163.4, C-4; 150.6, C-2; 145.8, C-3'; 142.6, trityl; 141,0, C-6; 138.7, C-2'; 128.9, 128.0, 127.6, trityl; 102.8, C-5; 88.2, C-1'; 87.7, trityl; 84.2, C-4'; 62.9, C-5'; 52.9, 2x-OCH_3; 52.3, -SO_2-CH_2; 49.2, CH- of dimethyl malonate; 21.3, -CH_2-.

MS (FAB) : m/z (M+23) 696.9 (100).

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-isobutylamino-3-S-(2-N-morpholino ethyl sulphonyl)-β-D-*xylo*furanosyl] uracil 16:

To a solution of compound **13** (0.3g, 0.47mmol) in chloroform (15ml), isobutyl amine (0.7g, 9mmol) was added and the reaction mixture was stirred at room temperature for 4 days. Chloroform and excess amine were removed under reduced pressure and the residue was purified over basic alumina column to give the only product **16**.

Yield: 72%

mp: 99-101°C

^{1}H NMR($CDCl_3$):δ 7.66 (d, 8.2Hz, 1H) H-6; 7.49-7.23 (m, 15H) trityl; 5.82 (d, 4.5Hz, 1H) H-1'; 5.68 (d, 8.1Hz, 1H) H-5; 4.58 (q, 1H) H-4'; 3.97-3.78 (m, 3H) and 3.59, (m, 5H) H-2', H-3', H-5', H-5", CH_2-O-CH_2; 3.10 (m, 2H) SO_2-CH_2; 2.89-2.37 (m, 4H) isobutyl-N-CH_2, morpholine -N-CH_2; 2.30 (m, 4H) -CH_2-N-CH_2; 1.74 (m, 1H) -isobutyl-CH; 0.92 (d, 6H) 2x-CH_3.

^{13}C NMR($CDCl_3$):δ 163.6, C-4; 151.0, C-2; 143.2, trityl; 140.3, C-6; 128.7, 128.0, 127.4, trityl; 102.9, C-5; 88.6, C-1'; 87.9, trityl; 77.9, C-4'; 67.9, C-3'; 66.7, -CH_2-O-CH_2; 65.4, C-2'; 62.2, C-5'; 55.3, SO_2-CH_2; 53.3, CH2-N-CH2; 51.5, 2x-N-CH_2, 28.4, isobutyl-CH; 20.5, 2x-CH_3.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-isobutylamino-3-S-(2-N-morpholino ethyl sulphonyl)-β-D-*xylo*furanosyl] uracil 16 and **1-[5-O-trityl-2,3-dideoxy-2-N-isobutylamino-3-S-(2-N-morpholino ethyl sulphonyl)-β-D-*ribo*furanosyl] uracil 17:**

To a solution of compound **13** (0.315g, 0.5mmol) in methanol (10ml), isobutyl amine (0.37g, 5mmol) was added and the reaction mixture was stirred at room temperature for 2.5 days. Methanol and excess isobutyl amine were removed under reduced pressure and the crude product was purified over silica gel column to give compound **16** (0.31g, 58%) and **17** (0.08g, 15%).

Compound 17:

mp: 91-92°C.

^{1}H NMR($CDCl_3$):δ 8.52 (bs, 1H) NH; 7.74 (d, 8.1Hz, 1H) H-6; 7.38-7.27 (m, 15H) trityl; 6.12 (d, 6.8Hz, 1H) H-1'; 5.28 (d, 8.1Hz, 1H) H-5; 4.91 (m, 1H), 4.31 (m, 1H), 3.95 (m, 1H), 3.75 (m, 2H), 3.51 (m, 5H), 3.20-2.95 (m, 2H), 2.62 (m, 4H), 2.41-2.27 (m, 3H), H-2', H-3', H-4', H-5', H-5", $-CH_2-O-CH_2-$, $N-CH_2-CH_2-$, $N-CH_2$ (isobutyl), $N-CH_2$, SO_2CH_2; 1.68 (m, 1H) isobutyl-CH; 0.91 (d, 6H) 2x-CH_3.

^{13}C NMR($CDCl_3$):δ 163.4, C-4; 150.6, C-2; 143.1, trtyl; 139.9, C-6; 128.8, 128.2, 127.8, trityl; 102.9, C-5; 88.7, C-1'; 88.0, trityl; 75.4, C-4'; 66.7, $-CH_2-O-CH_2-$; 65.9, C-3'; 64.8, C-5'; 63.5, C-2'; 57.1, $-SO_2-CH_2-$; 55.5, $-CH_2-N-CH_2-$; 52.0, $-N-CH_2-$; 51.3, $N-CH_2$.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-3-S-(4H-2,3,5,6-tetrahydro- thiopyran-4,4-dimethyl dicarboxylate-1,1-dioxide)-β-D-*ribo*furanosyl] uracil 18*cis* and **1-[5-O-trityl-2,3-dideoxy-3-S-(4H-2,3,5,6-tetrahydro- thiopyran -4,4-dimethyl dicarboxylate-1,1-dioxide)-β-D-*xylo*furanosyl] uracil 18*trans*:**

To a stirred solution of compound **15** (0.22g, 0.32mmol) in dioxane (15ml), NaH (0.03g, 1mmol) was added and the reaction mixture was stirred at room temperature for 40h. This

was then worked up as described for compound **15**. Silica gel purification produced inseparable mixture of **18-*cis*** and **18-*trans*.**

Yield: 69%

Synthesis of 1-[5-O-trityl-3-deoxy-3-S-(2-O-t-butyldimethylsilyl ethyl)-β-D-*arabino*furanosyl] uracil 19:

To a solution of compound **3** (1g, 1.8mmol) and imidazole (4mmol) in dimethylformamide (10ml), t-butyldimethylsilylchloride (2.5mmol) was added and the reaction mixture was stirred at room temperature for 8h. The solution was then poured into ice cold water and filtered. The residue was dissolved in ethylacetate, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness and the white residue was purified over silica gel column to give compound **19**.

Yield: 93%

mp: 77-79°C

^{1}H NMR($CDCl_3$):δ 9.50 (bs, 1H) NH; 8.11 (d, 8.2Hz, 1H) H-6; 7.46-7.27 (m, 15H) trityl; 6.16 (d, 5.2Hz, 1H) H-1'; 5.34 (d, 8.1Hz, 1H) H-5; 4.72 (d, 1H) -OH; 4.55 (m, 1H) H-2'; 3.83 (m, 3H) H-4', -O-CH_2; 3.50 (m, 3H) H-3', H-5', H-5"; 2.79 (m, 2H) SCH_2-; 0.88 (s, 9H) t-butyl; 0.06 (s, 6H) 2x-CH_3.

^{13}C NMR($CDCl_3$):δ 164.8, C-4; 151.4, C-2; 143.5, trityl; 142.4, C-6; 128.9, 128.2, 127.5, trityl; 101.4, C-5; 87.5, trityl; 85.6, C-1'; 81.7, C-4'; 78.1, C-2'; 63.3, C-5'; 62.4, -CH_2-0Si; 48.3, C-3'; 34.2, -CH_2-S; 26.1, t-butyl-CH_3; 18.5, 3°C of t-butyl; -5.0, 2xSi-CH_3.

MS (FAB^+): M^+ calc. for $C_{36}H_{44}N_2O_6SSi$: 660.2690, found 660.2648.

Synthesis of 1-[5-O-trityl-3-deoxy-3-S-(2-O-t-butyldimethylsilyl ethyl sulphonyl)-β-D-*arabino*furanosyl] uracil 20:

To a solution of compound **19** (0.9g, 1.36mmol) in methanol (25ml), magnesium monoperoxyphthalate (2.5g, 5.5mmol) was added and the reaction mixture was stirred at room temperature for 5h. The white precipitate was filtered and residue was washed with methanol (2x15ml). the filtrate was evaporated to dryness and the residue was partitioned between ethyl acetate (50ml) and saturated sodium bicarbonate solution (50ml). The ethylacetate part was washed with saturated sodium bicarbonate solution (1x25ml), followed by water (2x25ml). The organic layer was then dried over anhydrous sodium sulphate and filtered. The filtrate was then evaporated to dryness and the white residue was purified over silica gel column to give compound **20**.

Yield: 90%

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{36}H_{44}N_2O_8SSi$: 693.2666, found 693.2611.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-3-S-(2-O-t-butyldimethylsilyl ethyl sulphonyl) -β-D-glyceropent-2-enofuranosyl] uracil 21:

To a solution of compound **20** (0.8g, 1.18mmol) in pyridine (10ml), mesyl chloride (0.3ml, 3.6mmol) in pyridine (5ml) was added dropwise at 0°C. After the addition the reaction mixture was kept at +4°C overnight. Water (2ml) was added to the reaction mixture and heated at 40°C for 1.5h. It was then poured into saturated sodium bicarbonate solution. The residue was filtered, washed with water and then dissolved in ethylacetate. The ethylacetate part was dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified over silica gel column to give **21**.

Yield: 86%

mp: 87-90°C

^{1}H NMR($CDCl_3$):δ 8.96 (bs, 1H) NH; 7.90 (d, 8.0Hz, 1H) H-6; 7.41-7.27 (m, 15H) trityl; 7.09 (m, 1H) H-1'; 6.78 (t, 1H) H-2'; 5.20 (m, 1H) H-4'; 4.79 (d, 8.1Hz, 1H) H-5; 4.02 (t, 2H) -CH_2-OSi; 3.75 (m, 2H) H-5', H-5"; 3.30 (m, 2H) -CH_2-SO_2; 0.92 (s, 9H) t-butyl; 0.10 (s, 6H) 2xSi-CH_3.

^{13}C NMR($CDCl_3$):δ 163.3,C-4; 150.6, C-2; 147.8, C-3'; 142.8, trityl; 140.8, C-2'; 137.3, C-6; 129.1, 128.6, 127.6, trityl; 102.9, C-5; 88.4, trityl; 87.7, C-1'; 84.4, C-4'; 63.1, C-5'; 58.4, -CH_2-OSi; 56.9, -SO_2-CH_2; 25.9, 3xt-butyl-CH_3; 18.3, 3°C of t-butyl; -5.4, 2xSi-CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{36}H_{42}N_2O_7SSi$: 675.2560, found 675.2608.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-benzylamino-3-S-(2-O-t-butyldimethylsilyl ethyl sulphonyl)-β-D-*xylo*furanosyl] uracil 22:

Compound **21** (0.52g, 0.77mmol) was treated with benzylamine (1.3g, 12mmol) in dichloromethane (20ml) for 3 days. Dichloromethane was removed under reduced pressure and the gummy residue was triturated with pet-ether. The white residue was then purified over silica gel column to give the product **22**.

Yield: 79%

mp: 92-94°C.

^{1}H NMR(CDCl3):δ 7.58 (d, 8.2Hz, 1H) H-6; 7.51-7.22 (m, 20H) aromatic; 5.94 (d, 4.4Hz, 1H) H-1'; 5.62 (d, 8.2Hz, 1H) H-5; 4.61 (m, 1H) H-4'; 3.94-3.63 (m, 9H) H-2', H-3', H-5', H-5", N-CH_2, -CH_2-OSi, NH of benzylamine; 3.02 (m, 2H) SO_2-CH_2; 0.90 (s, 9H) 3x-CH_3 of *tert*-butyl; 0.05 (2xs, 6H) 2x-CH_3.

^{13}C NMR($CDCl_3$):δ 163.5, C-4; 150.9, C-2; 143.5, trityl; 140.4, C-6; 138.8, 128.9, 128.2, 128.1, 127.6, 127.4, aromatic; 102.9, C-5; 89.1, C-1'; 87.9, trityl; 78.1, C-4'; 69.2, C-3'; 64.5, C-2'; 62.6, C-5'; 57.7, -CH_2-OSi; 56.4, -SO_2-CH_2; 51.5, benzyl-CH_2; 26.0, 3x-CH_3 of t-butyl; 18.4, 3°C carbon of t-butyl; -5.4, 2xSi-CH_3.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{43}H_{51}N_3O_7SSi$: 782.3295, found 782.3276.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-benzylamino-3-S-(2-hydroxy ethyl sulphonyl)-β-D-*xylo*furanosyl] uracil 23:

Compound **22** (0.35g, 0.44mmol) was treated with tetrabutyl ammonium fluoride (0.18g, 0.68mmol) in dioxane (10ml) for 0.5h. The reaction mixture was then poured into ice cold water (50ml) and extracted with dichloromethane (2x20ml). The combined dichloromethane part was dried over anhydrous sodium sulphate and filtered. The gummy residue was purified over silica gel column to produce **23**.

Yield: 90%

mp: 125-126°C

^{1}H NMR($CDCl_3$):δ 7.56 (d, 8.1Hz, 1H) H-6; 7.46-7.28 (m, 20H) aromatic; 5.97 (d, 4.3Hz, 1H) H-1'; 5.63 (d, 8.1Hz, 1H) H-5; 4.60 (m, 1H) H-4'; 3.97-3.64 (m, 8H) H-2', H-3', H-5', H-5", $-CH_2$-OH, CH_2-N; 3.05 (m, 2H) SO_2-CH_2.

^{13}C NMR($CDCl_3$):δ 163.8, C-4; 150.9, C-2; 143.6, aromatic; 143.3, trityl; 140.6, aromatic; 138.6, C-6; 128.7, 128.3, 128.0, 127.4, aromatic and trityl; 103.1, C-5; 88.5, C-1'; 87.8, trityl; 77.5, C-4'; 68.1/63.9, C-2'/C-3'; 62.2, C-5'; 56.2, SO2-CH_2-CH_2; 51.1, benzyl-CH_2.

MS (FAB$^+$): M^+ calc. for $C_{37}H_{37}N_3O_7SSi$: 667.2352, found 667.2341.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-azido-3-S-(2-O-benzoyl ethyl) -β-D-*ribo*furanosyl] uracil 24:

To a solution of compound **4** (2g, 3.15mmol) in DMF (30ml), lithium azide (2g, 40mmol) was added and the reaction mixture was heated at 140°C for 3h. This was cooled to room temperature and poured into saturated sodium bicarbonate solution. The white precipitate was filtered, washed with water, dried and dissolved in ethylacetate. The ethylacetate part was dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified over silica gel column to give compound **24**.

Yield: 70%

mp: 81-83°C

IR: 2130 cm^{-1}

^1H NMR($CDCl_3$):δ 9.10 (bs, 1H) NH; 8.19 (d, 8.2Hz, 1H) H-6; 7.99(m, 2H) and 7.64-7.27 (m, 18H) aromatic; 5.91 (s, 1H) H-1'; 5.25 (d, 8.2Hz, 1H) H-5; 4.44 (m, 1H) one H of $-CH_2$-OBz; 4.30 (m, 2H) one H of $-CH_2$-OBz, H-2'; 4.08 (d, 10.8Hz, 1H) H-4'; 3.86 (d, 11.4Hz, 1H) H-5' or H-5"; 3.67 (m, 1H) H-3'; 3.52 (d, 11.4Hz, 1H) H-5' or H-5"; 2.74 (m, 2H) -S-CH2.

^{13}C NMR($CDCl_3$):δ 166.2, ester carbonyl; 163.9, C-4; 150.4, C-2; 142.7, trityl; 139.5, C-6; 133.4, 129.6, 128.8, 128.5, 128.3, 127.6, aromatic; 102.1, C-5; 89.6, C-1'; 87.7, trityl; 84.2, C-4'; 69.6, C-2'; 63.9, CH_2-Bz; 59.9, C-5'; 45.7, C-3';31.0, -S-CH_2.

MS (FAB$^+$): $(M+H)^+$ calc. calc. for $C_{37}H_{33}N_5O_6S$: 676.2230, found 676.2239.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-azido-3-S-(2-hydroxy ethyl) -β-D-*ribo*furanosyl] uracil 25:

To a solution of compound **24** (1.25g, 1.84mmol) in ethanol (50ml) and water (10ml), 10ml of 1(N) sodium hydroxide was added and the reaction mixture was stirred at room temperature for 2h. This was then neutralised with 1(N) hydrochloric acid and then saturated sodium bicarbonate (20ml) and water (100ml) were added. The precipitate was then filtered washed with water and dried. The residue was dissolved in ethylacetate, dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and the residue was purified over silica gel column to give compound **25**.

Yield: 95%

mp: 87-88°C

IR: 2140 cm^{-1}

^{1}H NMR($CDCl_3$):δ 9.54 (bs, 1H) NH; 8.17 (d, 8.1Hz, 1H) H-6; 7.44-7.27 (m, 15H) trityl; 5.87 (s, 1H) H-1'; 5.28 (d, 8.1Hz, 1H) H-5; 4.49 (d, 5.1Hz, 1H) H-2'; 4.05 (d, 10Hz,7H) H-4'; 3.80 (m, 4H) H-3', H-5' or H-5", -CH_2-OH; 3.54 (d, 1H) H-5' or H-5"; 2.64 (t, 2H) -SCH_2; 2.45 (bs, 1H) -OH.

^{13}C NMR($CDCl_3$):δ 164.1, C-4; 150.7, C-2; 143.1, trityl; 140.1, C-6; 128.8, 128.1, 127.6, trityl; 101.9, C-5; 89.7, C-1'; 87.6, trityl; 83.9, C-4'; 69.5, C-2'; 62.6, CH2-OH; 60.4, C-5'; 46.0, C-3'; 35.1, -S-CH_2.

MS (FAB$^+$): $(M+H)^+$ calc. for $C_{30}H_{29}N_5O_5S$: 572.1968, found 572.1925.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-azido-3-S-(2-hydroxy ethyl sulphonyl)-β-D-*ribo*furanosyl] uracil 26:

To a solution of compound **25** (0.86g, 1.5mmol) in methanol (30ml), magnesium monoperoxy phthalate (2.8g, 5.6mmol) was added and the reaction mixture was stirred at room temperature for 5h. The white precipitate was filtered and washed with methanol (2x20ml). The combined filtrate was evaporated to dryness under reduced pressure and the residue was partitioned between ethylacetate (60ml) and saturated sodium bicarbonate (50ml). The organic part was washed with water , dried over anhydrous sodium sulphate and filtered. The filtrate was evaporated to dryness and purified over silica gel column to give **26**.

Yield: 87%

mp: 110-112°C

IR: 2125 cm^{-1}

^{1}H NMR($CDCl_3$):δ 9.95 (bs, 1H) NH; 8.05 (d, 8.3Hz, 1H) H-6; 7.50-7.20 (m, 15H) trityl; 5.94 (d, 0.8Hz, 1H) H-1'; 5.31 (d, 8.1Hz, 1H) H-5; 4.79 (m, 2H) H-2', H-4'; 4.47 (m, 1H) H-3'; 3.96 (m, 3H) H-5' or H-5", -CH_2-O-; 3.56 (d, 1H) H-5'or H-5"; 2.97 (m, 2H) -SO_2-CH_2.

^{13}C NMR($CDCl_3$) :δ 163.5, C-4; 150.2, C-2; 142.4, trityl; 139.1, C-6; 128.5, 127.8, 127.3, trityl; 102.1, C-5; 88.5, C-1'; 87.6, trityl; 65.7, C-2'; 61.6, C-5'; 61.1, C-3'; 56.9, $-CH_2-O-$; 55.6, $-SO_2-CH_2$.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-4H-2,3,5,6-tetrahydro-1,4-thiazine-1,1-dioxi des-β-D-*ribo*furanosyl] uracil 28:

Compound **26** (0.5g, 0.82mmol) was dissolved in ethylacetate (7ml) and Pd/C (10% Pd, 0.08g) was added. The reaction mixture was then shaken under hydrogen pressure of 30lbs/inch for 4h. Pd/C was filtered and the filtrate was evaporated to dryness. The crude product, **27** and triphenyl phosphine (0.24g, 0.9mmol) were dissolved in dichloromethane (20ml), and diisopropylazadicarboxylate (0.2ml, 1mmol) was added dropwise at 0°C. After the addition the reaction mixture was stirred at room temperature for 2h. The organic solvent was removed under reduced pressure and the gummy residue was purified over silica gel column to give **28** .

Yield: 69% (for two steps)

mp: 162-165°C

^1H NMR($CDCl_3$):δ 9.46 (bs, 1H) NH; 8.15 (d, 8.2Hz, 1H) H-6; 7.46-7.25 (m, 15H) trityl; 5.66 (s, 1H) H-1'; 5.11 (d, 8.1Hz, 1H) H-5; 4.75 (d, 10.2Hz, 1H) H-4'; 3.91 (m, 3H) $-SO_2-CH_2$, -NH; 3.62 (d, 10.2Hz, 1H) H-3'; 3.40-3.06 (m, 5H) H-2', H-5', H-5", $-NCH_2$.

^{13}C NMR($CDCl_3$):δ 163.7, C-4; 150.8, C-2; 142.9, trityl; 139.8, C-6; 128.7, 128.1, 127.5, trityl; 101.9, C-5; 89.3, C-1'; 88.0, trityl; 79.2, C-4'; 64.9, C-3'; 61.5, C-5'; 59.3, C-2'; 50.9, $-SO_2-CH_2$; 42.6, $-N-CH_2$.

