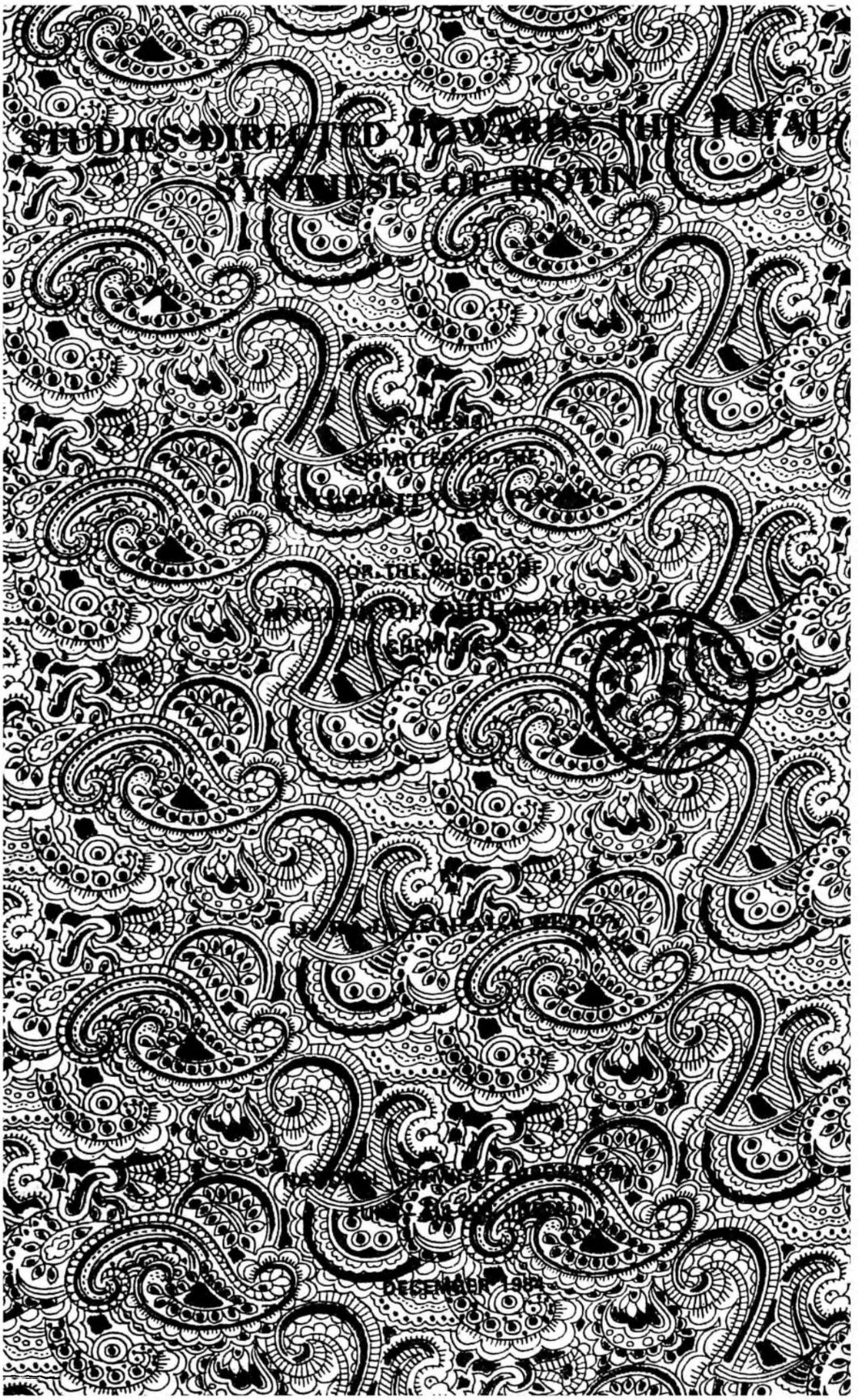


Certified that the work incorporated in the thesis "STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF BIOTIN" submitted by Mr. D. Rajagopala Reddy was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(A.V. RAMA RAO)
Supervisor

PREFACE

This work deals with the development of methodologies for the synthesis of a very important biologically active molecule BIOTIN. Apart from the key role played by biotin in biochemical mechanisms, its emerging importance in commerce, in particular in the areas of animal health and nutrition, cannot be overemphasized. Hence it was thought the study of a practical synthesis of BIOTIN from readily available starting materials would be more than an essay in development of methodology. This will also lead to a synthetic route amenable for possible scale-up and practice. In this context the choice of starting materials was limited to cis-bute-2-ne-1,4-diol, a readily available commercial intermediate for the preparation of racemic BIOTIN and α-D-glucose and L-cystein, again readily available and comparatively cheaper naturally occurring substrates, for the synthesis of optically active BIOTIN.

The account of the investigations presented would hopefully show, that a practical synthesis of this key biological molecule is possible from the above mentioned starting materials. The methodology employed in the elaboration of BIOTIN stereochemistry and structure is believed to be at least one of the more feasible, if not necessarily the best that can be thought of. It is also hoped that this work will at least invite more attention to the practical aspects of starting the synthesis from the materials mentioned.