MS (FAB^+): $(M+H)^+$ calc. for $C_{30}H_{29}N_3O_6S$: 560.1855, found 560.1830.

Synthesis of 1-[5-O-trityl-2,3-dideoxy-2-N-benzylamino-3-S-(2-hydroxy ethyl sulphonyl)-β-D-*ribo*furanosyl] uracil 29:

To a solution of **27** (0.32g, 0.55mmol) in ethanol (50ml), was added water (6ml) and acetate buffer (1.4ml), which was prepared from sodium acetate trihydrate (2.5g), glacial acetic acid (8.4ml) and water (25ml). Benzaldehyde (150mg, 1.4mmol) was added to the mixture. The reaction mixture was stirred at 0-5°C for 0.5h and then sodium borohydride (150mg, 5mmol) was added portionwise over a period of 1h. The solvent was removed under reduced pressure. To the residue was added water (25ml) and the mixture was extracted with chloroform (3x20ml). The combined organic extracts were washed with water (25ml), dried over sodium sulphate, filtered and the filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to give **29**.

Yield: 40%

mp: 77-79°C

^{1}H NMR($CDCl_3$):δ 8.86, (bs,1H) NH; 7.67 (d,8.0Hz,1H) H-6; 7.30 (m,20H) aromatic; 6.14 (d,6.5Hz,1H) H-1'; 5.30 (d,8.2Hz,1H) H-5; 4.86 (m,1H) H-4'; 4.10-3.25 (m,10H) H-2', H-3', H-5', H-5", -SO_2-CH_2-CH_2-O, benzyl-CH_2, OH, NH.

^{13}C NMR($CDCl_3$+d_6DMSO):δ 163.3, C-4; 151.0, C-2; 143.5, trityl; 140.1, phenyl; 139.6, C-6; 128.7, 128.3, 128.1, 127.5, 127.2, trityl+ phenyl; 102.3, C-5; 87.5, C-1'; 87.4, trityl; 75.7, C-4'; 64.9, C-5'; 63.1\62.9, C-2'\C-3'; 56.5, CH_2-OH; 55.5, SO_2-CH_2; 51.5, N-CH_2.

MS (FAB$^+$): M^+ calc. for $C_{37}H_{37}N_3O_7S$: 667.2352, found 667.2332.

Compound 28 from compound 9:

To a solution of compound **9** (0.42, 0.64mmol) in 4% formic acid in methanol (25ml), Pd/C (0.3g, 10% Pd) was added and the solution was heated at 80°C for 10 mins. The suspension was filtered. To the filtrate excess aqueous ammonia solution was added and was evaporated

to dryness. The residue was partitioned between ethyl acetate and water. The ethylacetate part was dried over sodium sulphate and evaporated to dryness. The solid residue was purified over silica gel to give compound **28**.

Yield: 75%

Compound 10 from Compound 28 :

To a solution of compound **28** (0.11g, 0.19mmol) and allyl bromide (0.05g, 0.41mmol) in DMF (2ml), silver oxide was added and the reaction mixture was stirred at room temperature for 1.25h. Solid matters were allowed to settle and the DMF solution was slowly decanted. The precipitate was washed with chloroform (3x5ml). The combined organic part was washed with 0.5% aqueous sodium cyanide solution (50ml) The aqueous part was washed with chloroform (2x10ml). The combined chloroform part was then washed throughly with water, dried over sodium sulphate and evaporated to dryness. The residue was purified over silica gel column to yield compound **10**.

Yield: 87%

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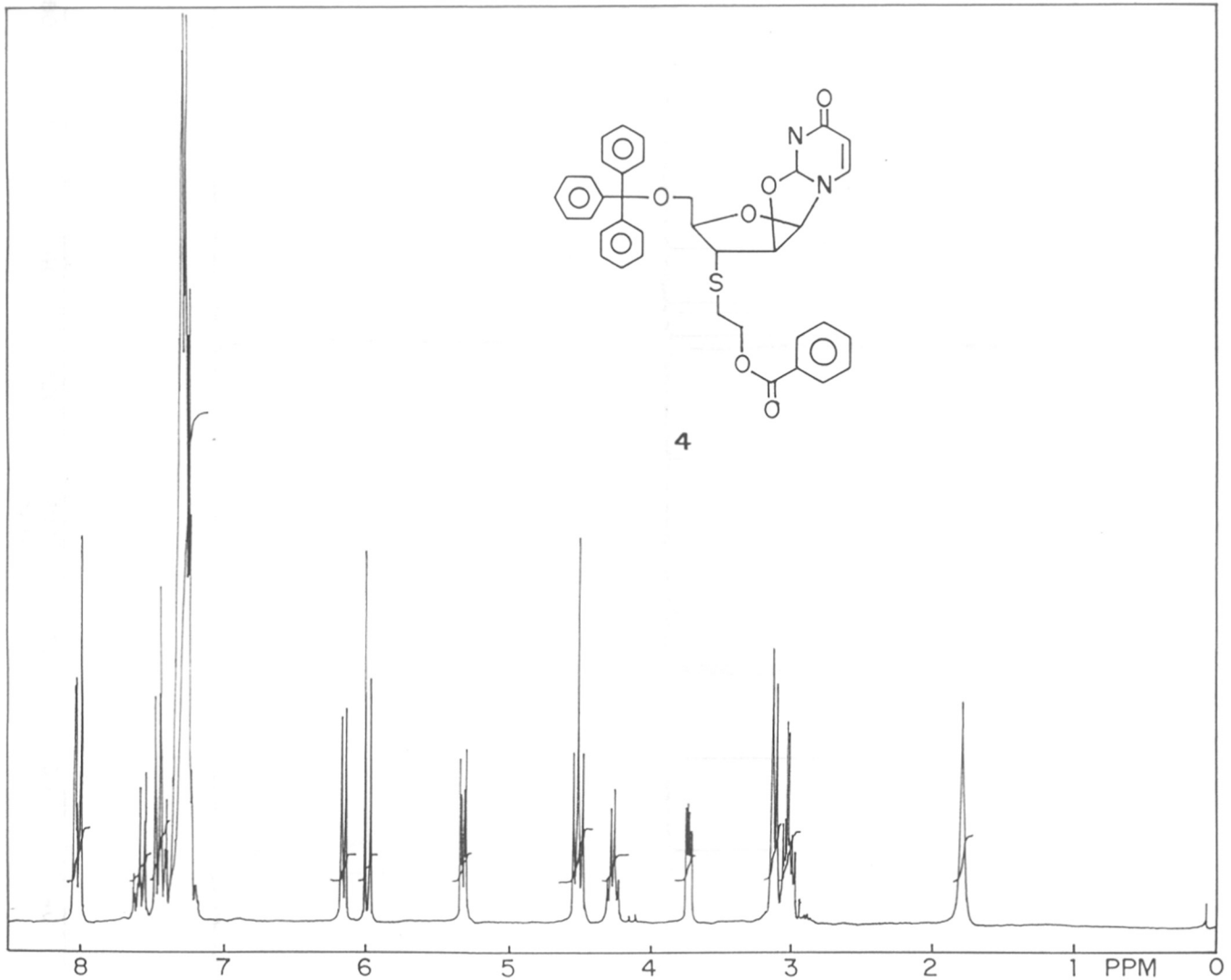

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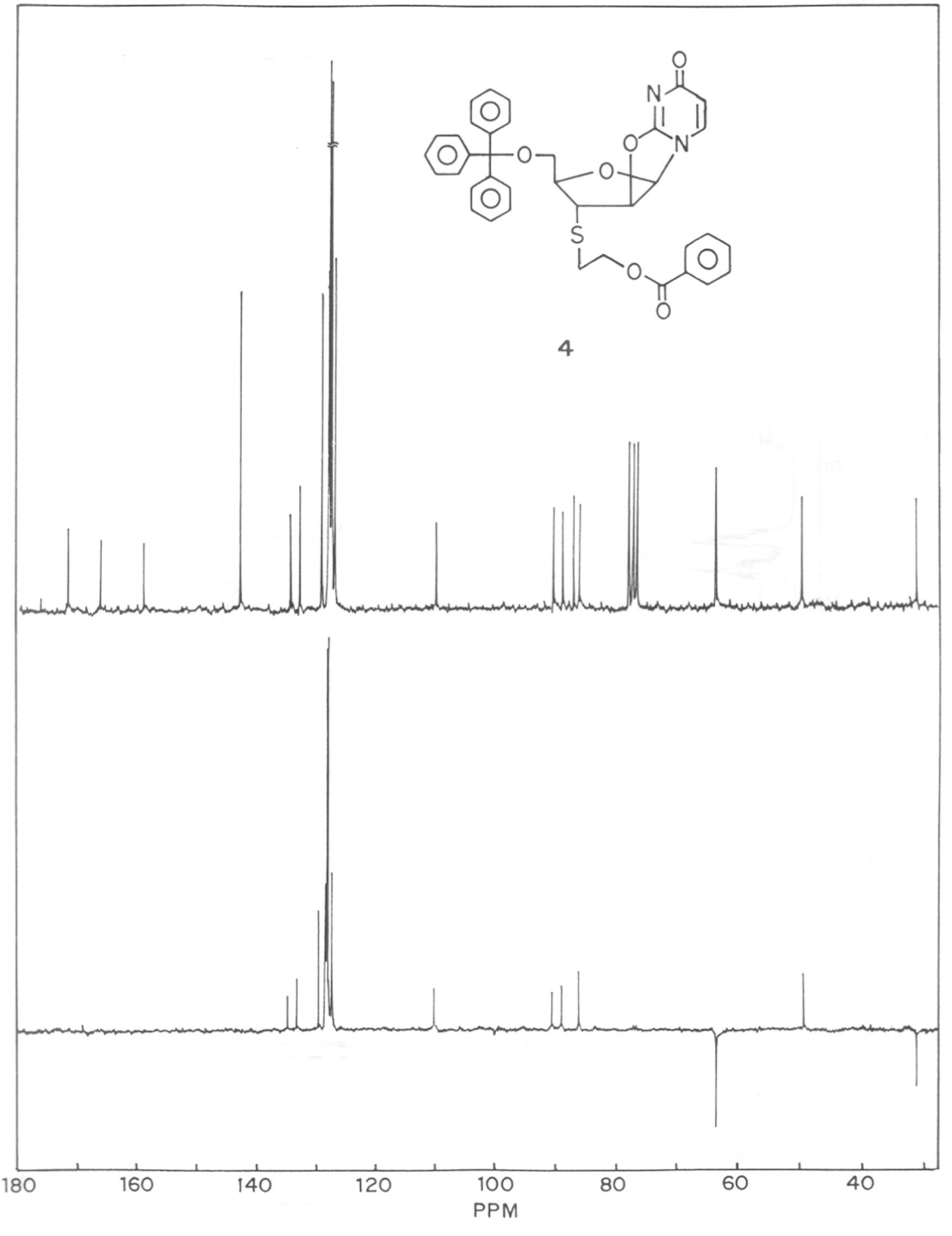

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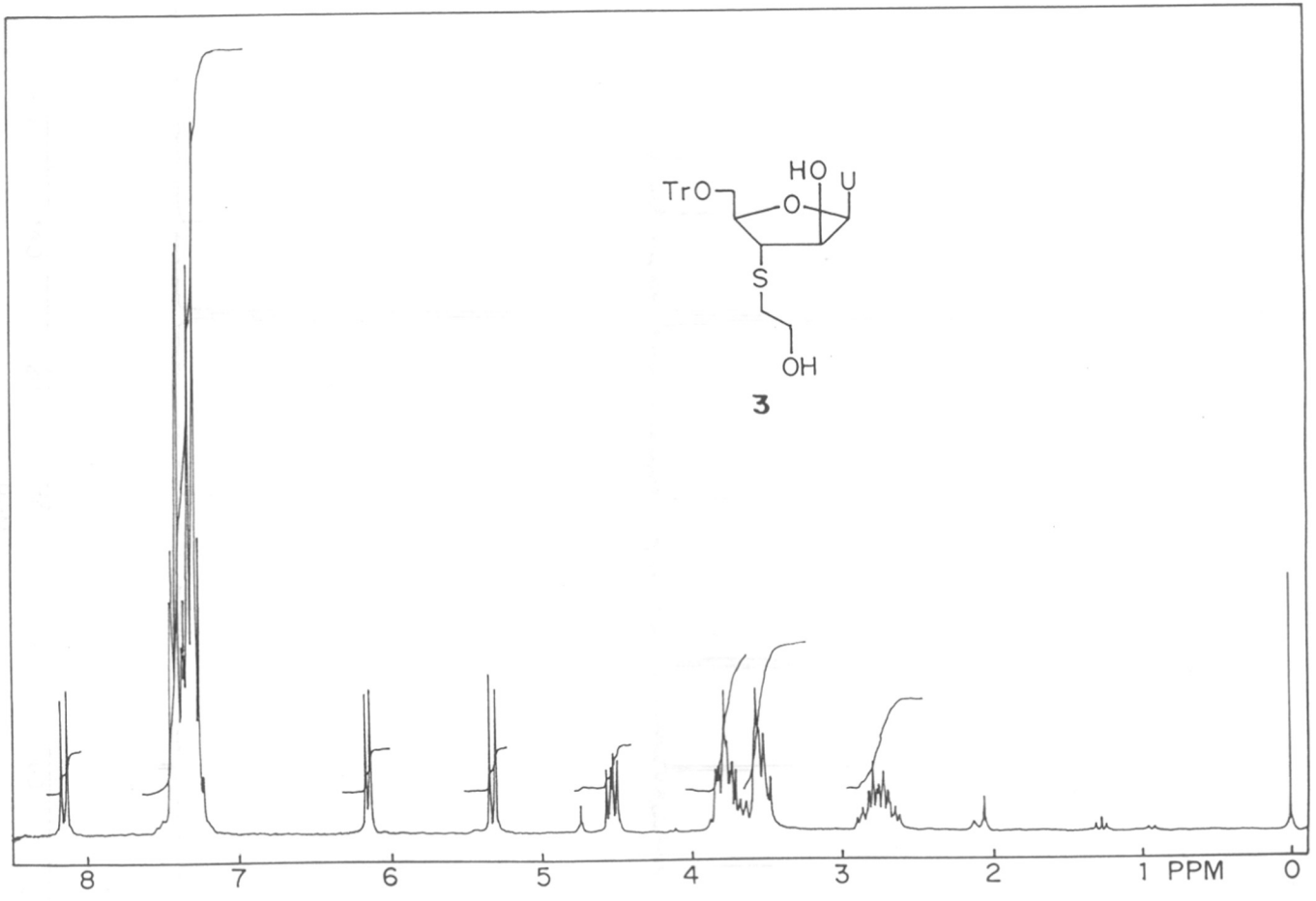
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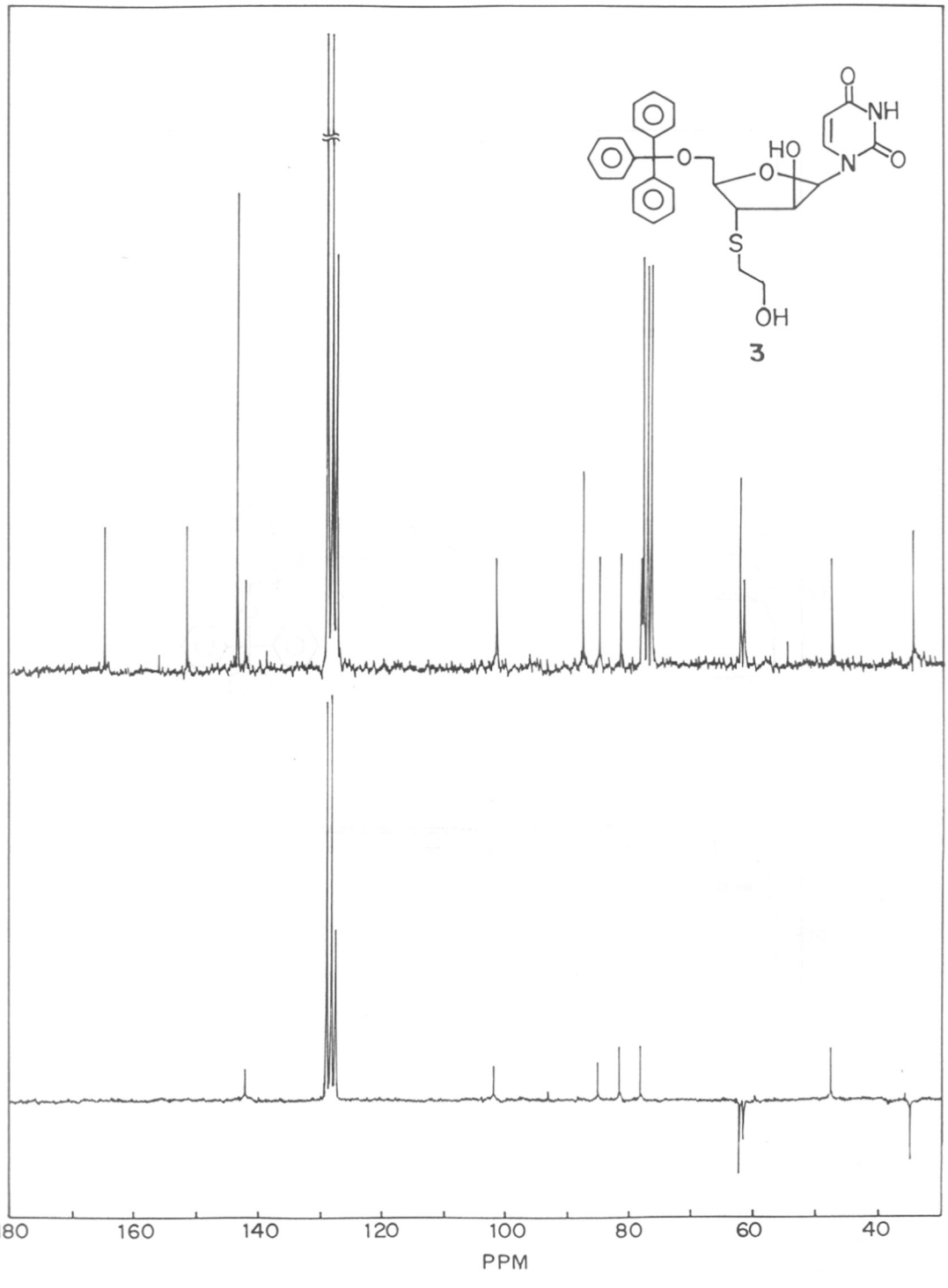
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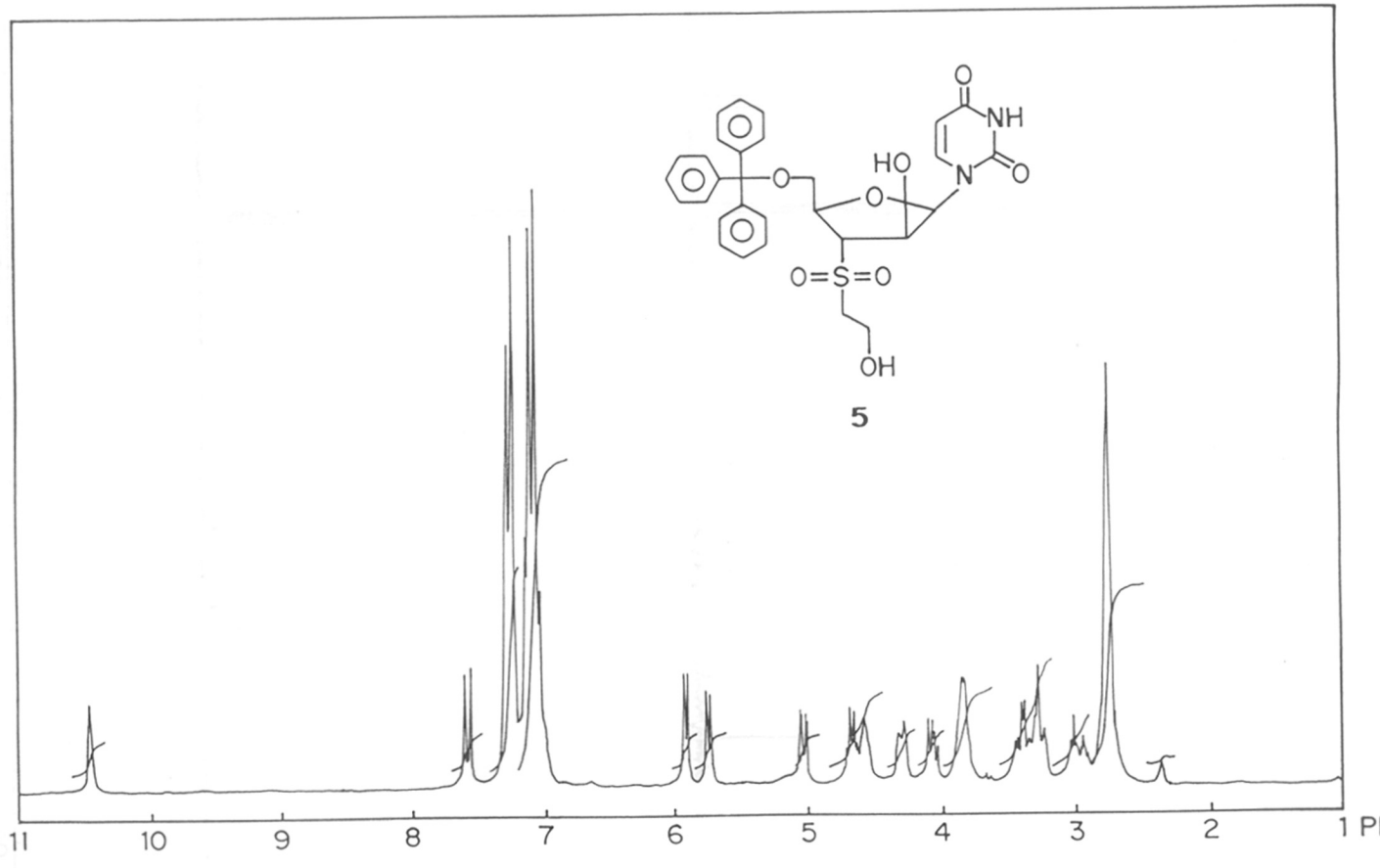

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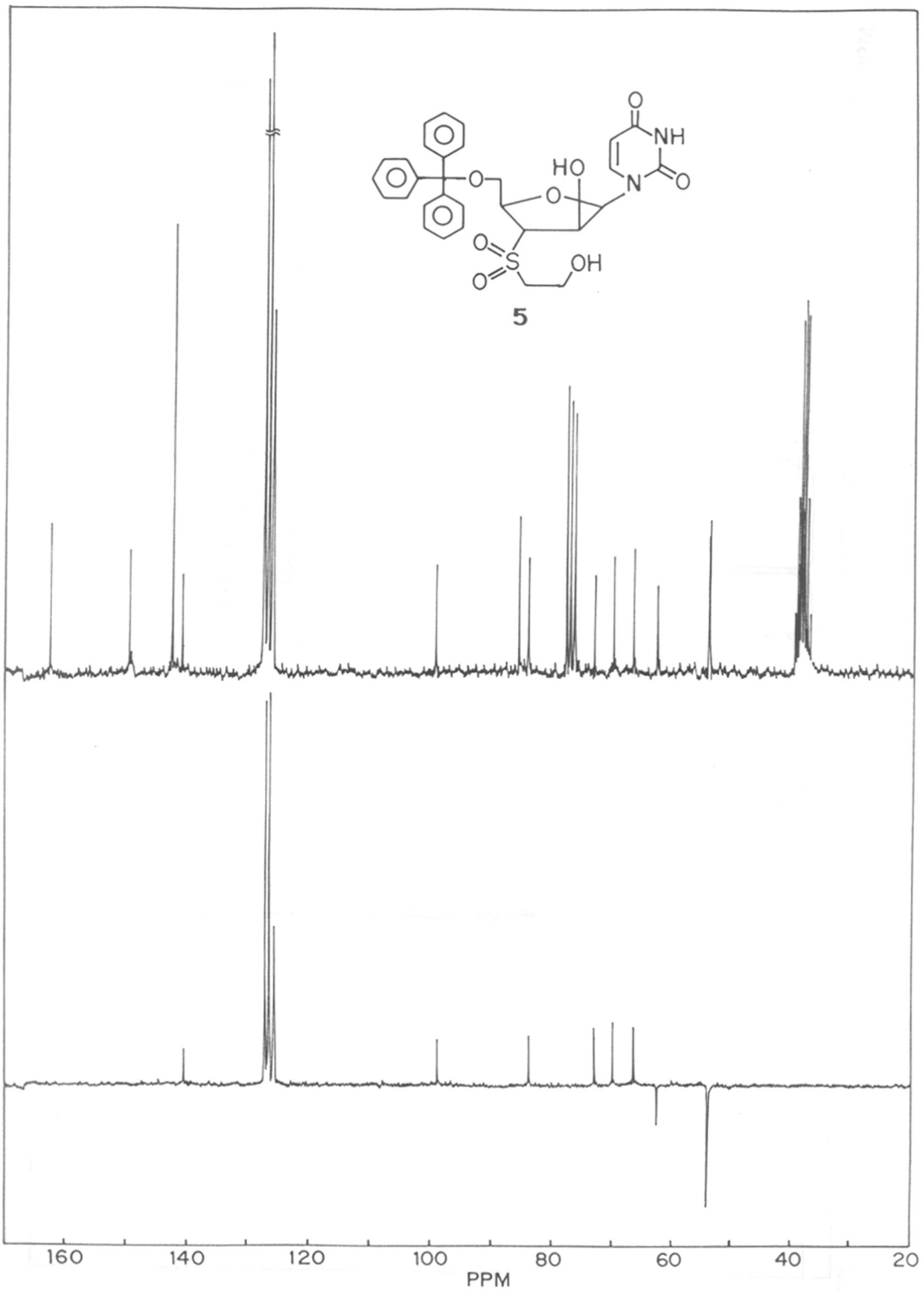

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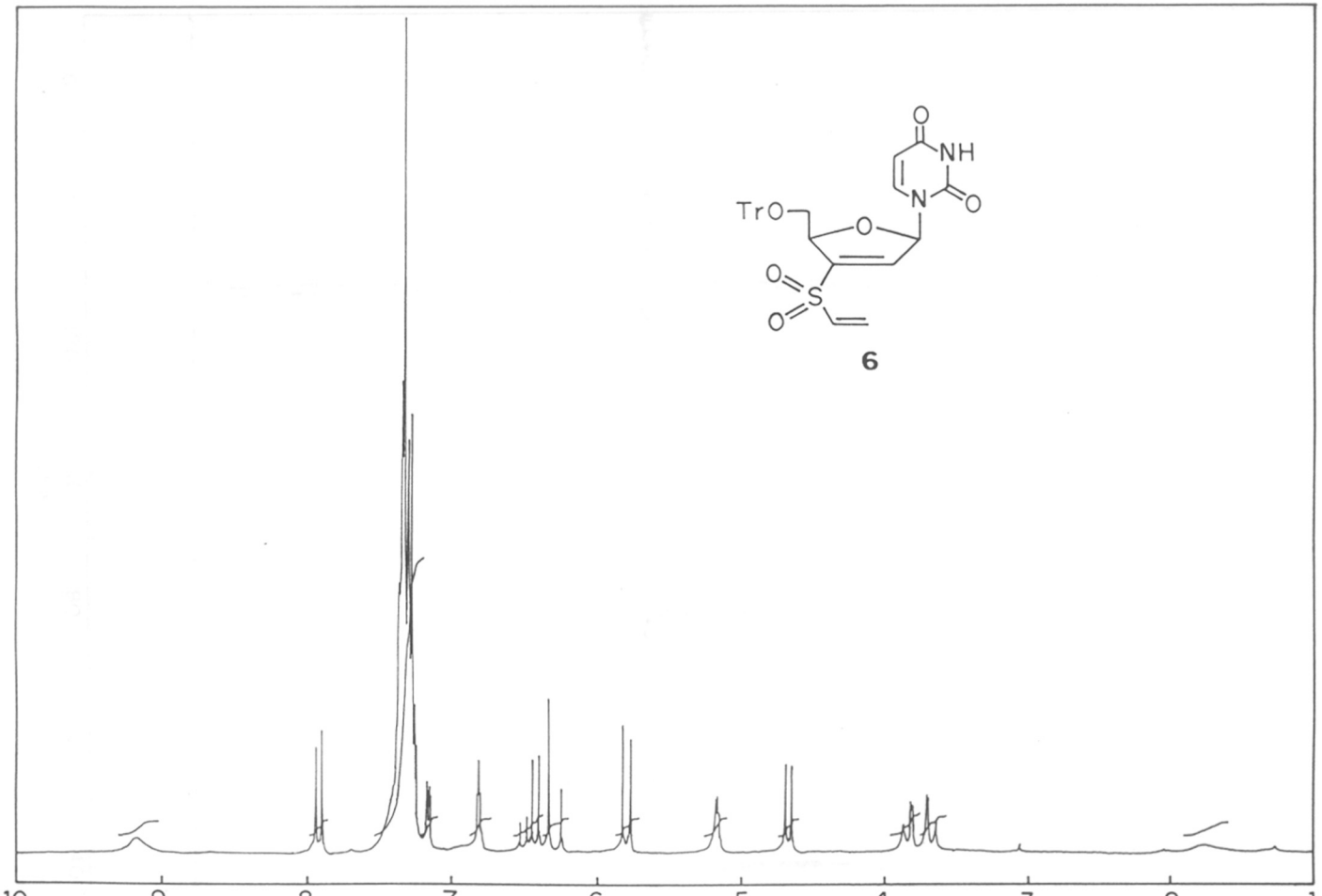

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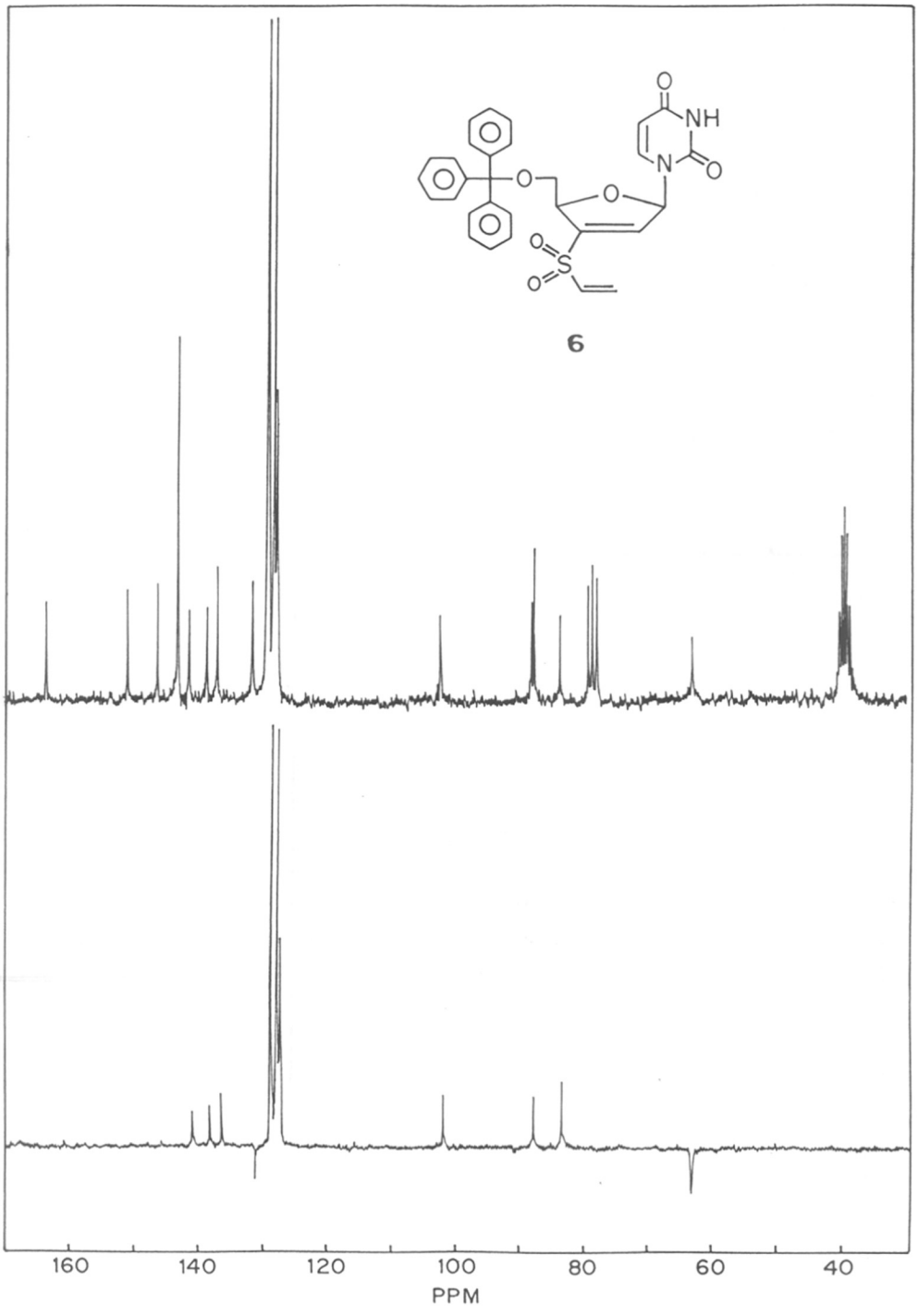

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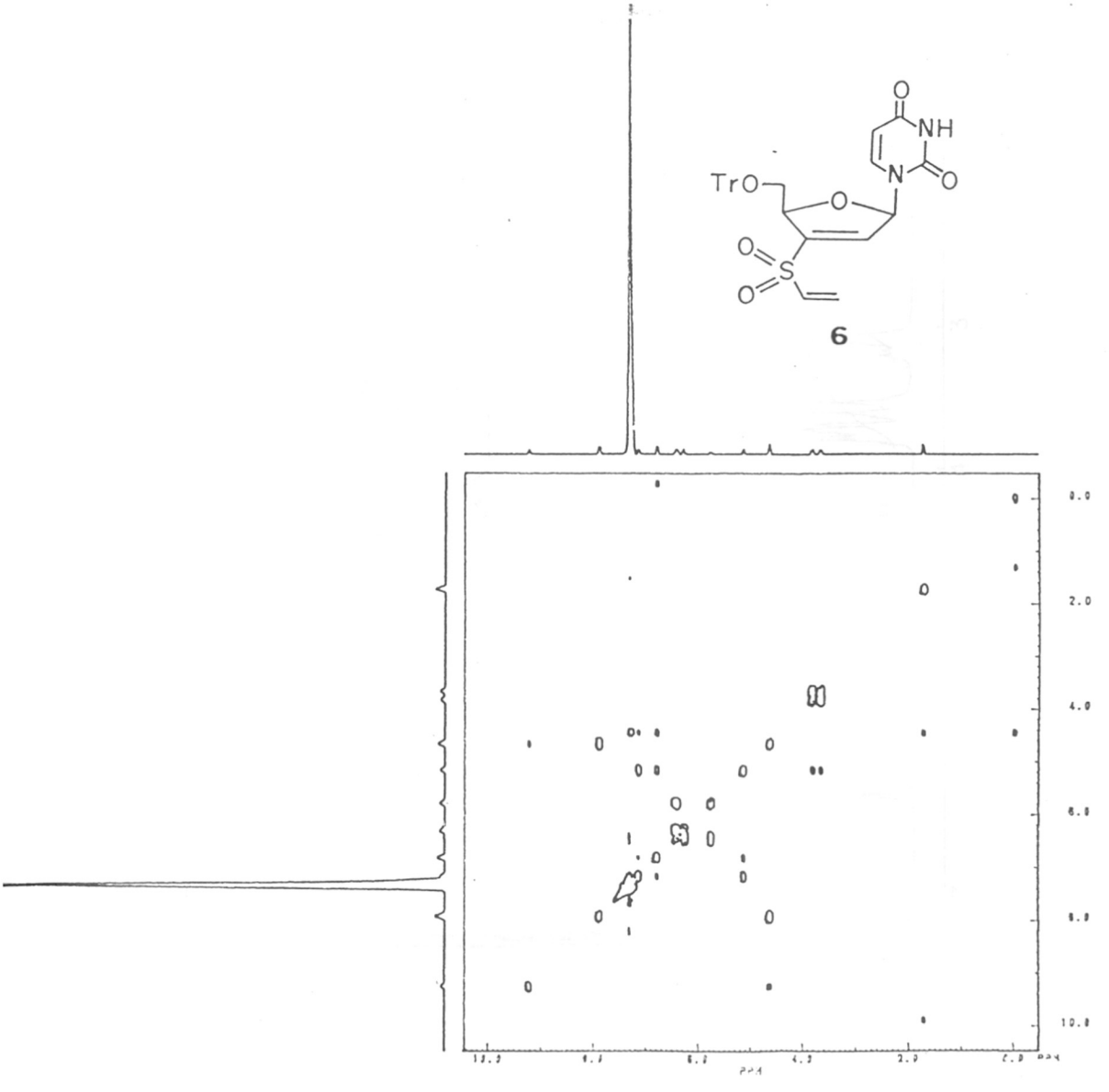
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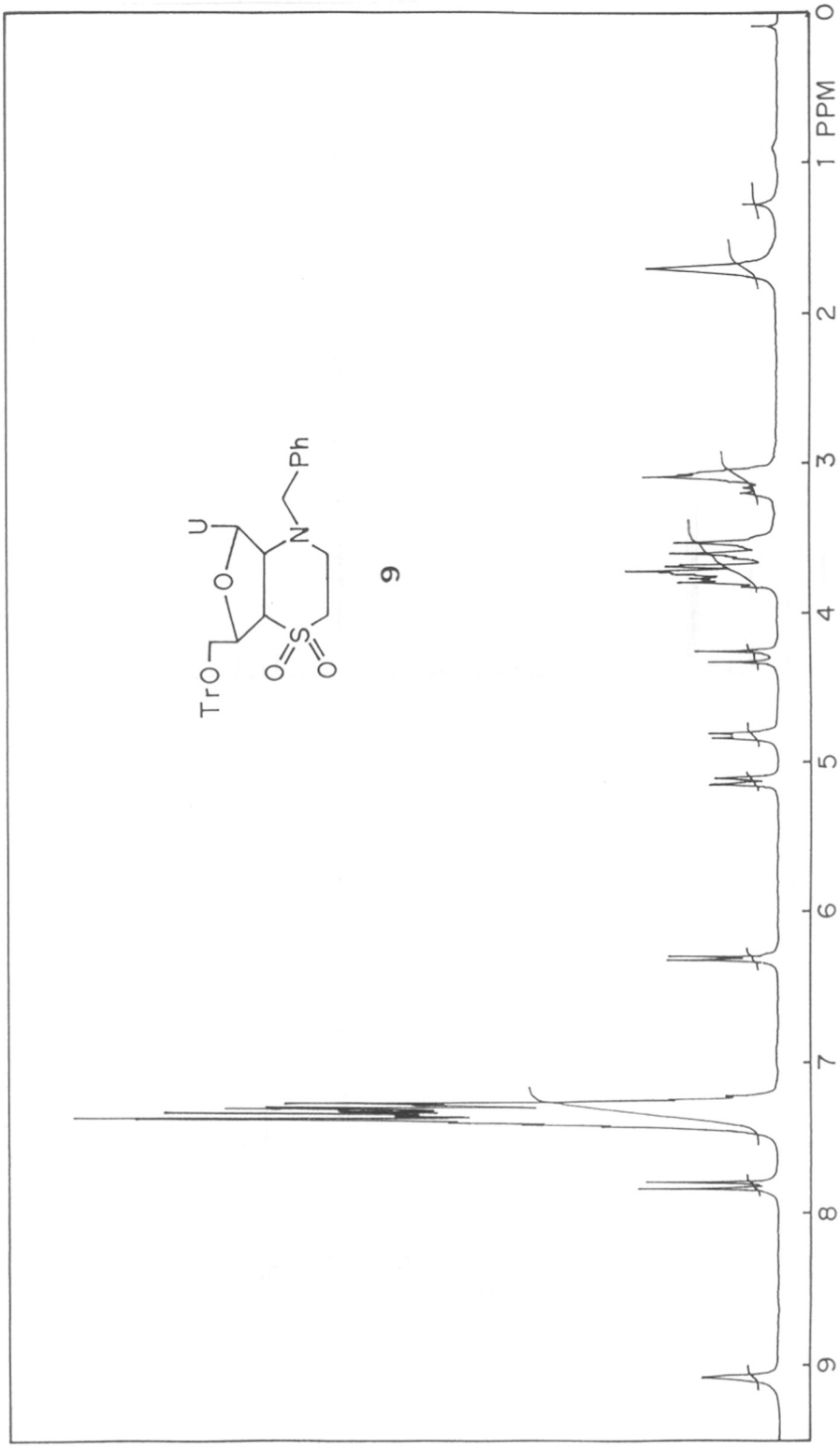
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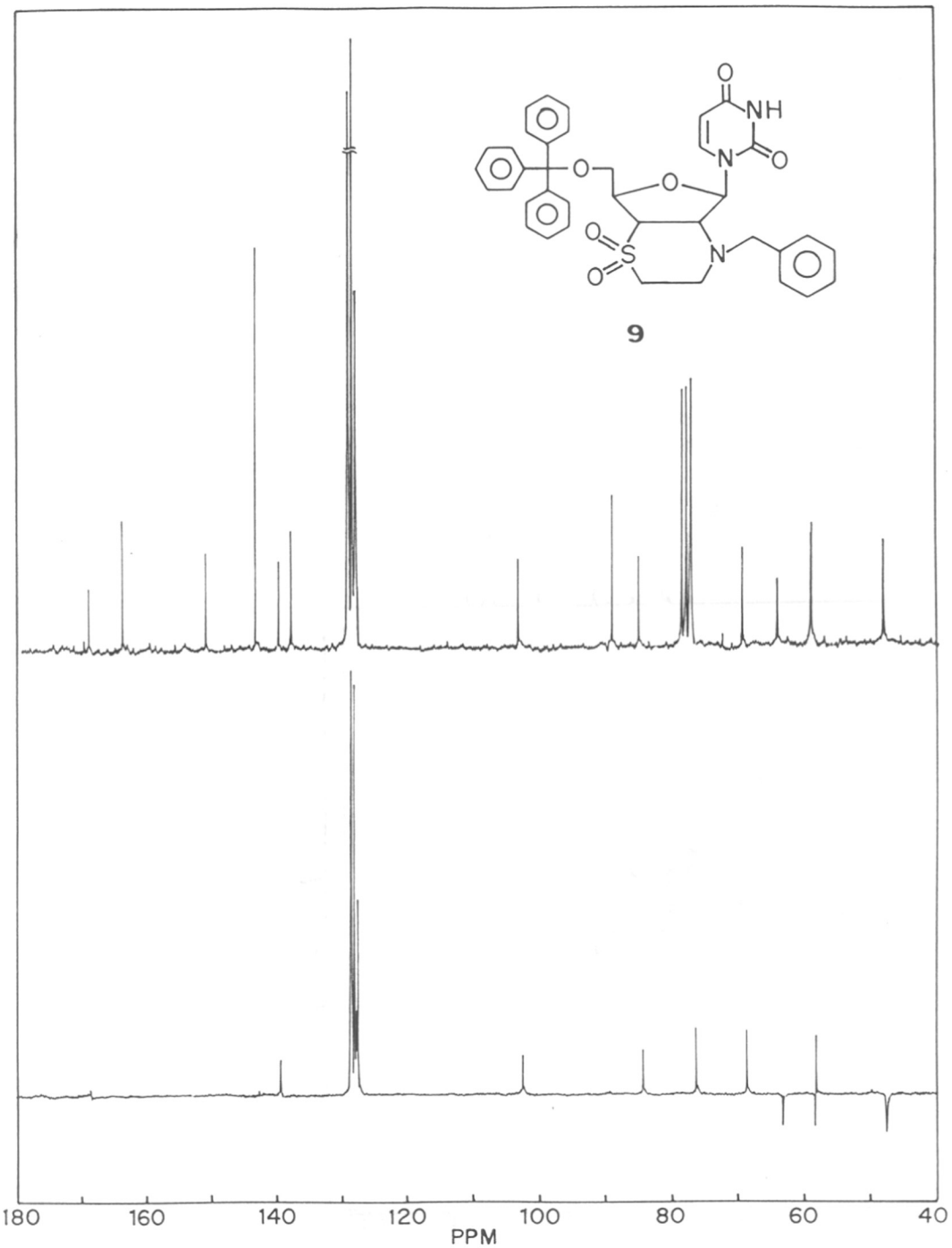