In the reviews and discussions presented in the work, always due credit and references are given to other authors wherever warranted. If, by chance, any information is taken for granted and no accreditation is made, it is requested to view the same as completely unintentional.

I am deeply indebted to my research guide, Dr.A.V. RAMA RAO, Dy. Director & Head, Division of Organic Chemistry, National Chemical Laboratory, Poona,who proposed the research problem and Dr. T. Ravindranathan who suggested additional work and supervised my work throughout the course of my Ph.D.

It is my pleasure to thank Dr.S.V. Hiremath who initiated me in laboratory techniques for the first time and for his help which will always be remembered.

I am thankful to Dr.M.K. Gurjar, Shri B.M. Dubash and Shri M.M. Awachat for their help and fruitful discussions.

My thanks are due to all my colleagues and friends in the laboratory for their sincere co-operation.

Assistance from Spectroscopic and Microanalytical sections of this laboratory is gratefully acknowledged.

The financial assistance by a grant from the Science & Technology Cell, Education and Youth Service Department, Maharashtra State, is gratefully acknowledged.

I am also thankful to the Director, National Chemical Laboratory, Poona, for kindly allowing me to submit this work in the form of a thesis.

(D. RAJAGOPALA REDDY)

NCL, POONA 411 008

31st December 1984

GENERAL REMARKS

1. Proton Magnetic Resonance spectra were recorded either on a Varian T-60 Spectrometer or a Bruker WH-90 FT NMR Spectrometer. Unless otherwise stated carbon tetrachloride was used as the solvent and tetramethylsilane as the internal standard.

2. Infra Red spectra were scanned on a Perkin-Elmer Infrared-683 Spectrophotometer with sodium chloride optics.

3. The optical rotations were measured with a Jasco Dip 181 Digital Polarimeter.

4. Mass spectra were recorded on a CEC-21-110B double focussing mass spectrometer operating at 70 eV using a direct inlet system.

5. Melting points and boiling points are uncorrected.

C O N T E N T S

SUMMARY

SUMMARY

CHAPTER 1.0.0

Biotin is one of the B-complex group of vitamins. Recent recognition of its importance in food and nutrition has attracted the attention of many synthetic organic chemists and has culminated in several elegant syntheses of this vital molecule in the last 10 years. These syntheses are reviewed in brief in this chapter.

CHAPTER 2.0.0

This chapter deals with the synthesis of (±)biotin from cheap and readily available cis-butene-1,4-diol via the intermediate thienoimidazolidone (10), and also describes a new methodology for the conversion of vicinal diamines to N-substituted imidazolidones as shown in Chart-1. Cis-But-2-ene 1,4-diol (1) was converted to the dioxepin (2) which was subsequently transformed into cis-diamine (4) in four steps (Chart-1). The diurethane (5) obtained from (4) on heating with benzylbromide in presence of sodium hydride in dry benzene furnished the imidazolidone (9). The diurethane was also prepared by another route via the epoxide (6). The compound (9) was converted into the desired sulfide (10) by sequential acid hydrolysis, methanesulfonylation and finally treatment with sodium sulfide in ethanol.