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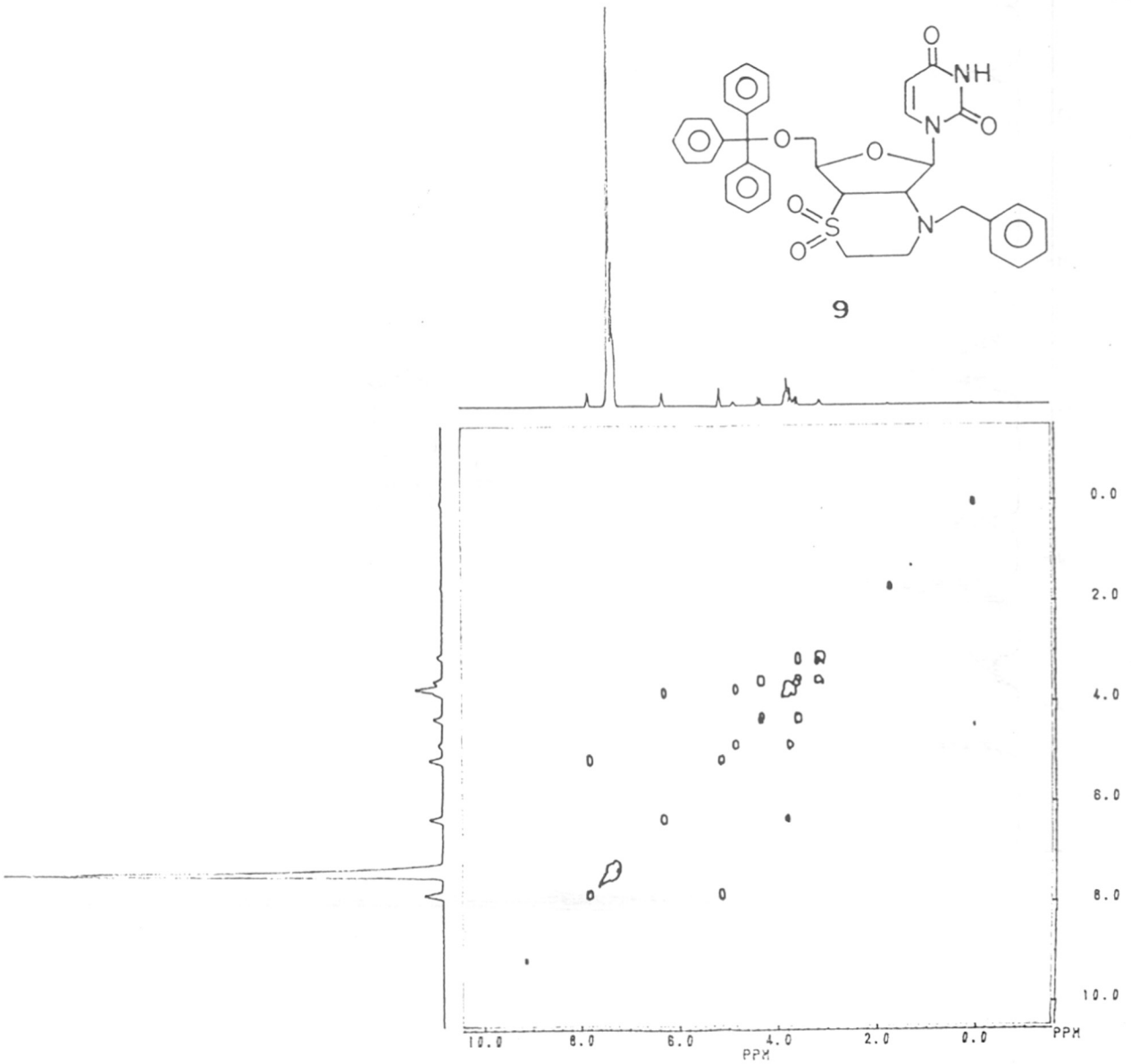
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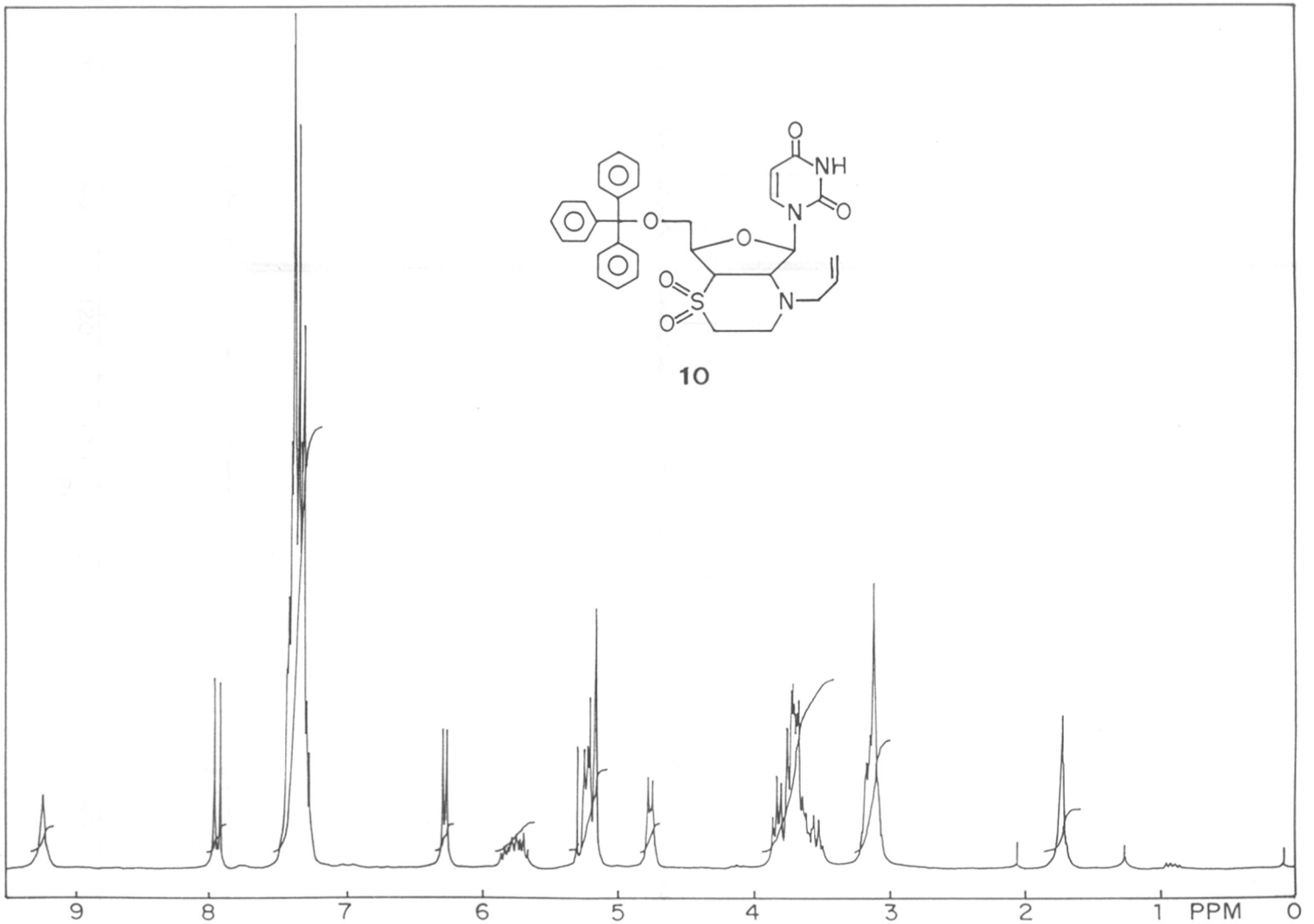

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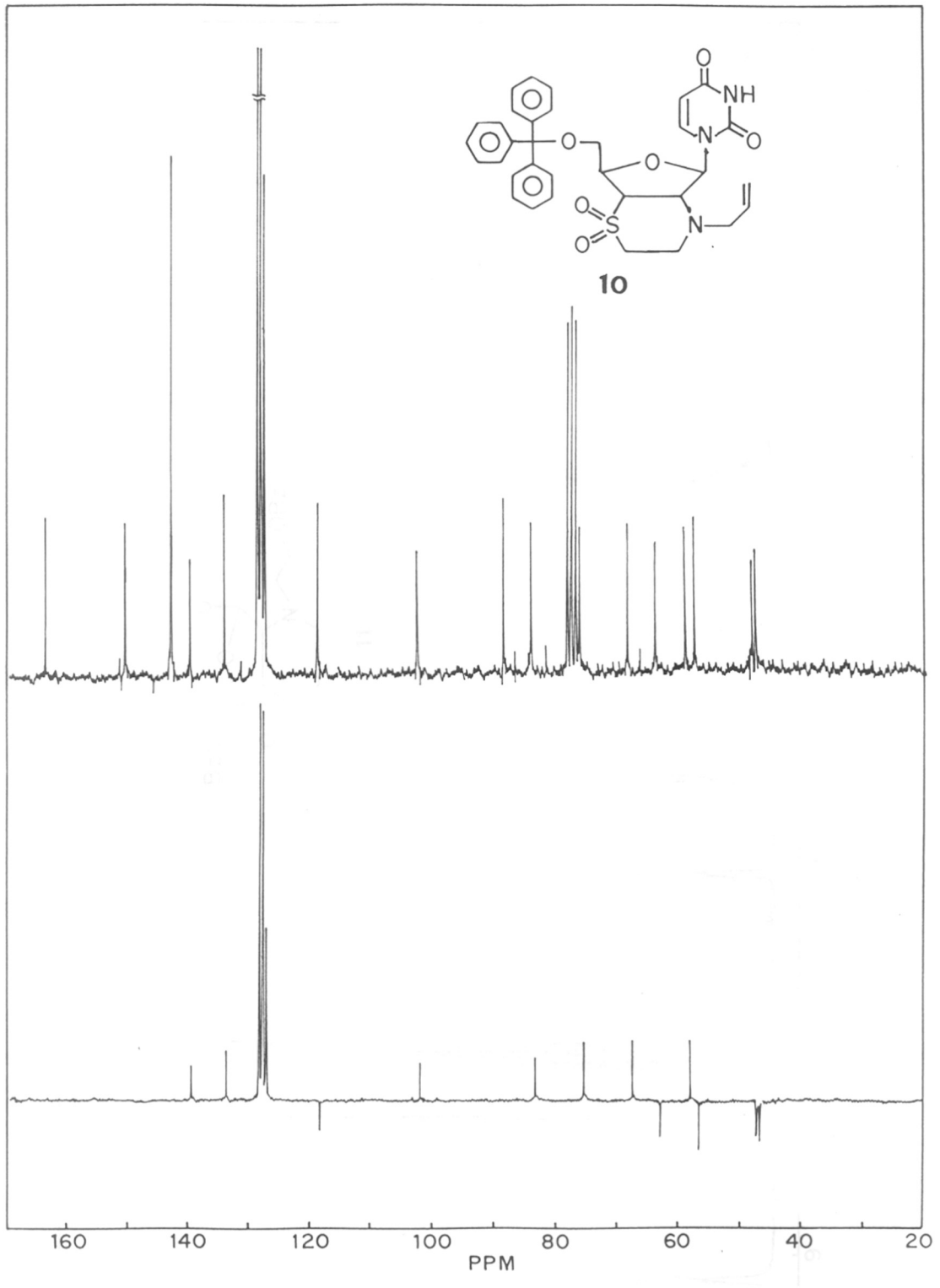

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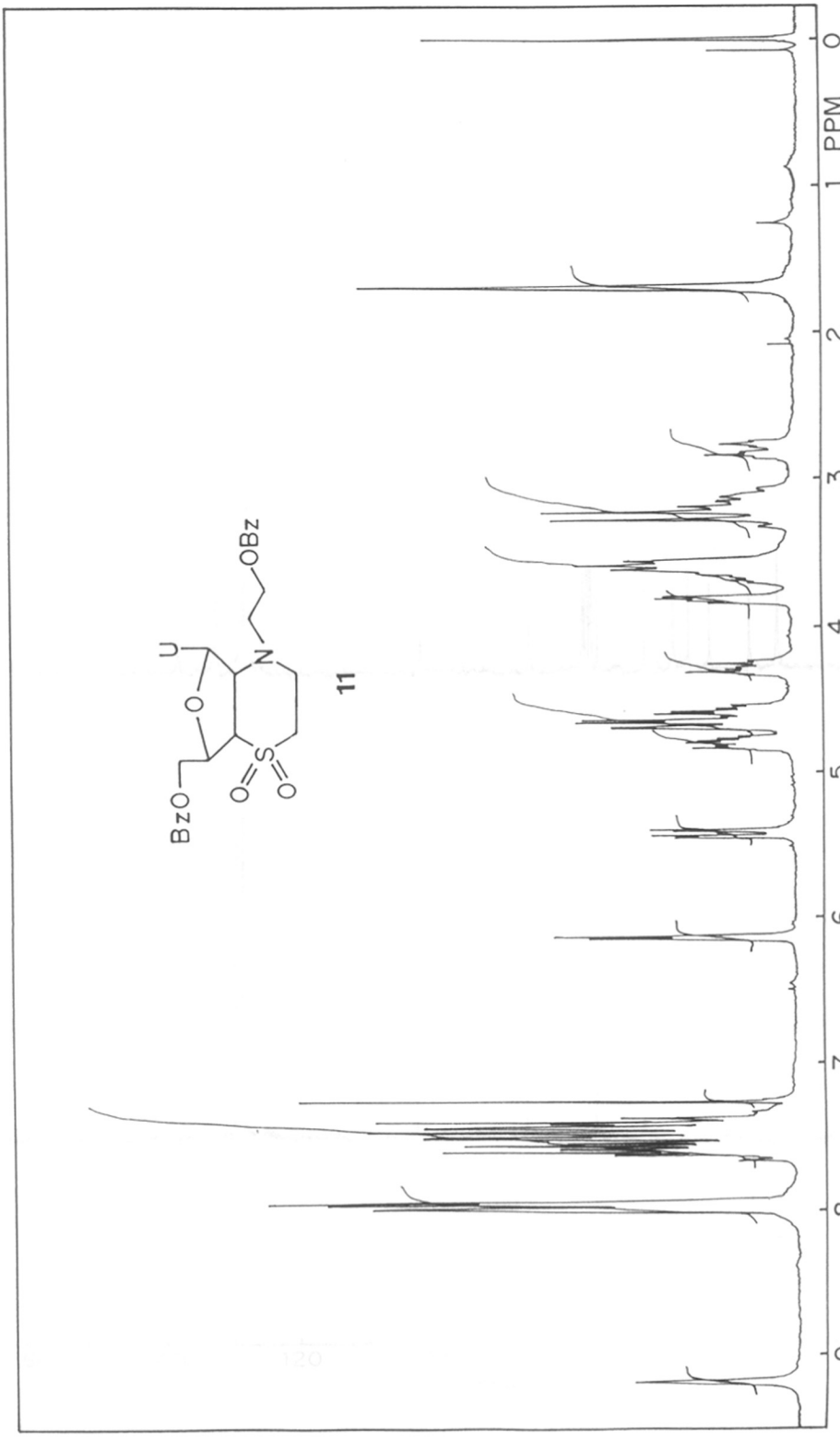
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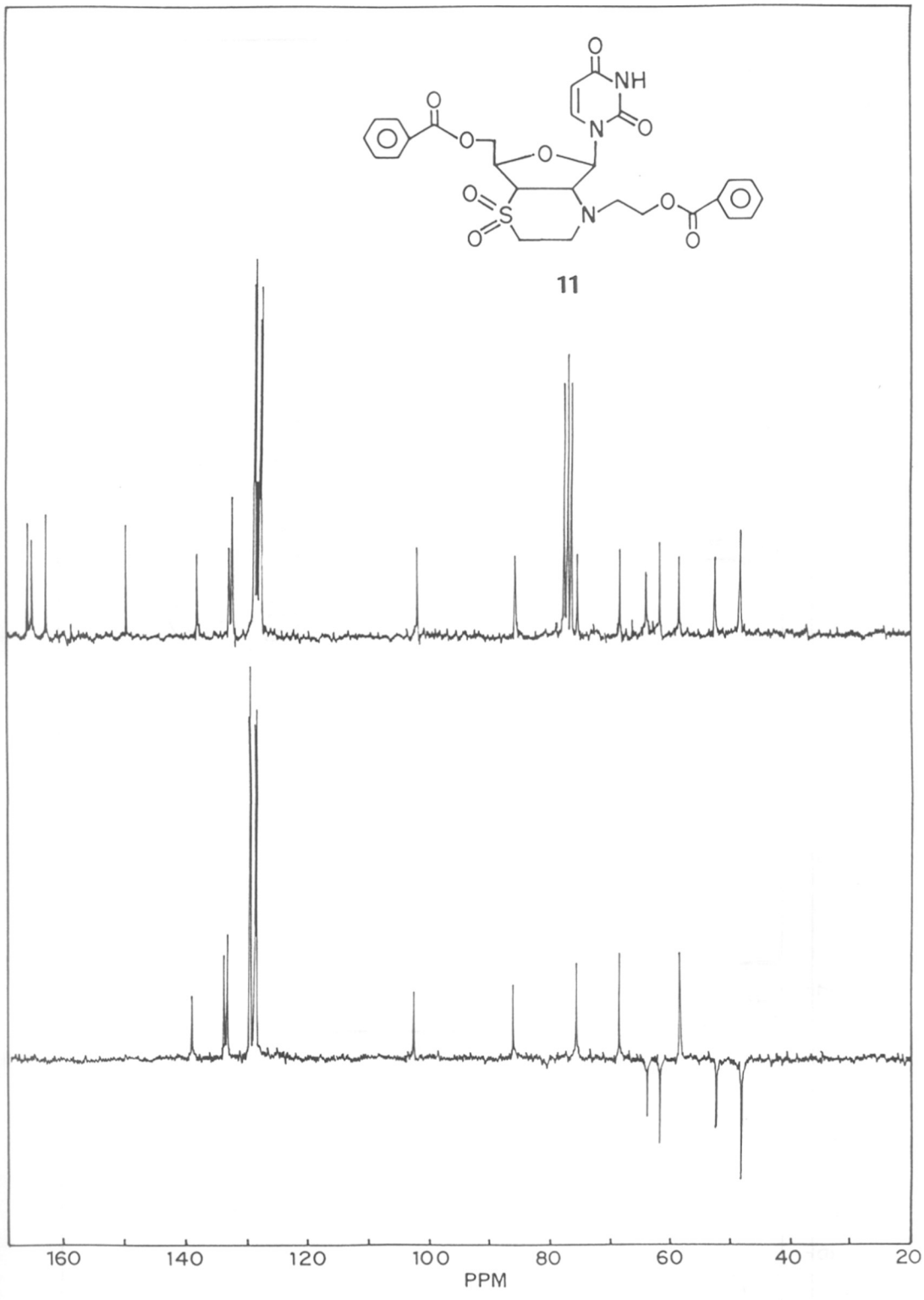

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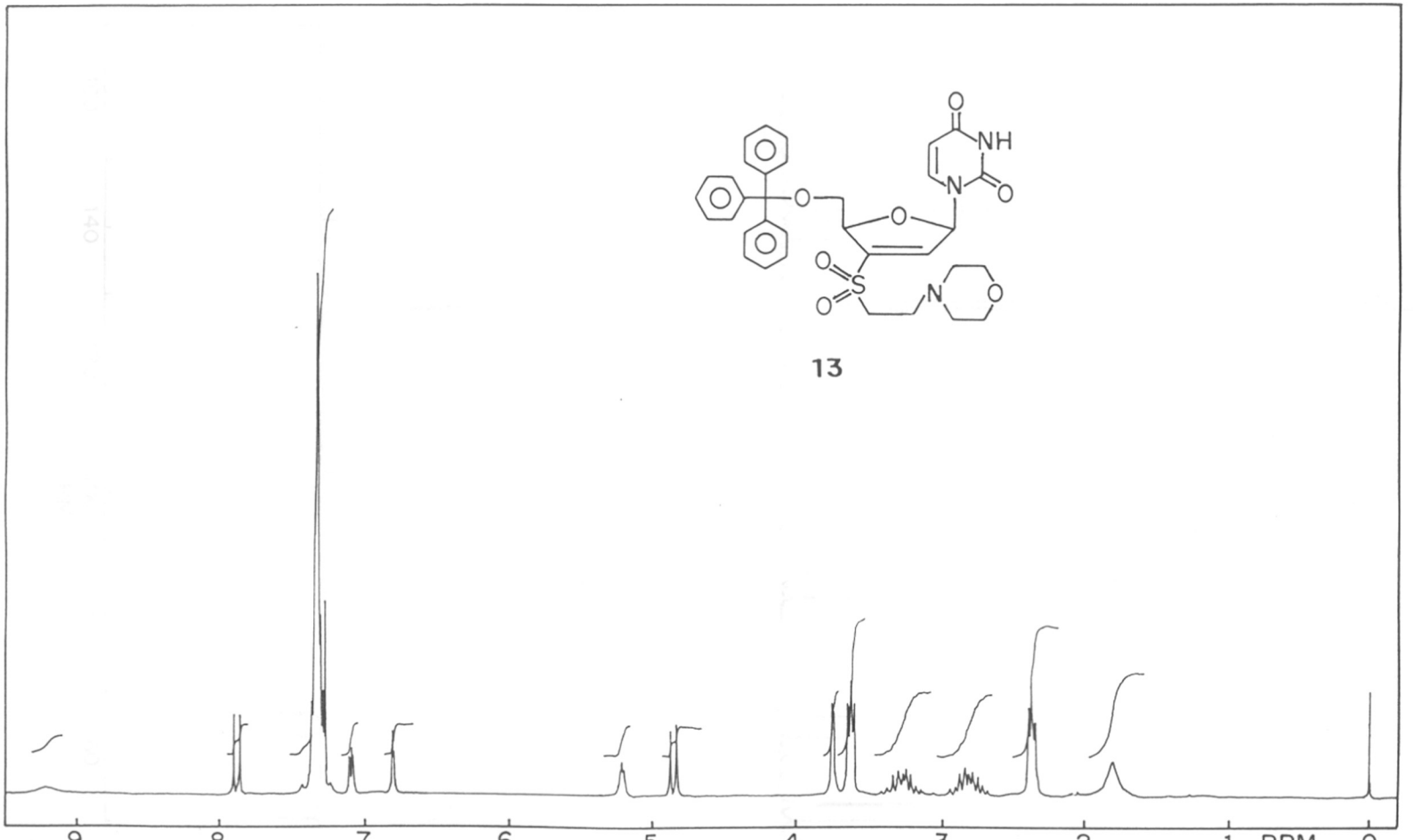

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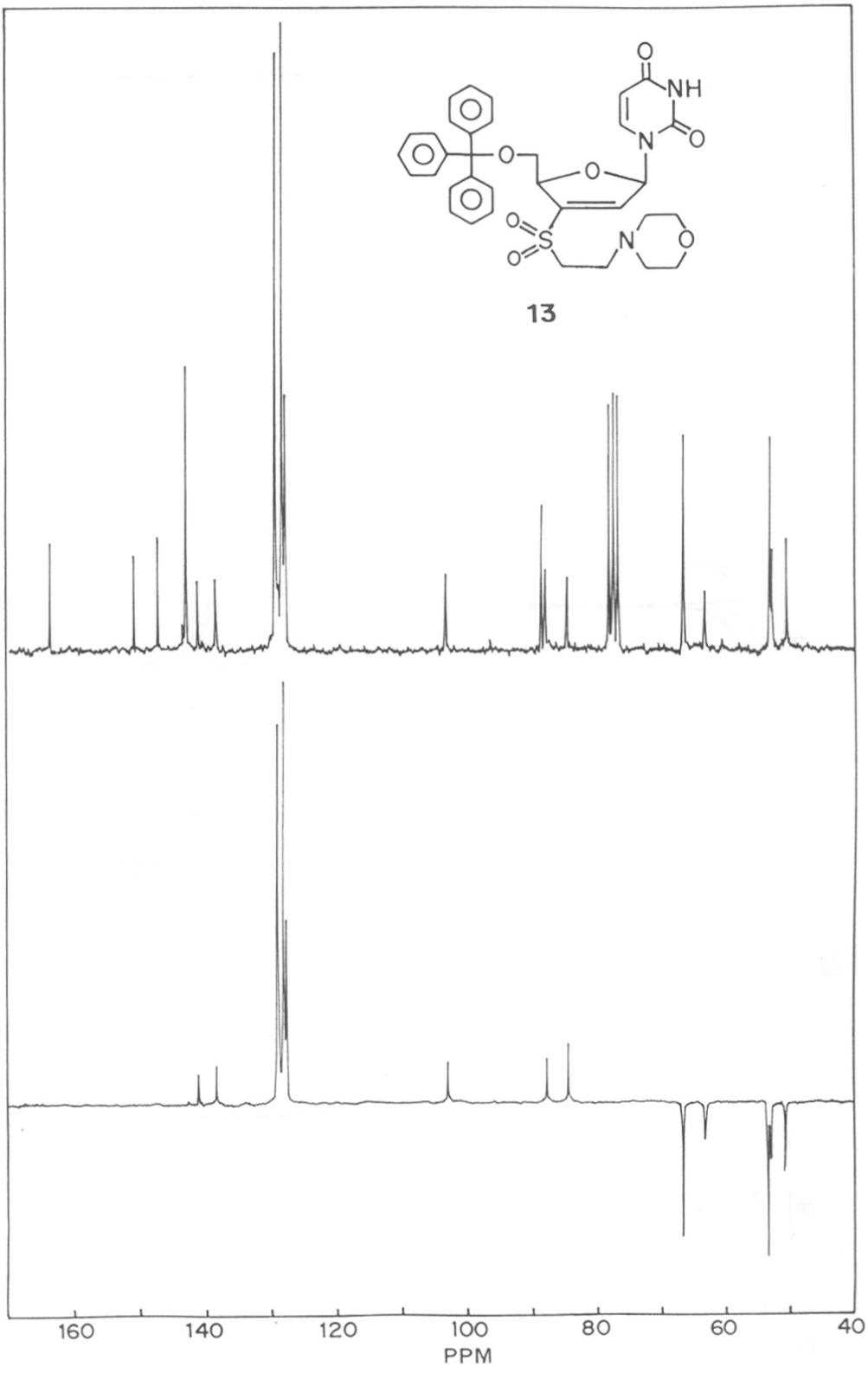

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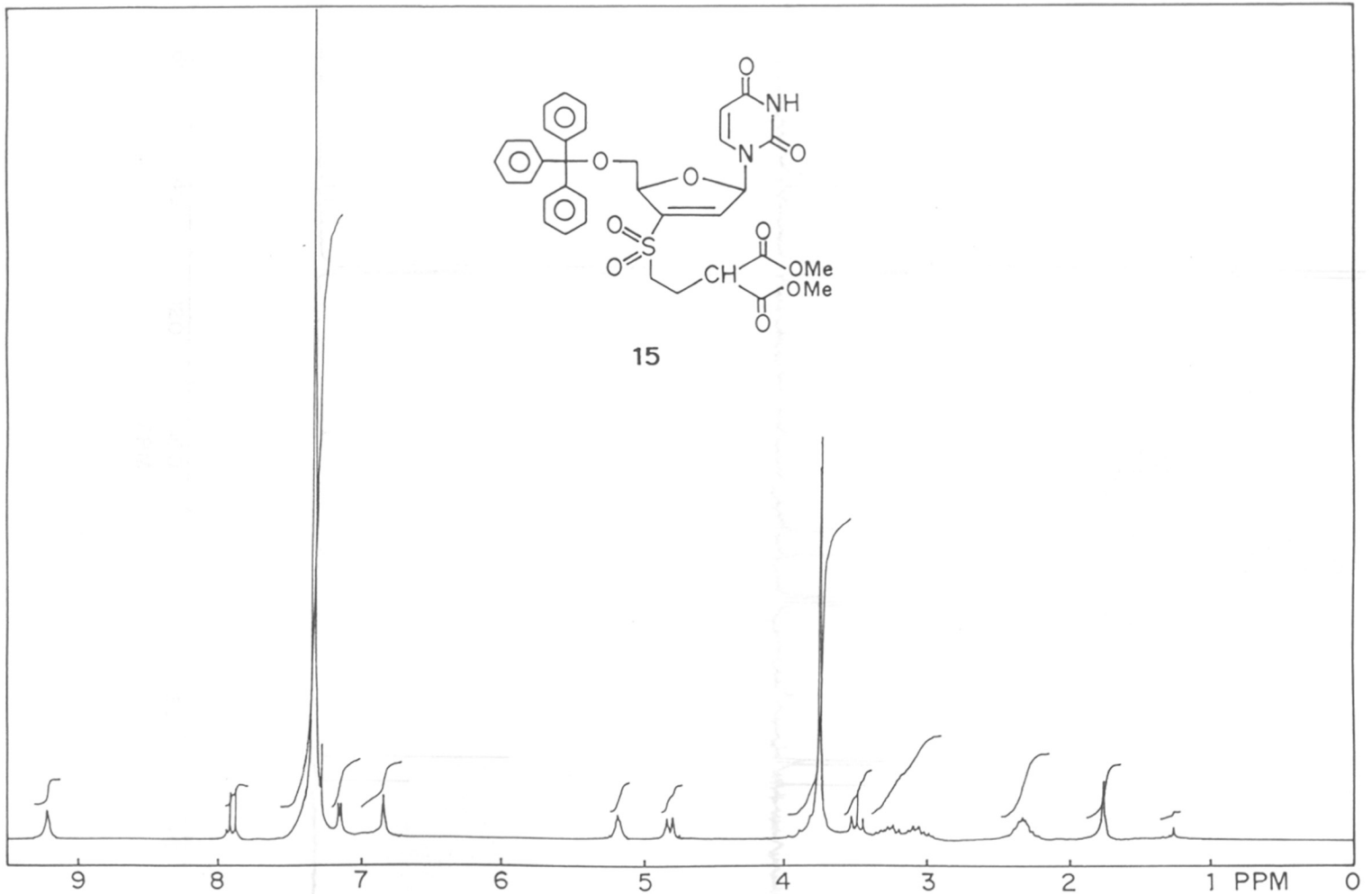

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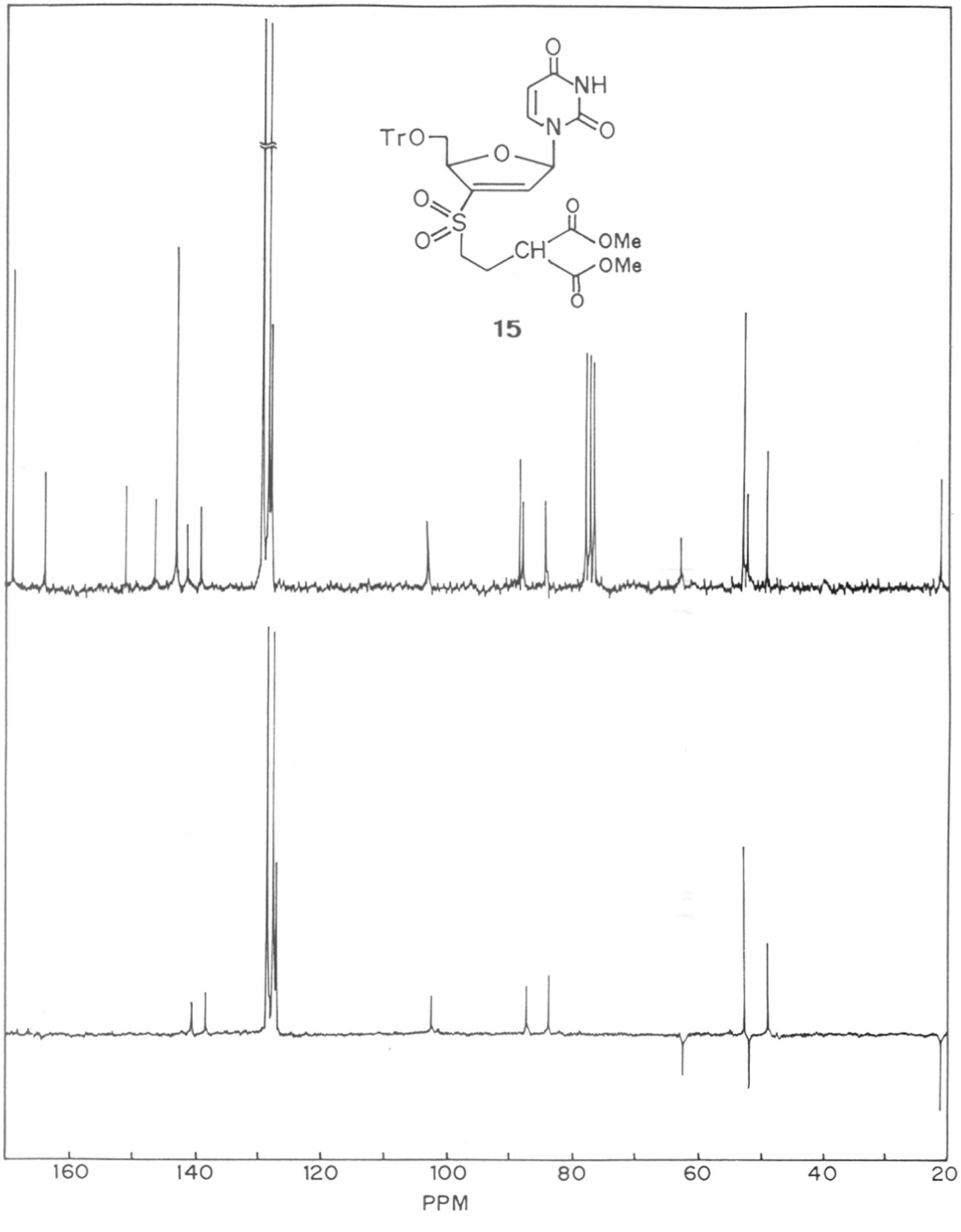

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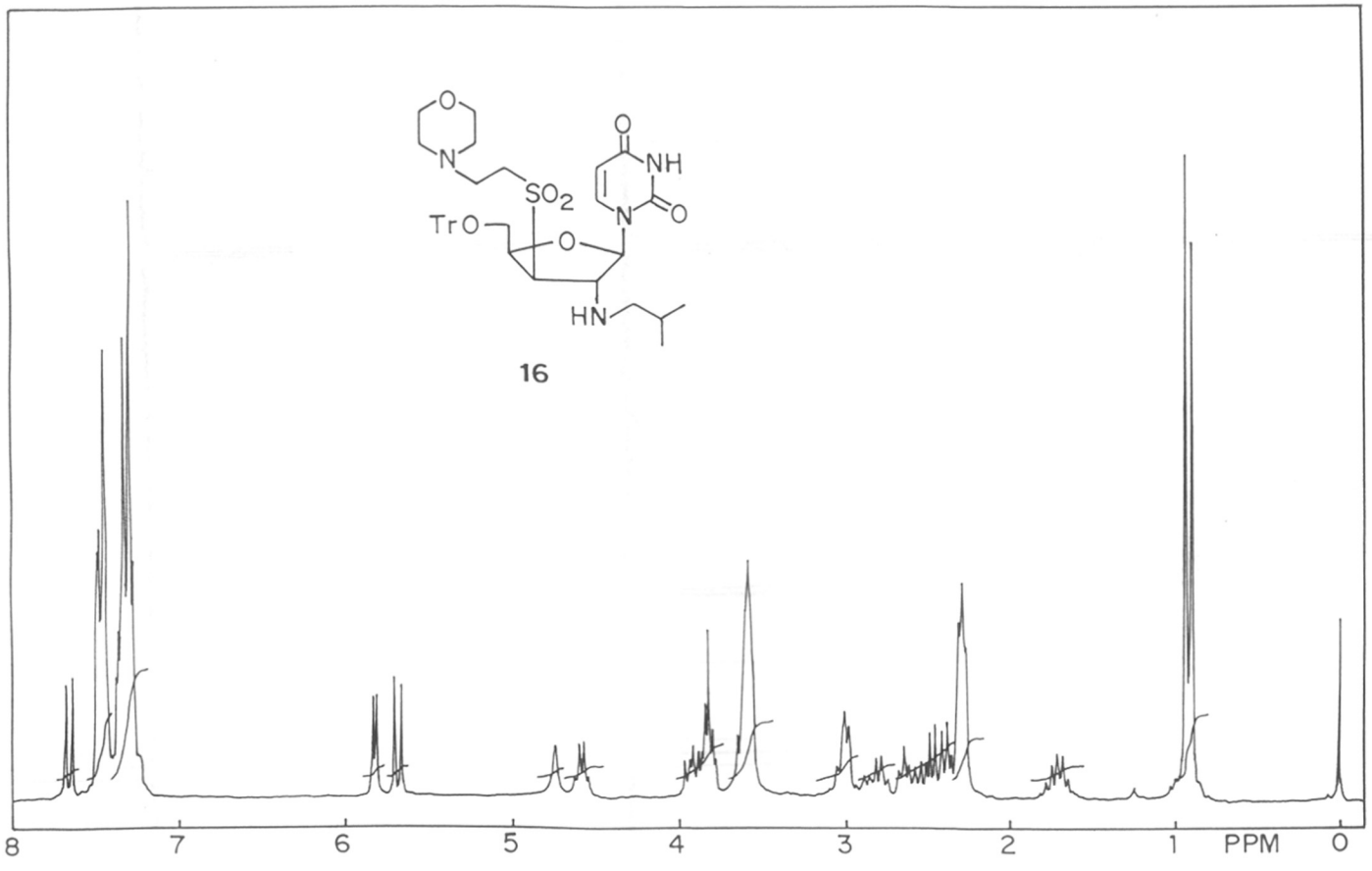