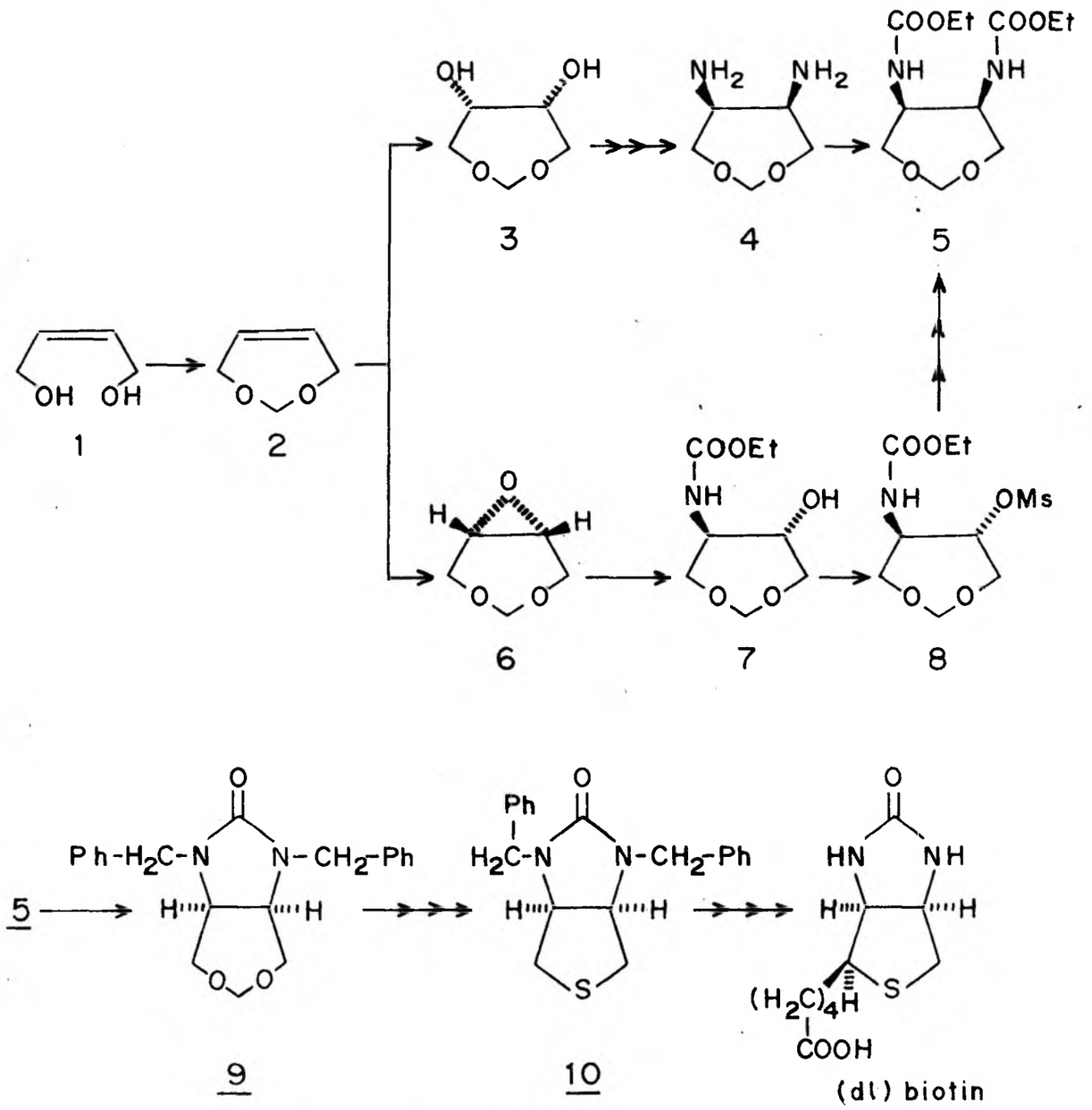


CHART – 1

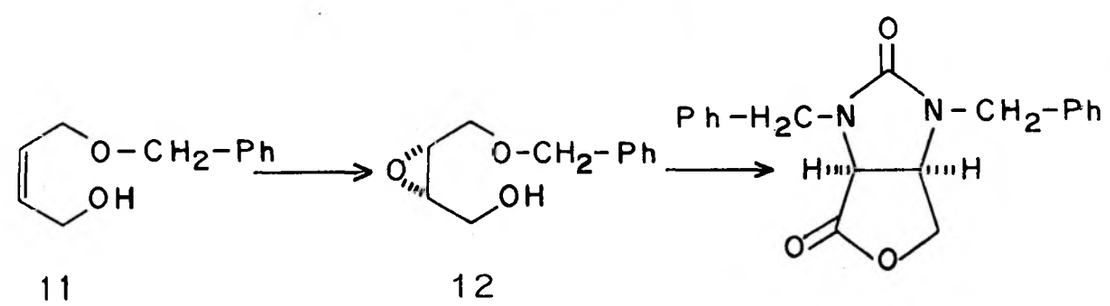


CHART – 2

As the conversion of (10) into (±)biotin was earlier reported by Bory et al.[1] this synthesis is in effect constituted a total synthesis of (±)biotin.

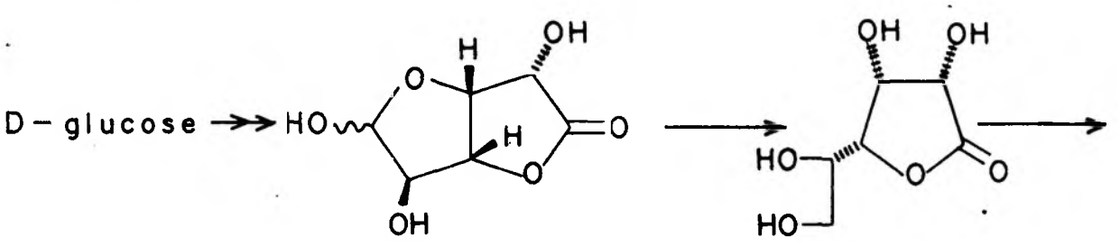
This chapter also discusses some of our efforts towards shorter and alternative synthesis of (10) and also an optically active lactone (13) from an optically active epoxide (12) obtained by Sharpless epoxidation[2] of the butenediol monobenzyl ether (11). (Chart-2).

CHAPTER 3.0.0

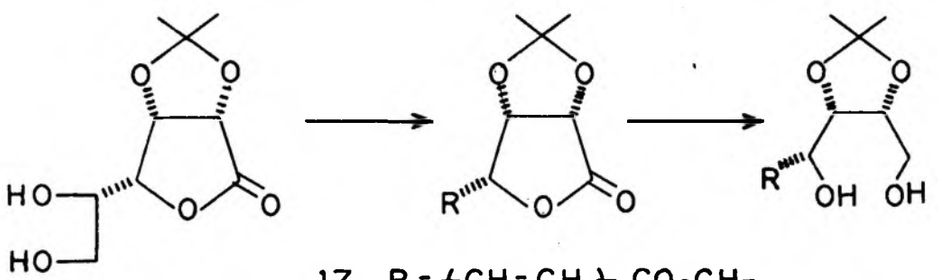
This chapter describes the synthesis of (+)biotin by a simple and straightforward method, starting from an inexpensive and easily accessible chiral synthon, viz. D-glucose via L-gulono-1,4-lactone (15), where C-2/5 D-glucose become C-6,2*,3*,4*,5 of biotin via the intermediate diol (19) (Chart-3).