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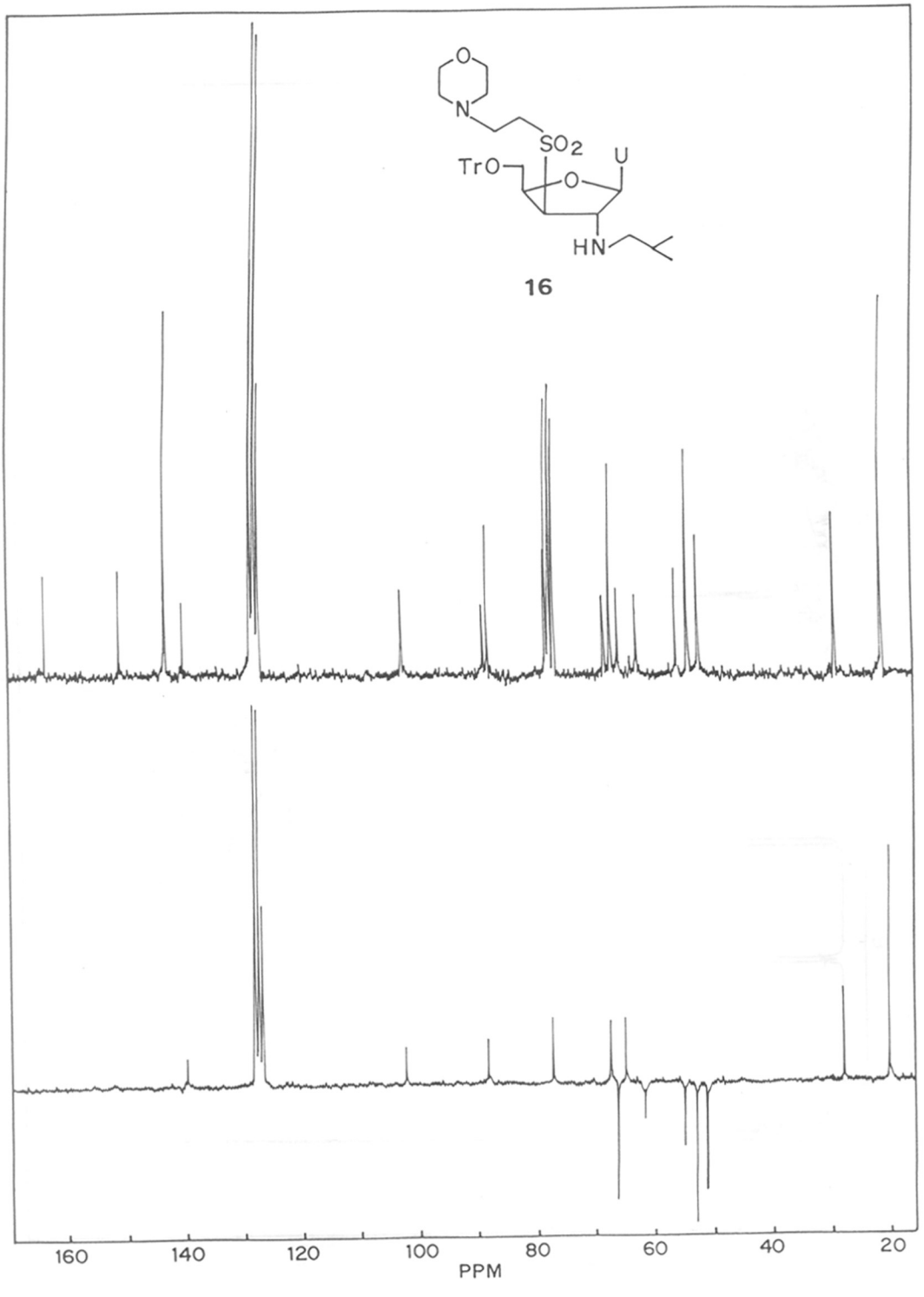

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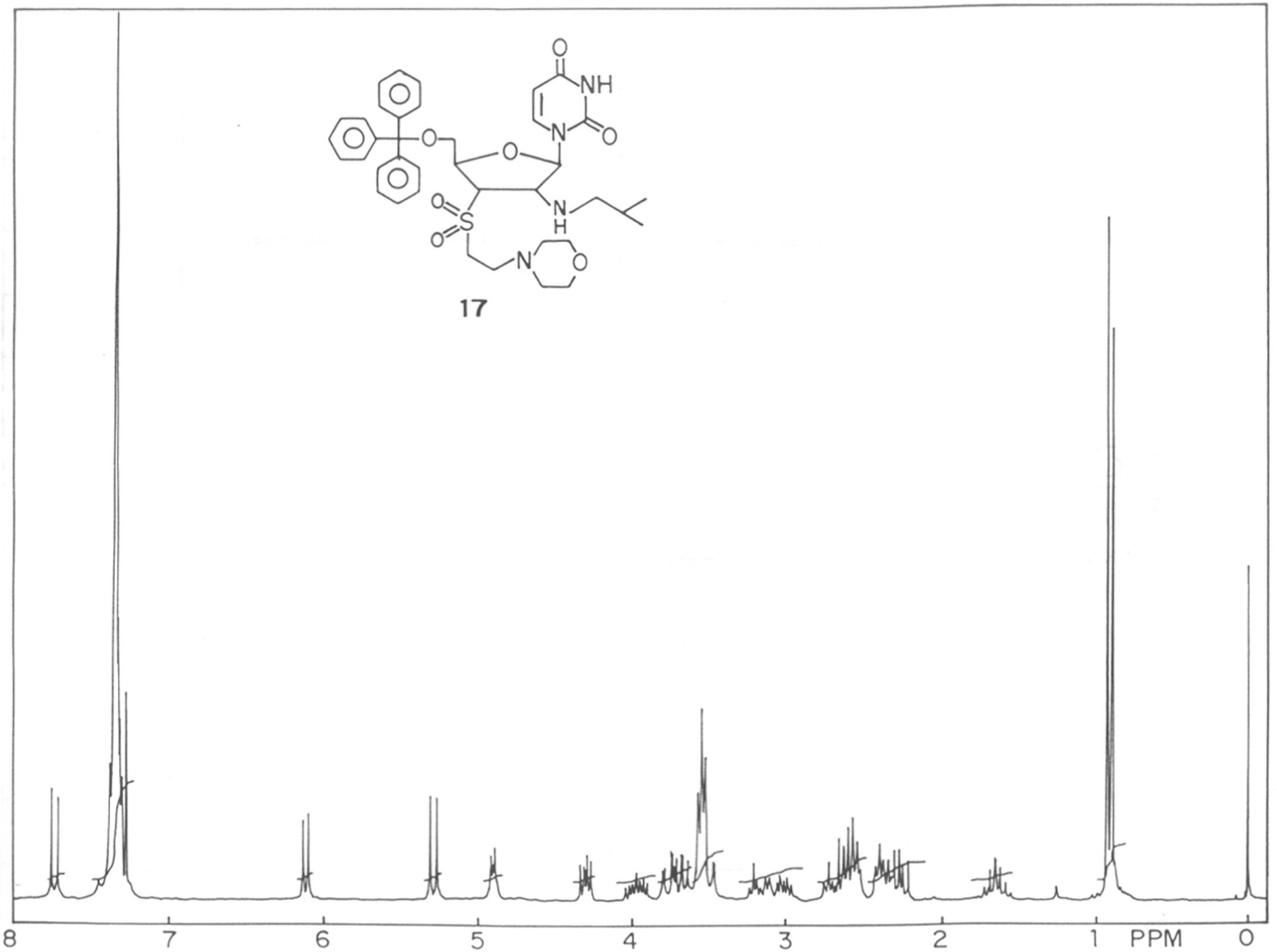

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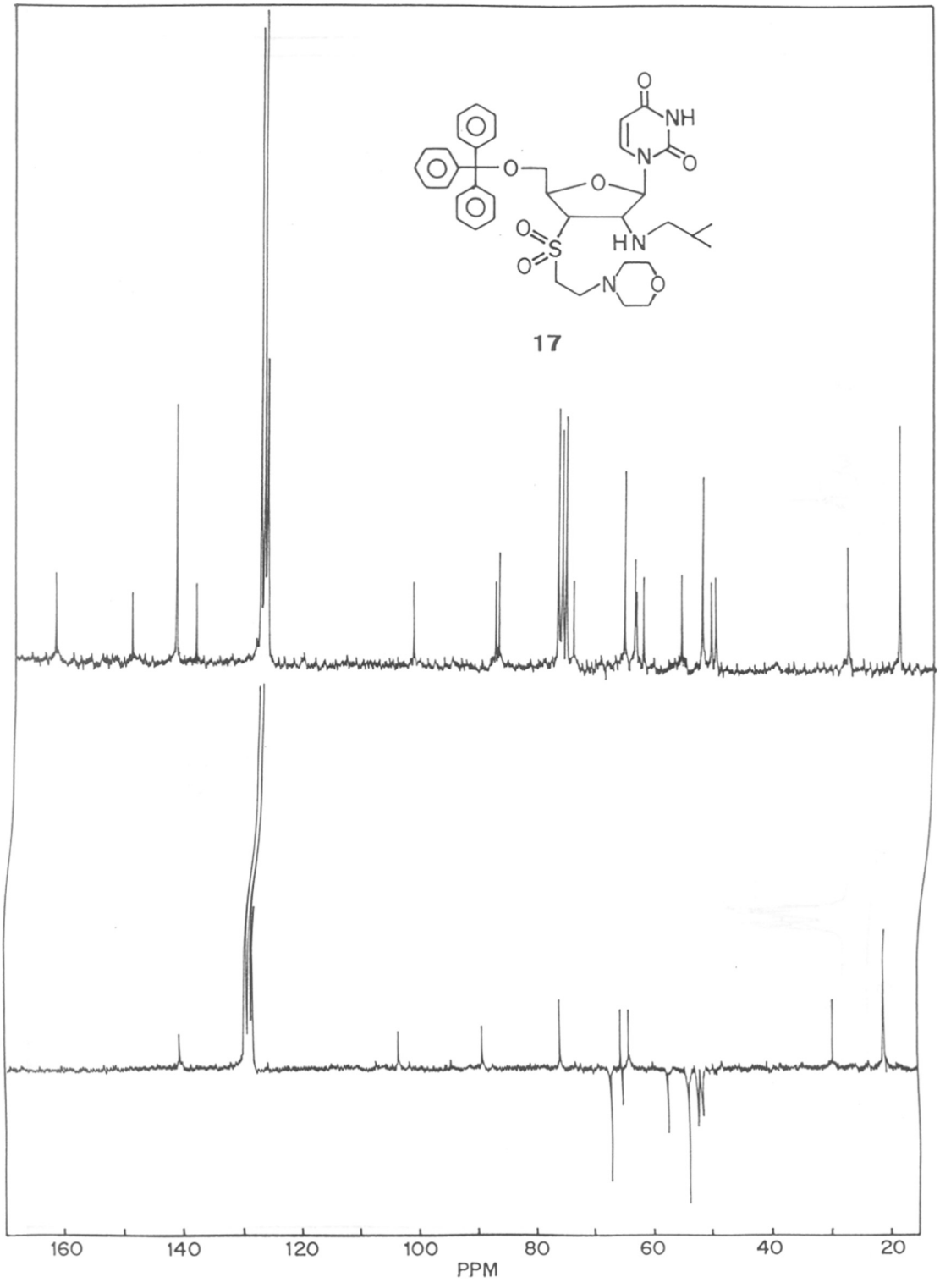

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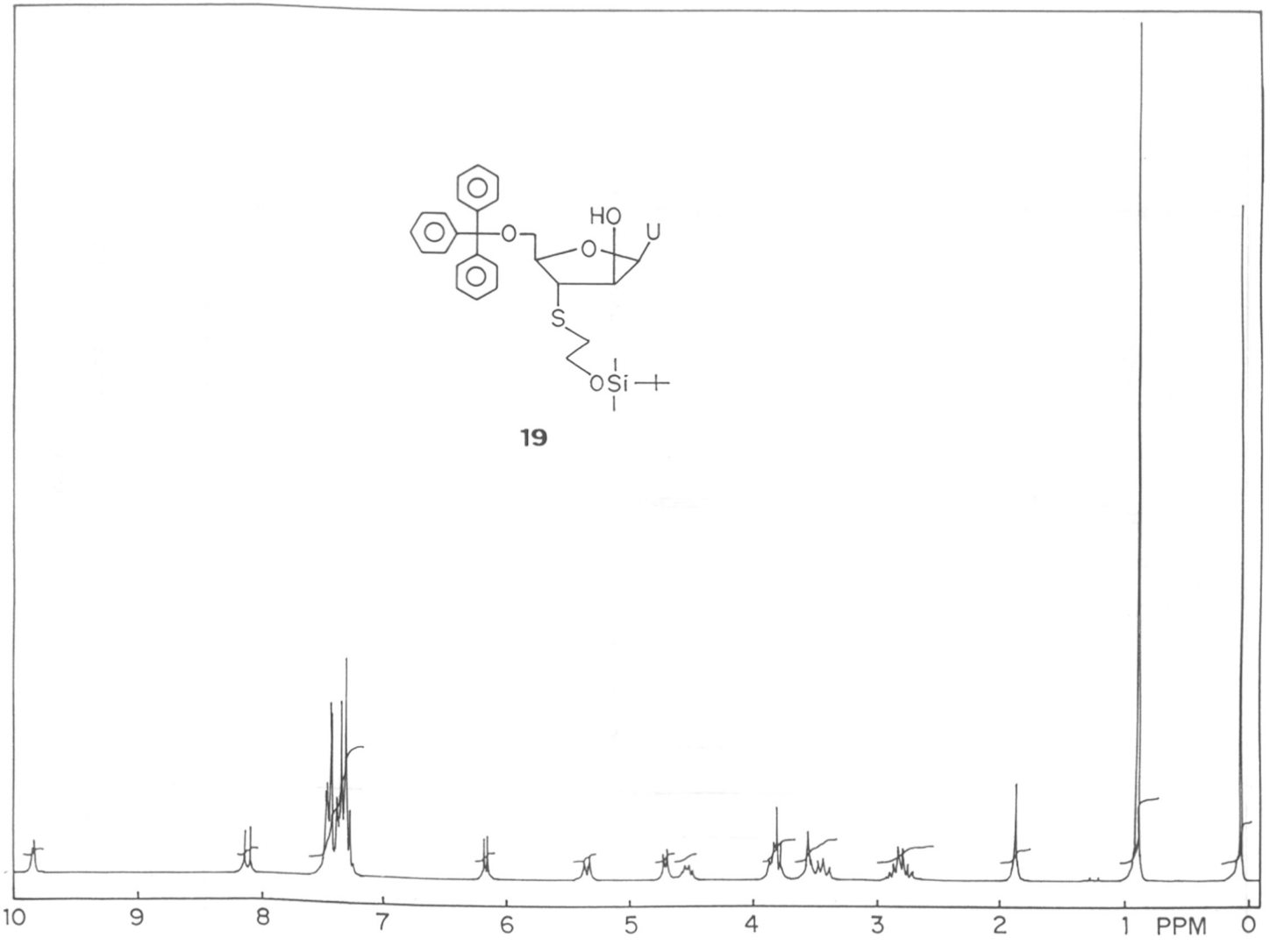

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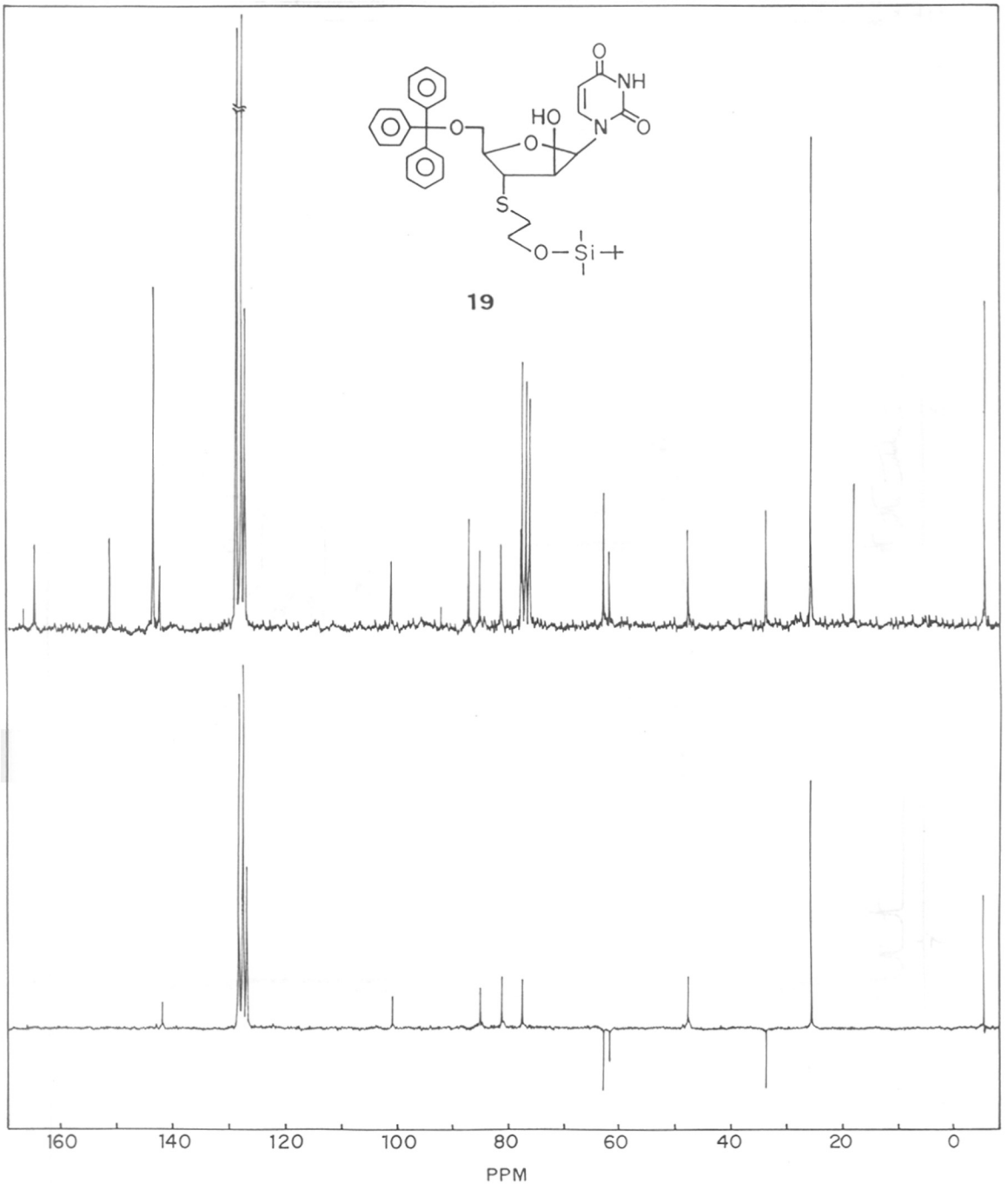

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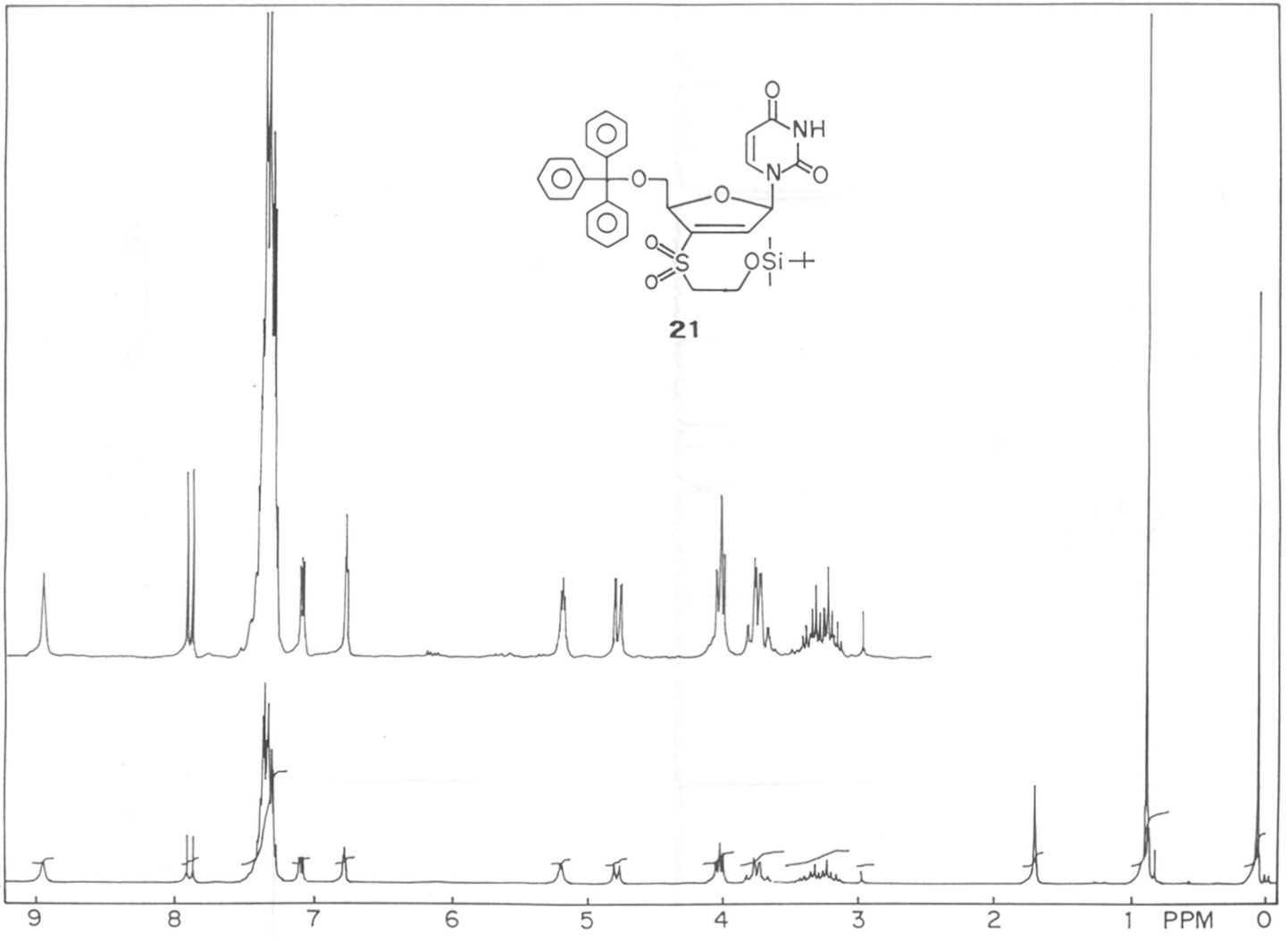