Commercially available D-glucuronolactone on hydrogenation gave L-gulono-1,4-lactone (15). This was converted to 2,3-O-isopropylidene derivative (16). Periodate oxidation of (16) followed by treatment with 3-carbomethoxypropen-(2)-ylidene (1) triphenylphosphorane afforded the unsaturated lactone (17). This on hydrogenation using borohydride reduced palladium catalyst gave the saturated lactone (18).

Controlled borohydride reduction of (18) in methanol at 0°C gave the required intermediate (19).



14 15

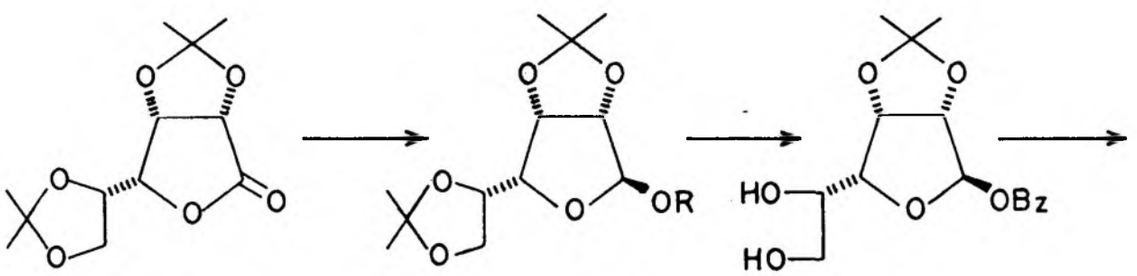


16

17 R = $+CH=CH\frac{}{}_2 CO_2CH_3$

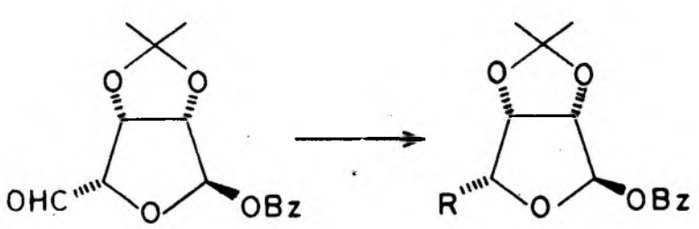
18 R = $+CH_2\frac{}{}_4 CO_2CH_3$

19 R = $+CH_2\frac{}{}_4 CO_2CH_3$



20 21 R = H 23

22 R = Bz



24 25 R = $+CH=CH\frac{}{}_2 CO_2CH_3$

26 R = $+CH_2\frac{}{}_4 CO_2CH_3$

CHART – 3

Since the yield of (17) in the Wittig reaction was poor, the diol (19) was prepared by another route starting from 2,3,5,6-di-O-isopropylidene-1,4-gulonolactone (20). Treatment of (20) with sodium borohydride in methanol 0°C gave the lactol (21) which was converted to the benzoate (22). Selective acid hydrolysis of the benzoate furnished the 5,6-diol (23) which on periodate oxidation gave the aldehyde (24). The Wittig reaction on aldehyde with required phosphorane furnished the unsaturated lactol benzoate (25). Catalytic hydrogenation of (25) afforded the saturated lactol benzoate (26).

Since the conversion of (26) ⟶ (19) ⟶ (+)biotin has been reported[3], the present work constituted the total synthesis of (+)biotin from D-glucose.

This chapter also describes our efforts in the conversion of vitamin C (L-Ascorbic acid) to (+)biotin derivatives.

CHAPTER 4.0.0

This chapter describes the synthesis of potential chiral intermediates of (+)biotin from L-cystine and the studies for their conversion into (+)biotin (as shown in Chart-4).

L(+)cystine (27) was converted to dimethyl ester hydrochloride (28). Neutralisation of the hydrochloride

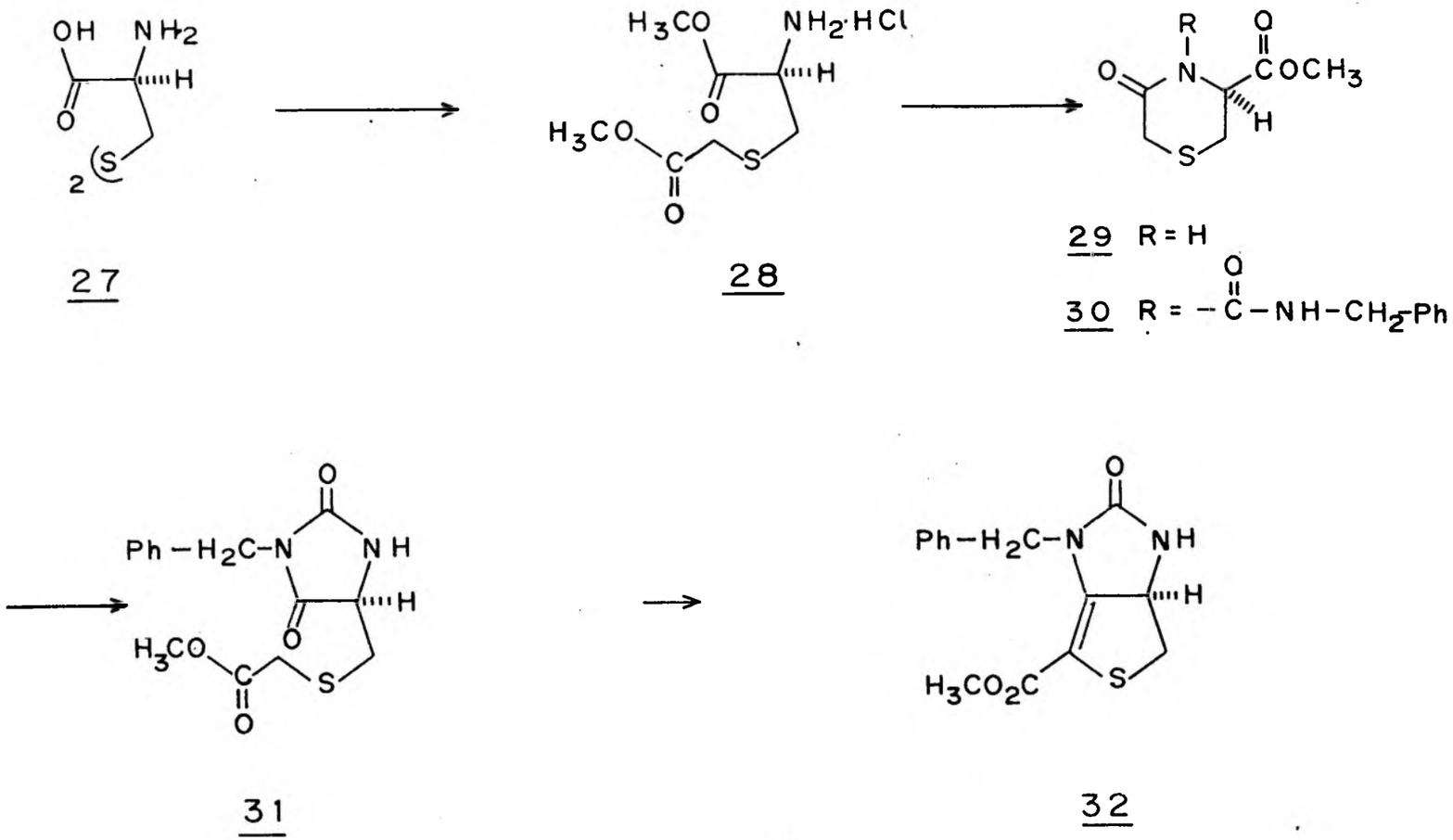

OH
NH2
H
O
S
2
27
H3CO
NH2·HCl
H
O
H3CO
C
S
O
28
R
O
N
COCH3
O
H
S
29 R = H
30 R = -C-NH-CH2-Ph
Ph-H2C-N
NH
H
O
H3CO
C
S
O
31
Ph-H2C-N
NH
H
O
H3CO2C
S
32

CHART - 4

with sodium acetate in methanol followed by refluxing the free amine in dichloro ethane gave the thiolactam (29), which on treatment with benzyl isocyanate afforded the adduct (30). The adduct was rearranged to a potential intermediate (31) without any racemisation by using catalytic amount of triethylamine in dry methanol. Compound (31) would serve as a key asymmetric intermediate for production of (+)biotin by cyclisation. This part deals with some of our unsuccessful attempts at this cyclisation.

REFERENCES

1 S. Lauielle, S. Bory, B. Moreau, M.J. Luche and A. Marquet
J. Am.Chem. Soc., 100, 1558 (1978).

2 K.B. Sharpless
J. Am. Chem. Soc., 102, 5976-5978 (1980).

3 T. Ogawa, T. Kawano and M. Matsui
Carbohydrate Res., 57, C31-C35 (1977).

CHAPTER - 1.0.0

SYNTHESIS OF BIOTIN, RACEMIC AND NATURAL - A REVIEW

Biotin (1), one of the B-complex group of vitamins was first isolated by Kogl[1] from egg yolk. Because of its important biological functions, it is present in every living cell. The richest sources of this vitamin are liver, kidney, yeast, egg yolk, milk and it occurs bound with proteins.

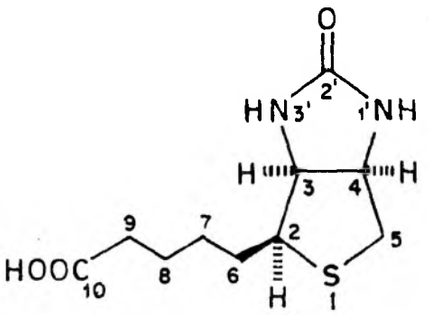
Biotin is also known by anti-eggwhite-injury factor, bios II B, vitamin H etc. Chemically biotin is (+)cis-hexahydro-2-keto-1H-thieno(3,4-d)-imidazole-4-valeric acid.

1.1.0 Structure and absolute configuration

The structure of biotin was established in 1942 by Du-Vigneaud[2] and was confirmed by its total synthesis by Harris and coworkers in 1945[3]. X-ray crystallographic studies of its derivatives revealed its absolute configuration[4] (Chart 1.1.1).