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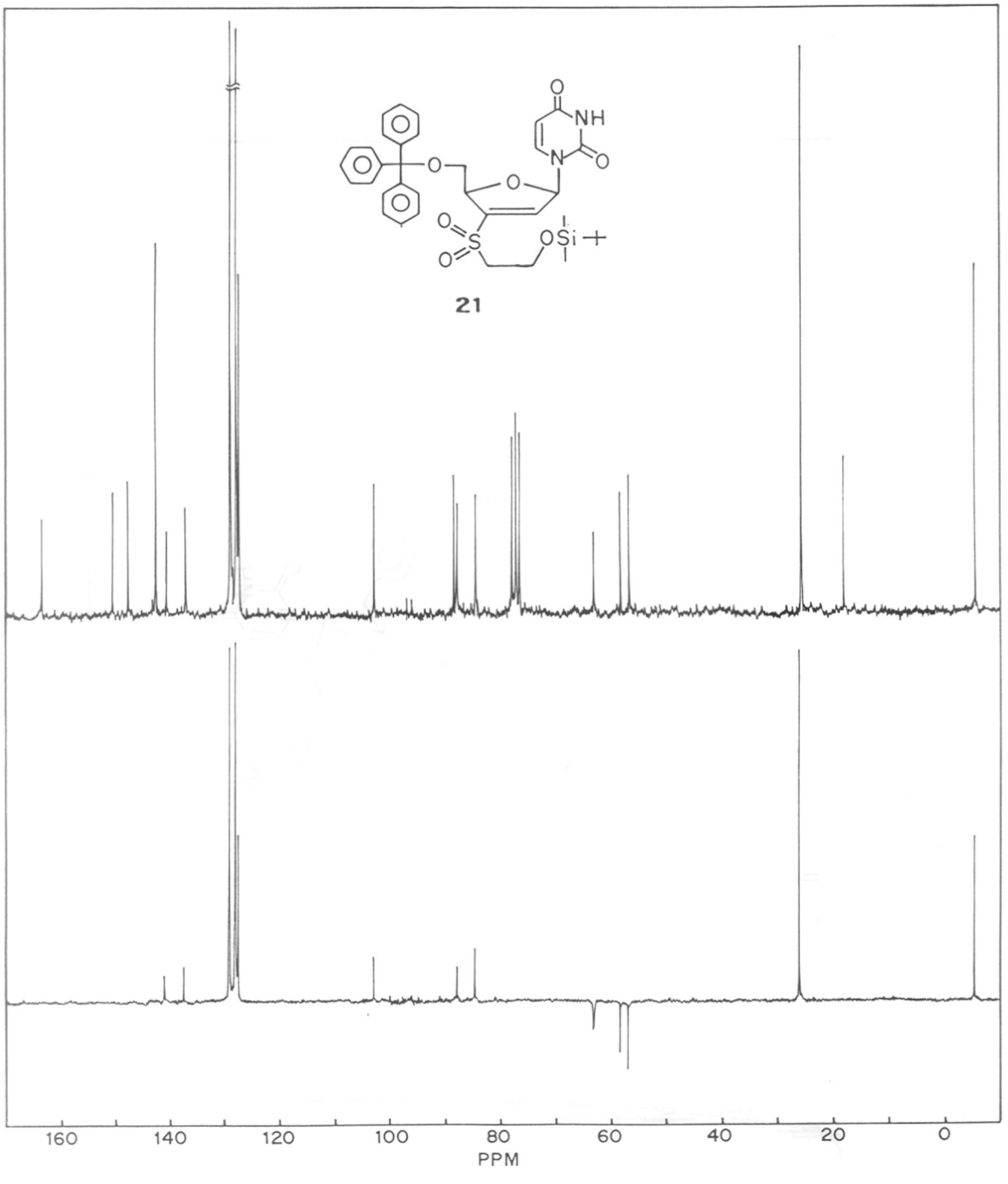

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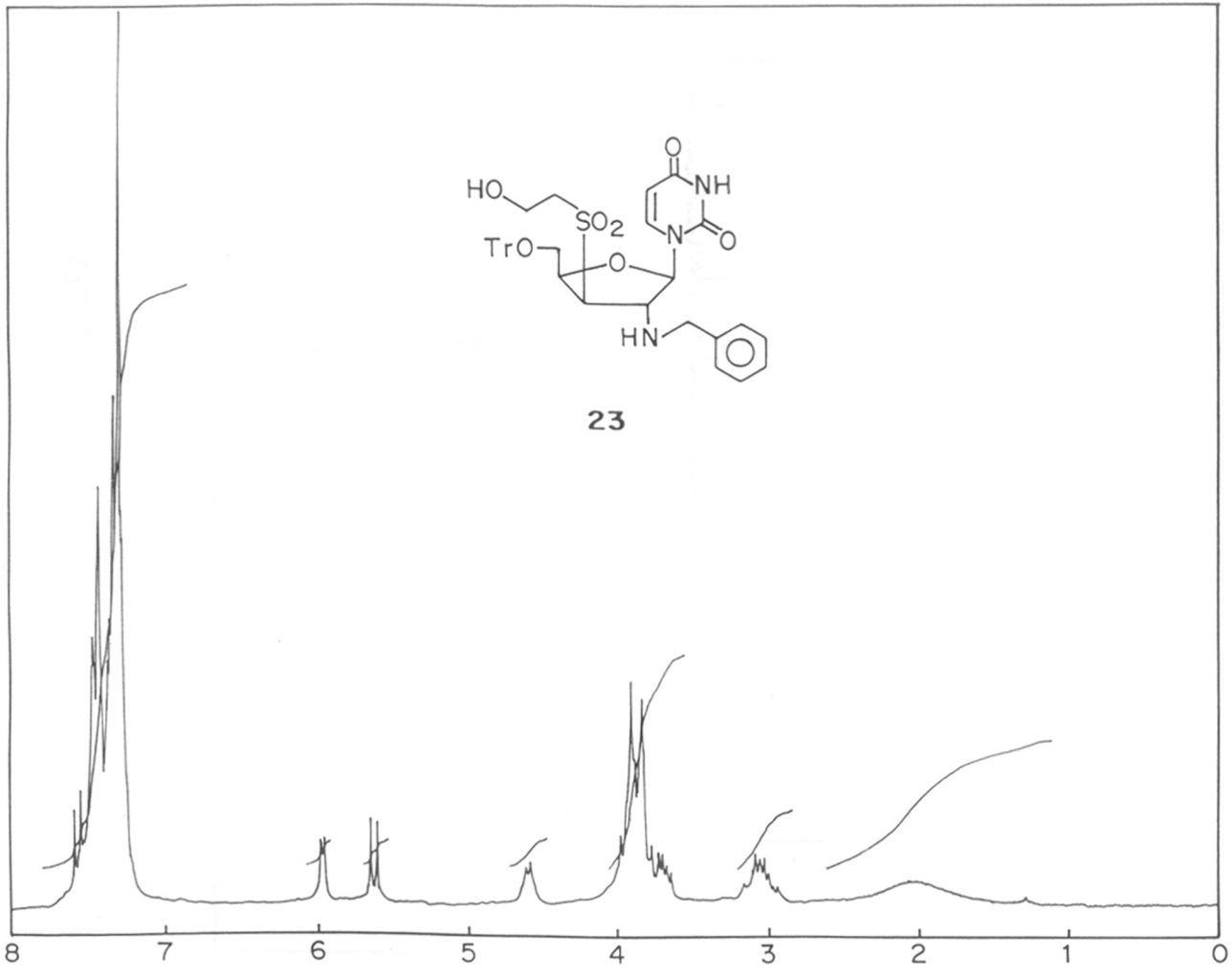

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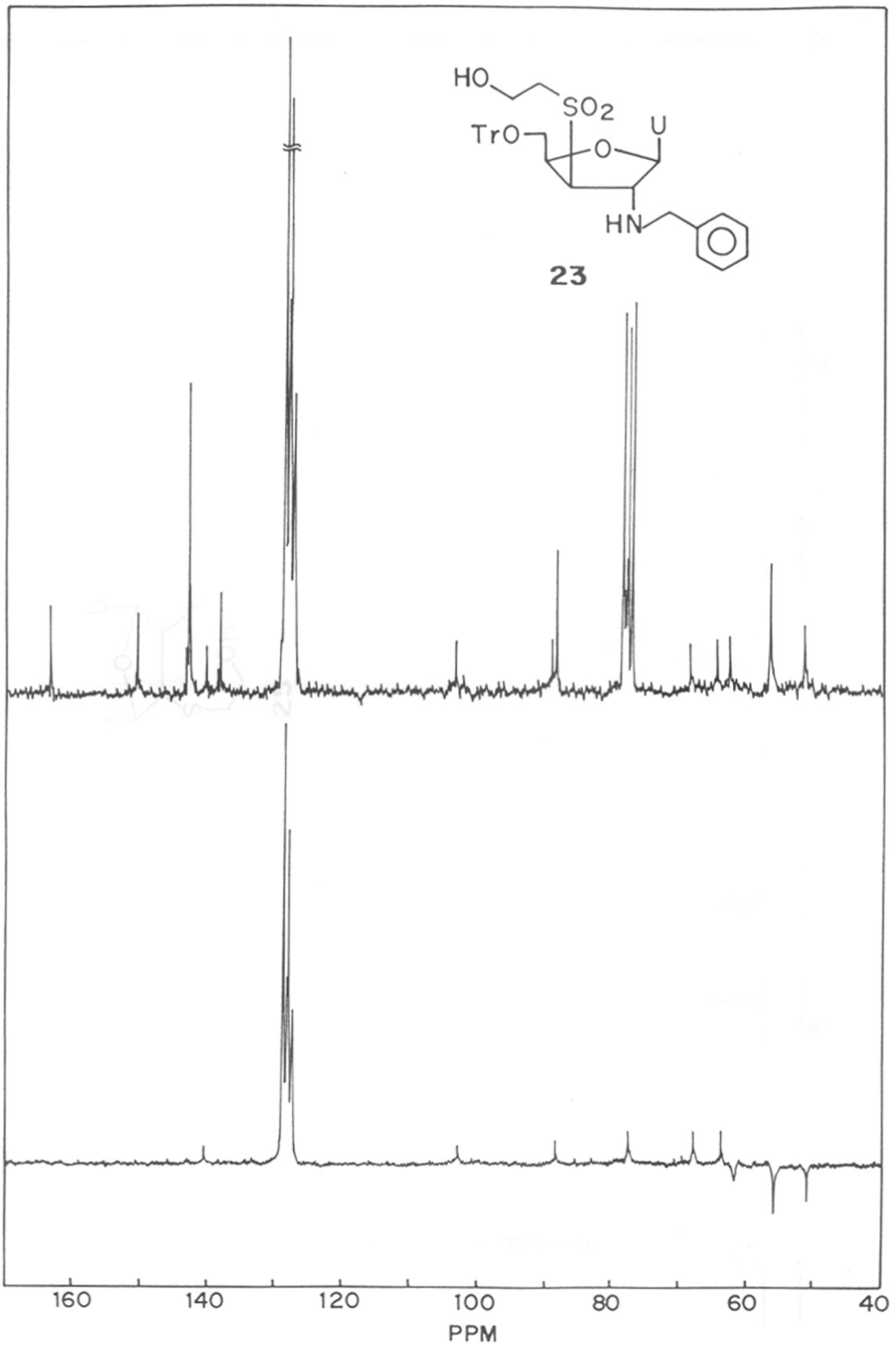
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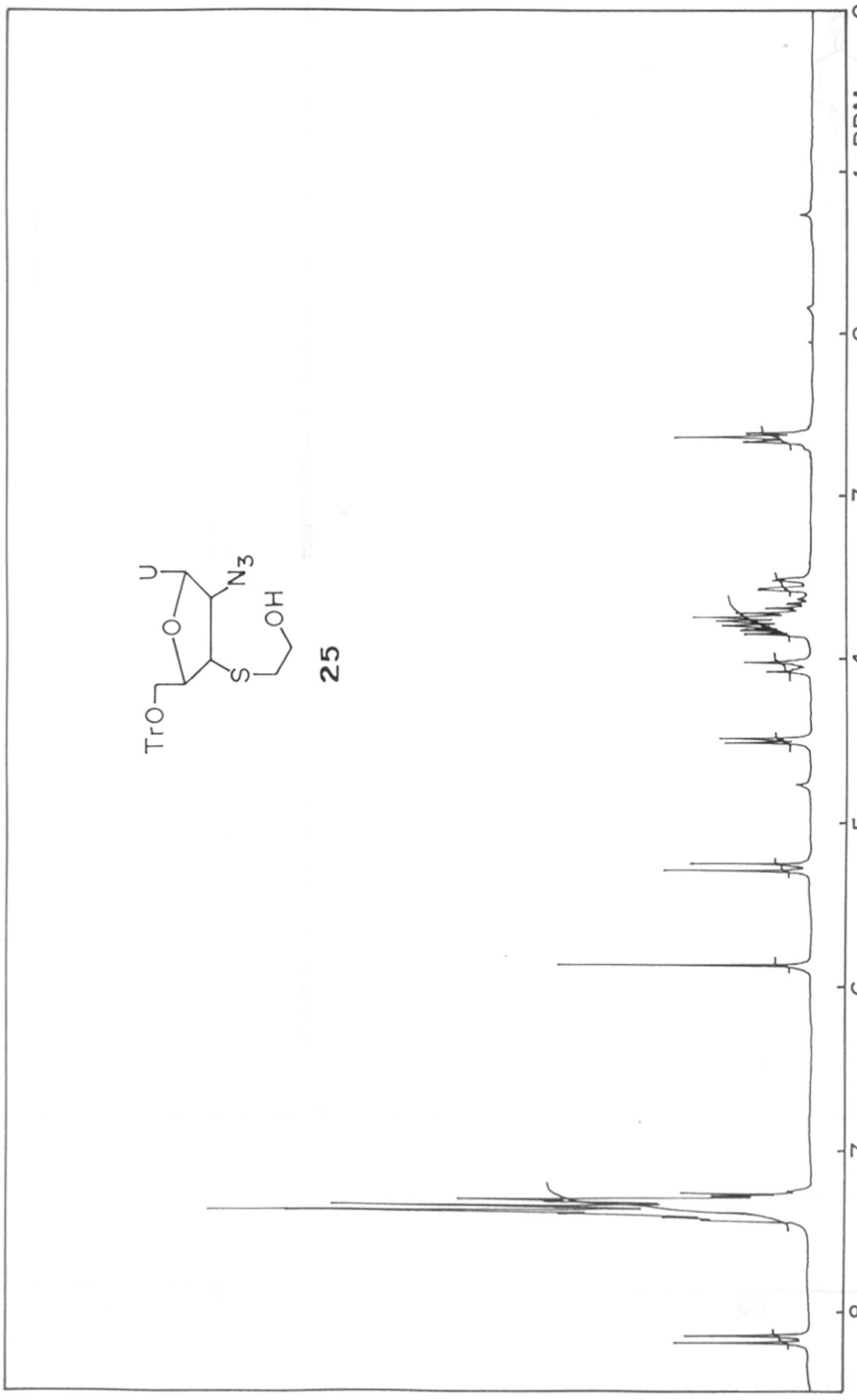
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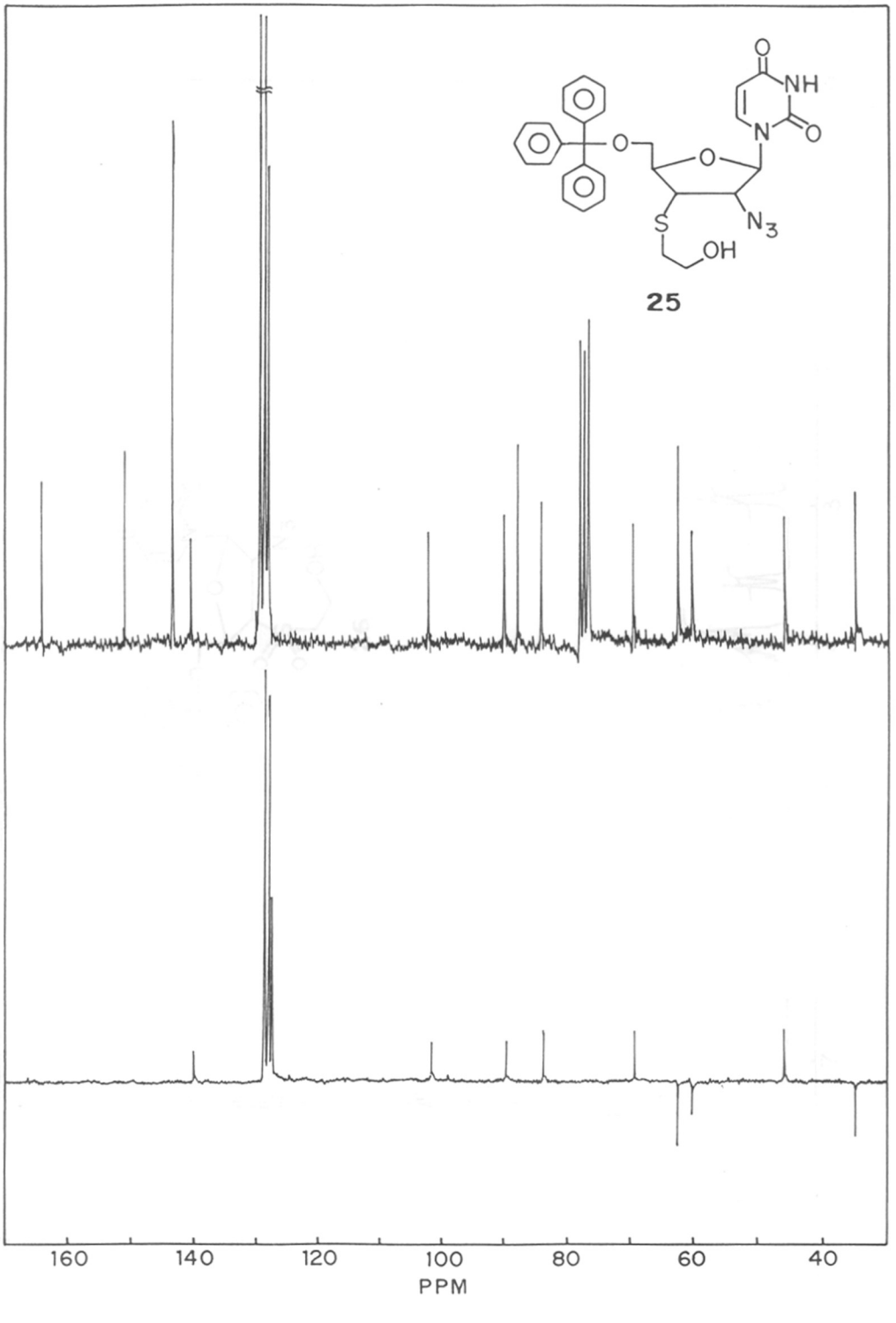