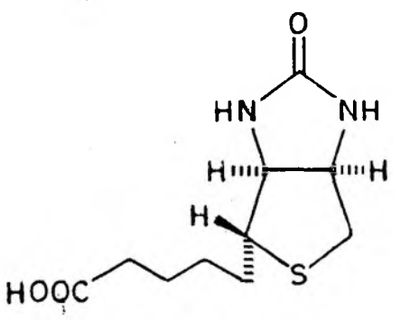
Biotin has three chiral carbon atoms and therefore four diastereomeric racemic forms are possible, of which only (+)biotin (1) is biologically active, while epi-, allo-, and epiallo- biotin 2, 3 and 4 respectively and their enantiomers are biologically inactive. (Chart 1.1.1).

In 1976 two groups redetermined the crystal structure of biotin and the results reported were in agreement with the previous ones, but more accurate[5,6]. According to these data the ureido ring is planar whereas the thiophane ring has an envelope confirmation (5). The valeric acid side chain is not

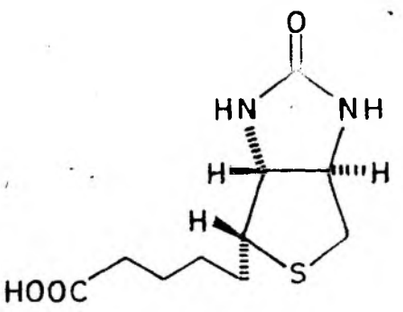


Fine long needles
M.P. 232 - 233°
$[\alpha]_D^{21}$ + 91°
(C=1 in 0·1 NaOH)

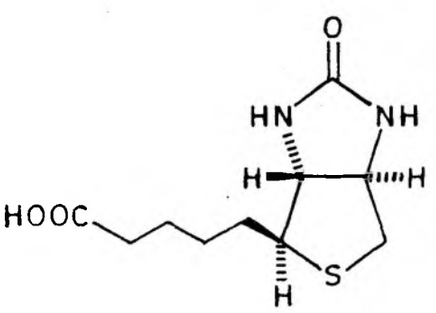
1 d (+) biotin



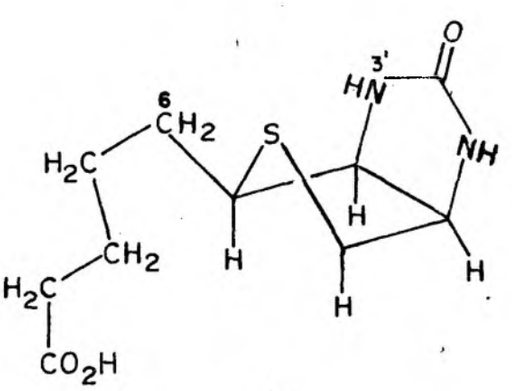
2
epi-biotin



3
allo-biotin



4
epi allo biotin



5

CHART-1·1·1

fully extended but twisted and there is a strong interaction between C_6 and N_3, a feature of importance in the biochemical reactivity of biotin. This envelope confirmation of thiophane ring is also found in solution as shown by NMR studies by Glassel and Marquet[7].

1.2.0 Biochemical function

Before its specific biological role was recognised[8], biotin was studied as a growth factor. The product isolated by Kogl was a yeast nutrient. Its identity with other growth factors was checked and was established finally to be vitamin H Vitamin H was known as anti-eggwhite-injury factor. Rats fed with a diet containing raw eggwhite as a sole source of amino acids, developed severe dermatatis together with hair loss. These symptoms were relieved by an unknown factor from yeast named vitamin H. The toxic properties of raw eggwhite were later shown to be due to avidin, a glycoprotein with an extraordinary affinity for biotin. One molecule of avidin binds with four molecules of biotin, which clearly indicates that avidin has got four binding sites for biotin.

Progress in the chemistry of biotin and its biochemistry have been so rapid that a large volume of information has accumulated in recent years. Recent research has made it more and more evident its importance in food and nutrition. It is an exogeneous essential nutritional factor. It is one of the biocatalysts of reversible metabolic reactions of

carbondioxide transport in micro and macro-organisms, e.g. carboxylation, trans-carboxylation and mono-decarboxylation of polybasic organic acids. Biotin performs its biochemical functions in the form of N-carboxy-biotin, the co-enzyme of a number of co-enzyme-A-dependent carboxylases. A very important one is, for instance, acetyl Co-A carboxylase which carried out the transformation of acetyl Co-A into malonyl Co-A.

$$CH_3CoSCoA \longrightarrow \bar{O}OC - CH_2 - CoSCoA$$

The other biotin enzymes catalyse chemically analogous reactions, namely fixation of carbondioxide at:

i) α - to an thioester

$$CH_3CH_2\text{-}CoSCoA \xrightarrow[\text{carboxylase}]{\text{propionyl CoA}} CH_3\text{-}\underset{\bar{C}O\bar{O}}{\underset{|}{CH}}\text{-}CoSCoA$$

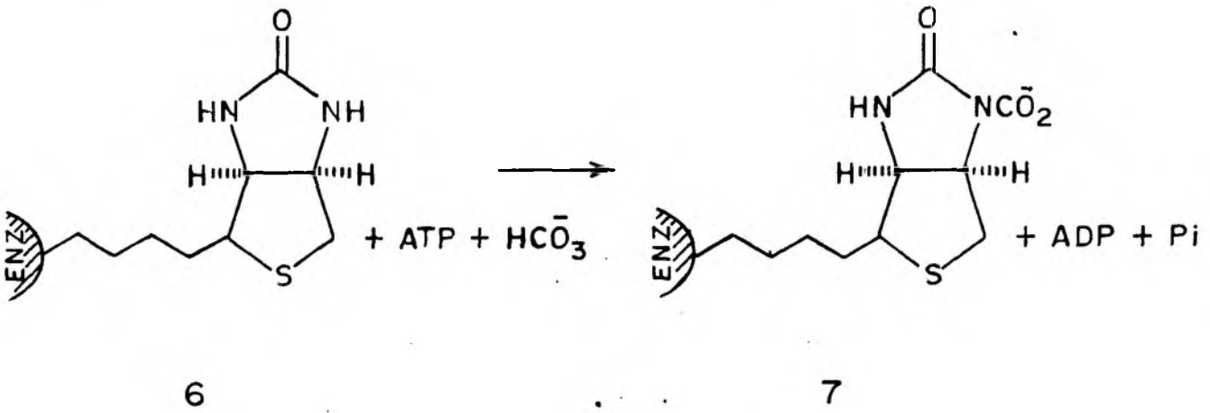
ii) Vinylogous position

$$CH_3\text{-}\underset{CH_3}{\underset{|}{C}}\text{=}CH\text{-}CoSCoA \xrightarrow[\text{Carboxylase}]{\text{B-methylcrotonyl CoA}} \bar{O}OC\text{-}CH_2\text{-}\underset{CH_3}{\underset{|}{C}}\text{=}\overset{H}{\overset{|}{C}}CoSCoA$$

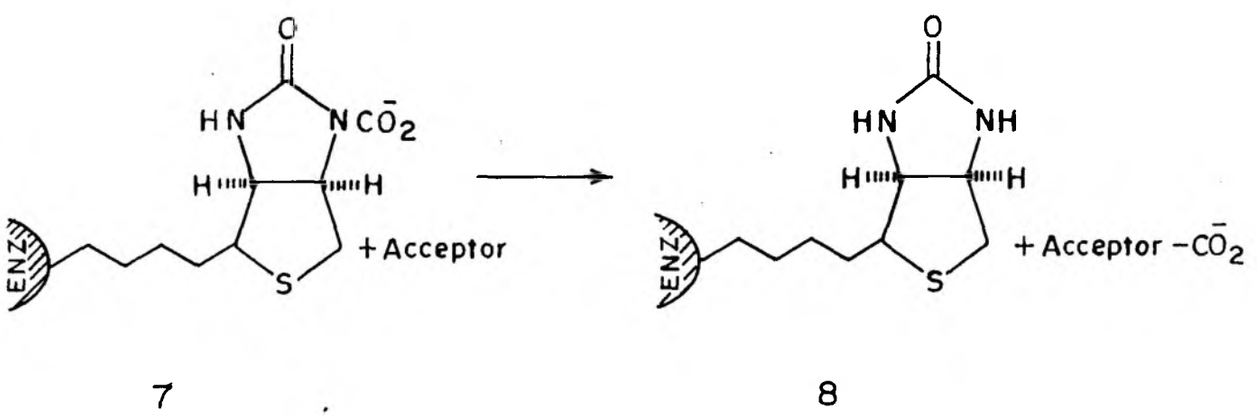
iii) α - to ketone

$$CH_3\text{-}Co\text{-}C\bar{O}\bar{O} \xrightarrow[\text{carboxylase}]{\text{pyruvate}} \bar{O}OC\text{-}CH_2\text{-}CO\text{-}C\bar{O}\bar{O}$$

Although the details of biotin catalysis are not known, the overall process involves two successive half reactions.



6 7



7 8

CHART-1·2·1

An initial N-carboxylation of biotin was first elucidated in 1959 by Lynen and his group[9]. They identified the 1-nitrogen as the site of carbondioxide fixation by isolation of the unstable N-carboxybiotin as a methyl ester. The necessary co-factor for this reaction is adenosinetriphosphate bicarbonate and a divalent Mg^{++} or Mn^{++}. The above N-carboxybiotin is the starting substrate for a subsequent trans carboxylation reaction. These two half reactions occur at different sites and even on different subunits of the enzyme. Biotin is covalently linked to the enzymes through the amino group of lysine. The length of the linkage (Valeric acid chain of biotin and lysine side chain) allows biotin to act as a carboxyl carrier between the two active sites of the enzyme (Chart 1.2.1).

1.3.0 Uses

It is used in pharmaceutical preparations as ointments, tonics, etc. It is also used in poultry feeds, for rapid growth of chicks and for healthy hatching of eggs.