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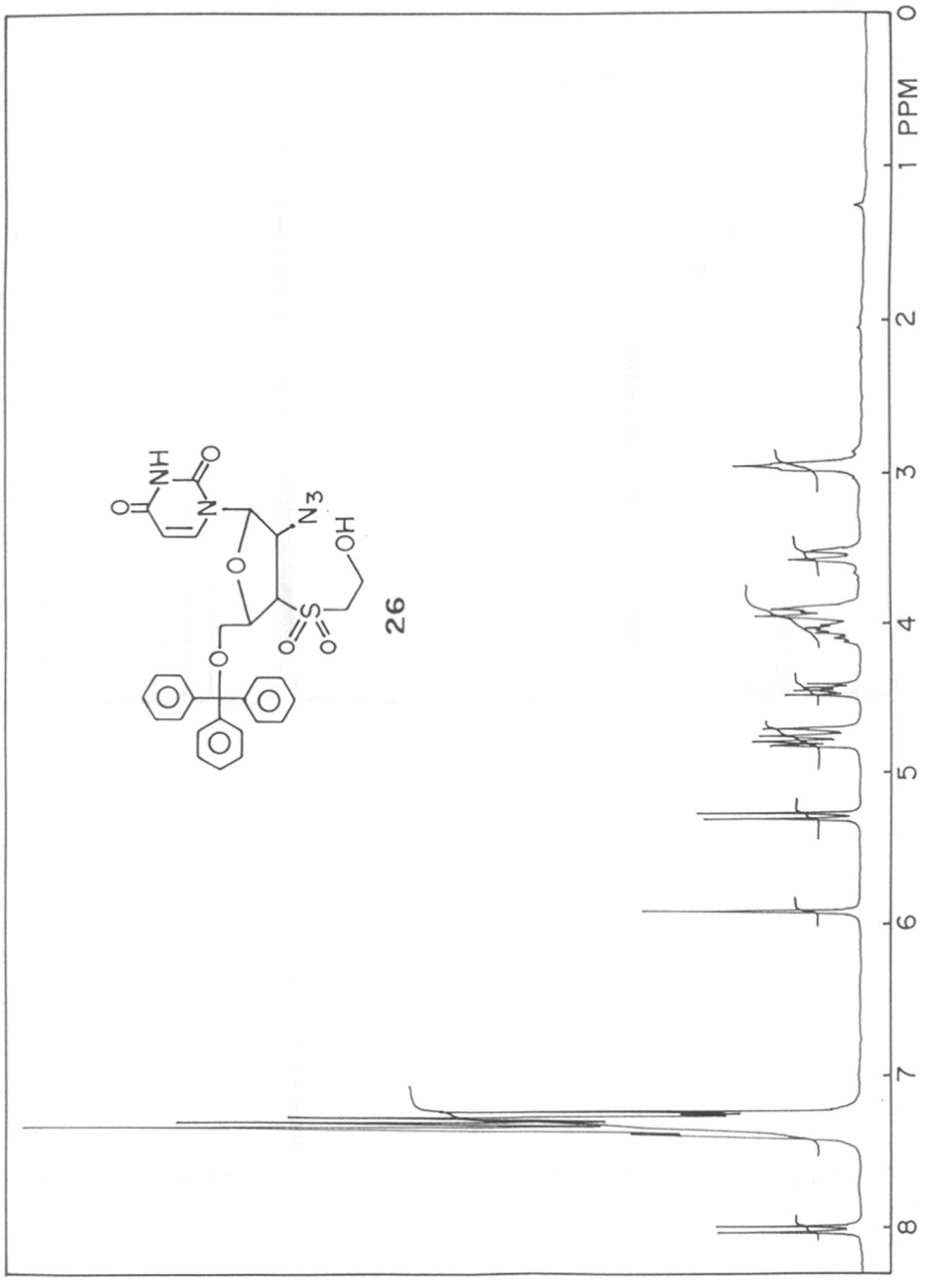

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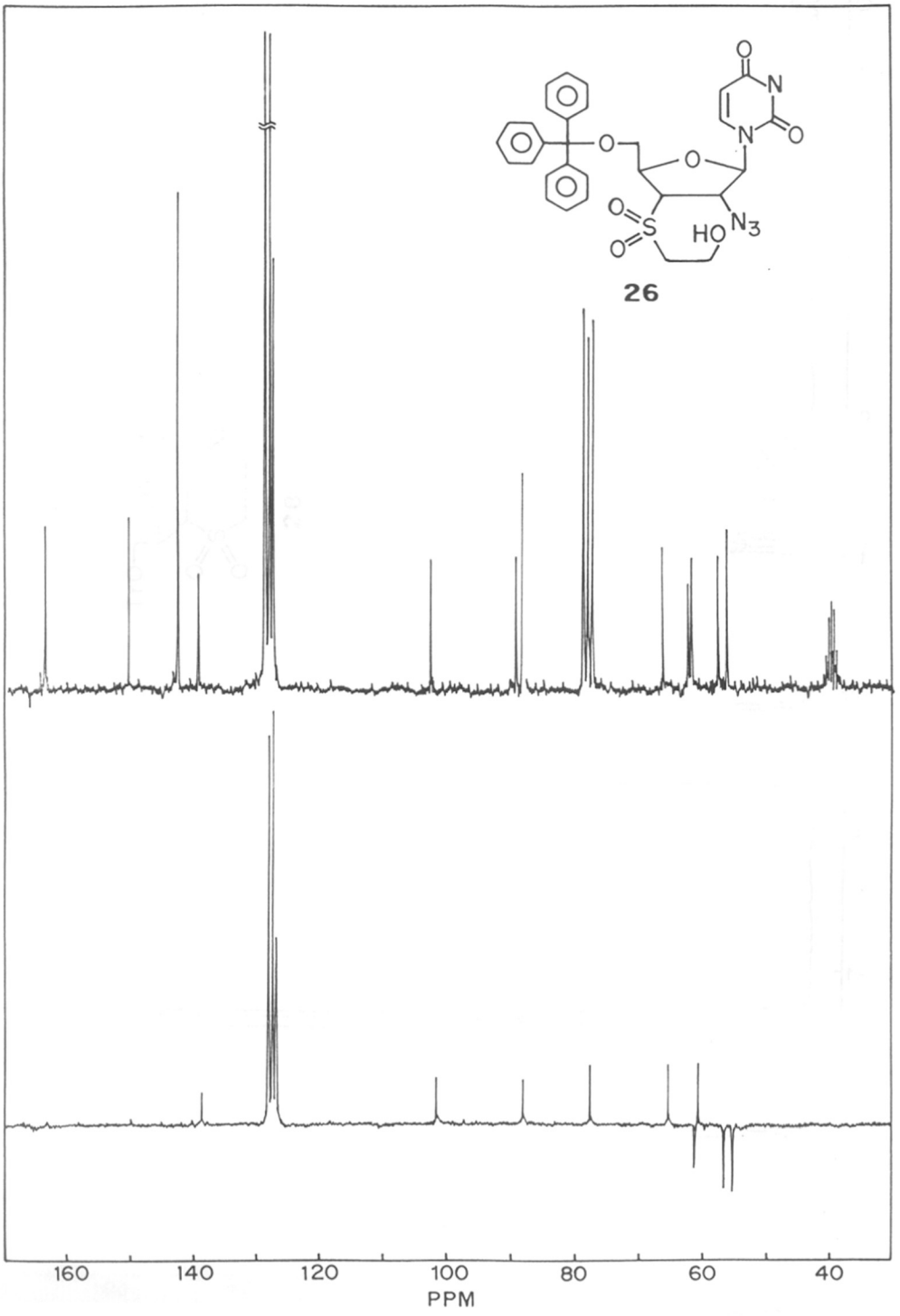

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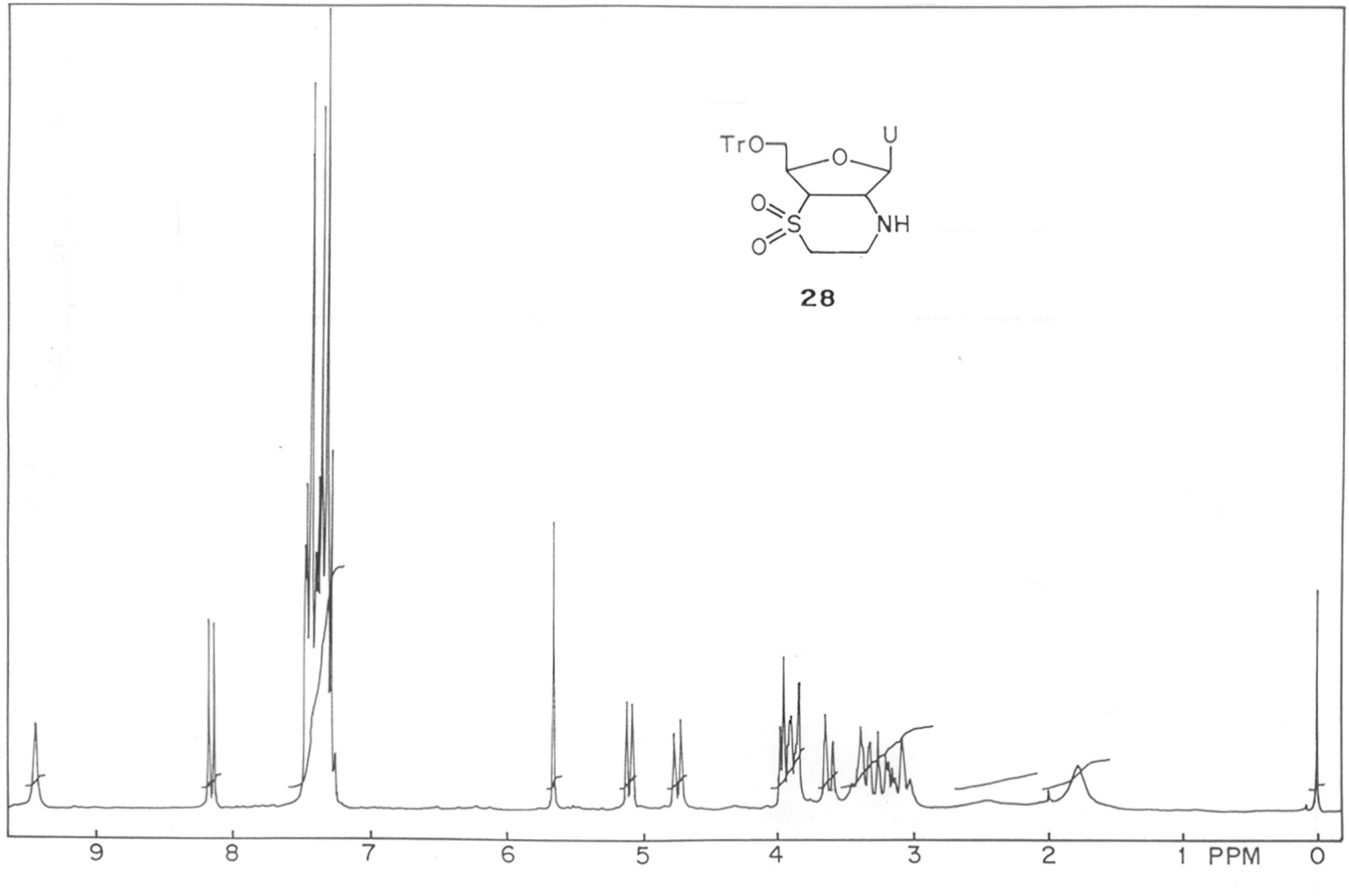

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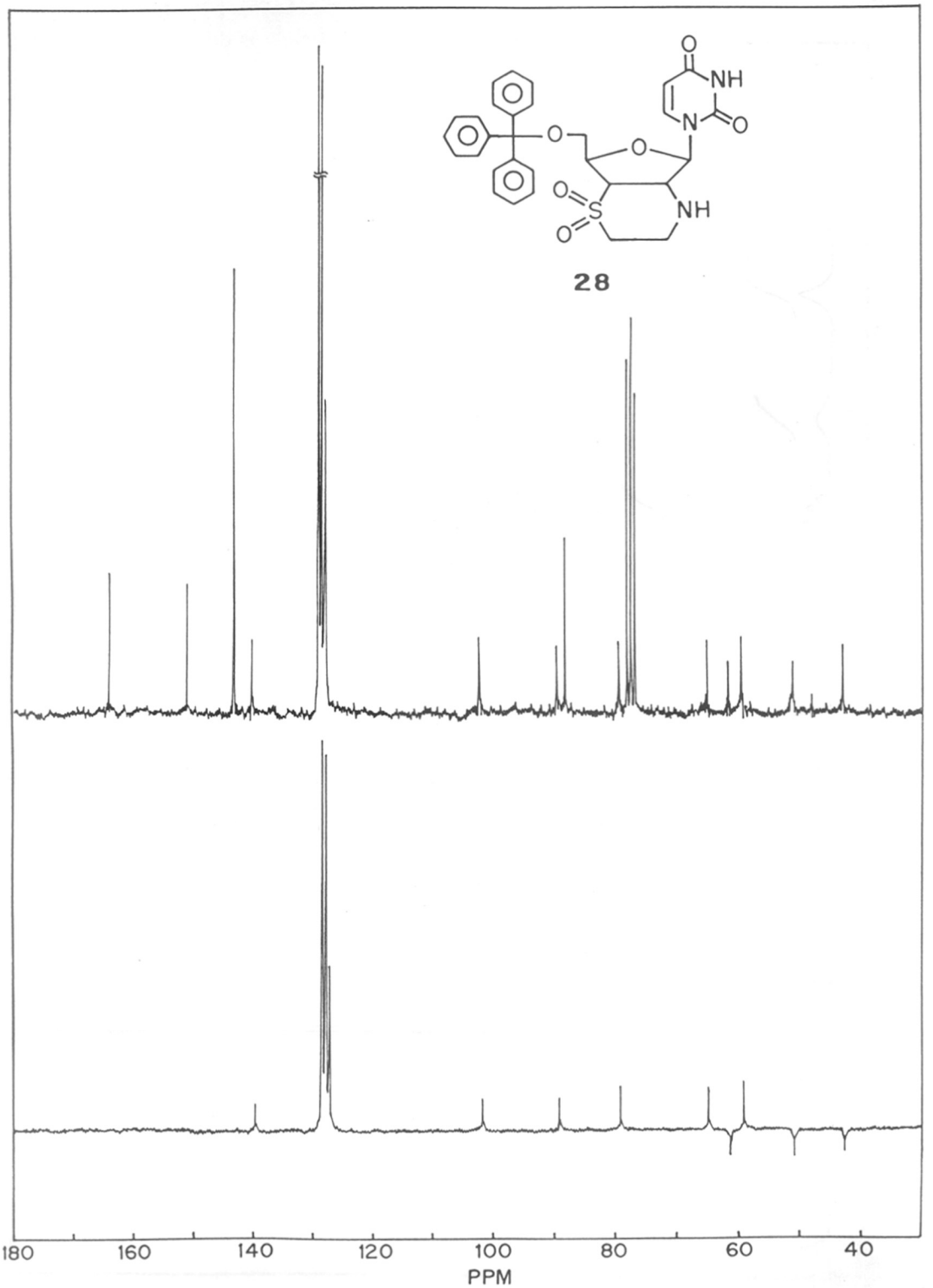
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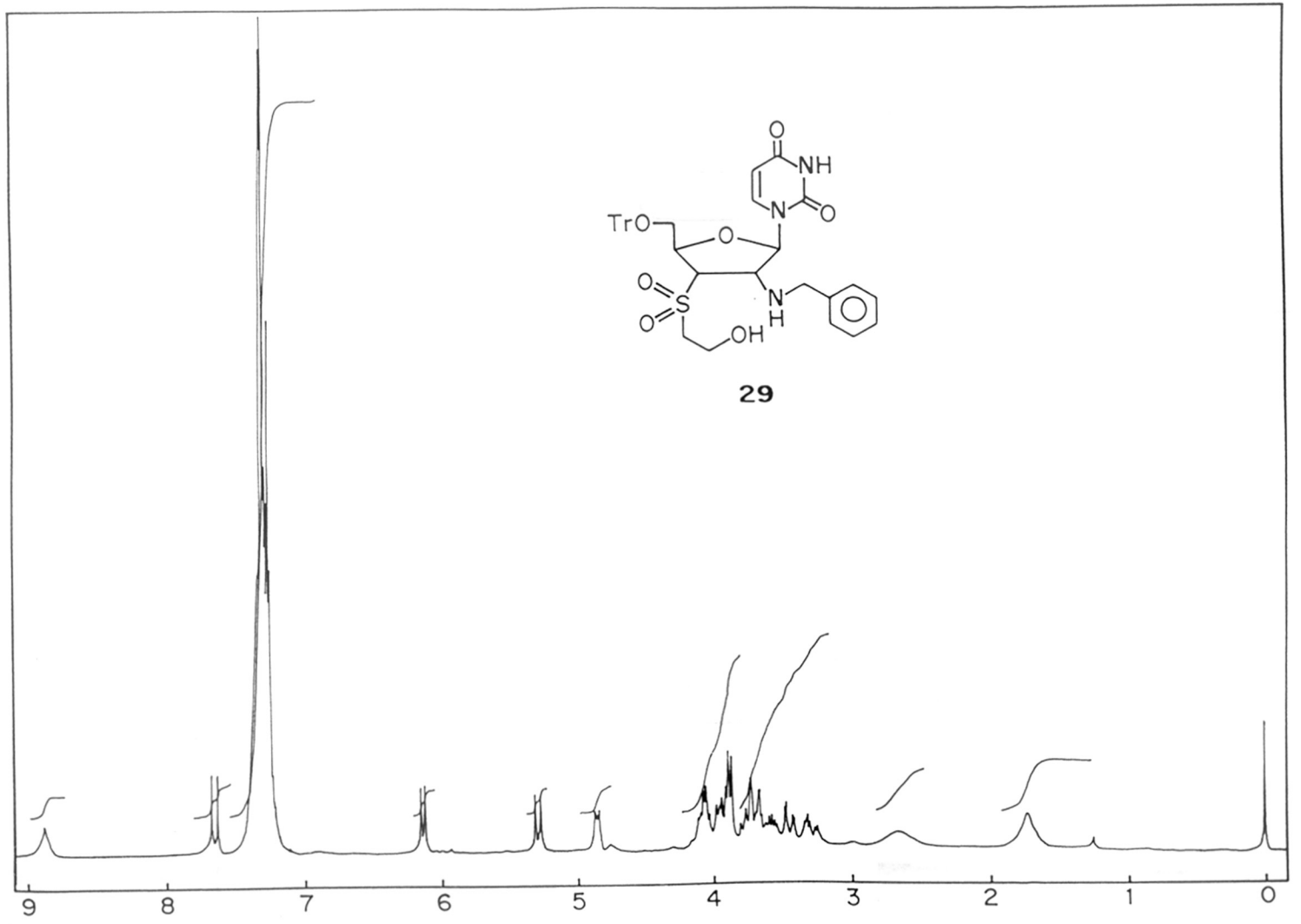

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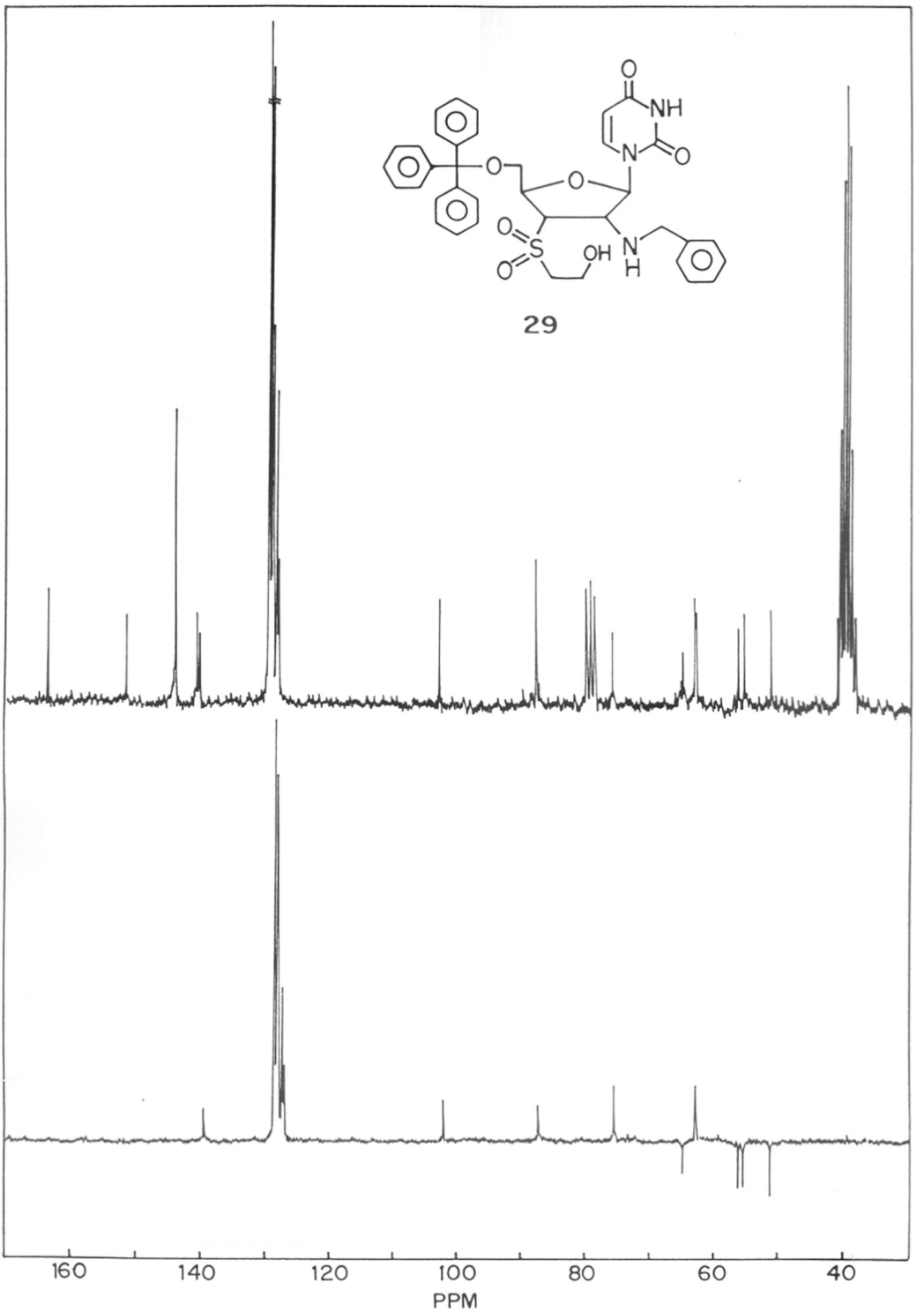

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