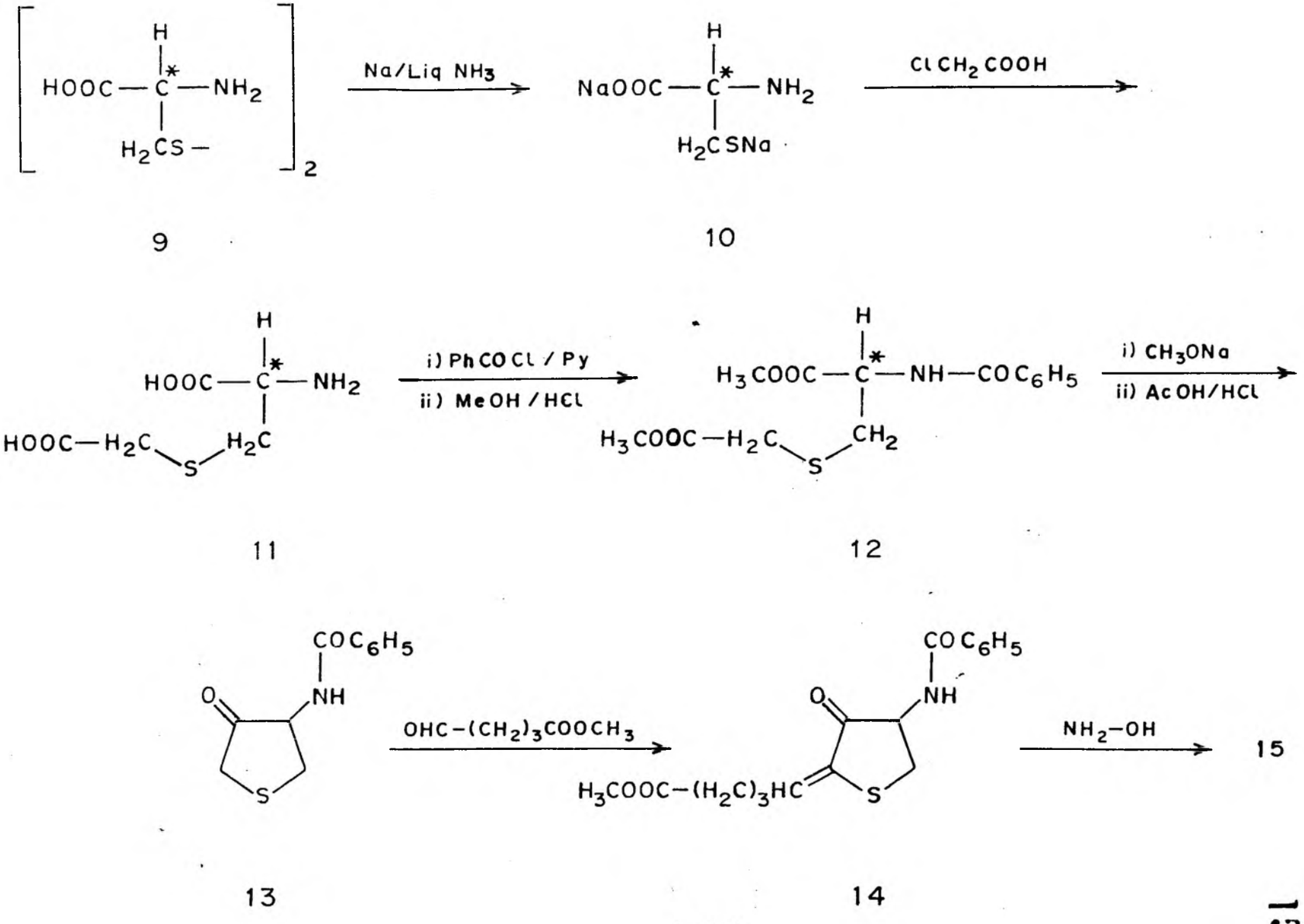
1.4.0 Synthesis of Biotin, racemic and natural - A review

Several syntheses of biotin are reported in literature. The earlier syntheses[10-12] of biotin achieved shortly after its structure elucidation are of historical importance only. They are very long and involve a number of steps without any steric control. An industrial synthesis of biotin was published in 1949 by Hofmann La Roche group. Although it is

long (13 steps) it is very stereoselective and produces only the natural isomer. Then there was a long gap of almost twentyfive years during which no significant progress in biotin synthesis was made. However, the recent recognition of the importance of biotin in food and nutrition coupled with the intricate chemistry involved in the construction of its all cis skeleton has attracted the attention of many organic chemists, and has culminated in numerous elegant syntheses in the last ten years. Some of these syntheses are short and the chemistry involved in them can be exploited for the development of a commercial synthesis for biotin.

In the following pages some of the synthesis of biotin are discussed briefly.

The first successful total synthesis of biotin, by Harris et al[10] (Chart 1.4.1) starts from L-cysteine (9) which was converted through a series of reactions into 4-N-benzoyl-amino-3-oxo-thiophene (13). The aliphatic side chain characteristic of biotin molecule was introduced by aldol reaction of (13) with methyl-α-formyl butyrate to form (14). The oxime (15) of (14) on reduction with Zn/AcOH-Ac_2O gave an isomeric mixture of (16 and 17) which were separated by crystallisation and were catalytically hydrogenated to give a mixture of (18) + (19) and (19) + (20) respectively. These were separated, hydrolysed to the corresponding diamines, which on treatment with phosgene furnished (±)biotin and



9 10

11 12

13 14

CHART-1·4·1

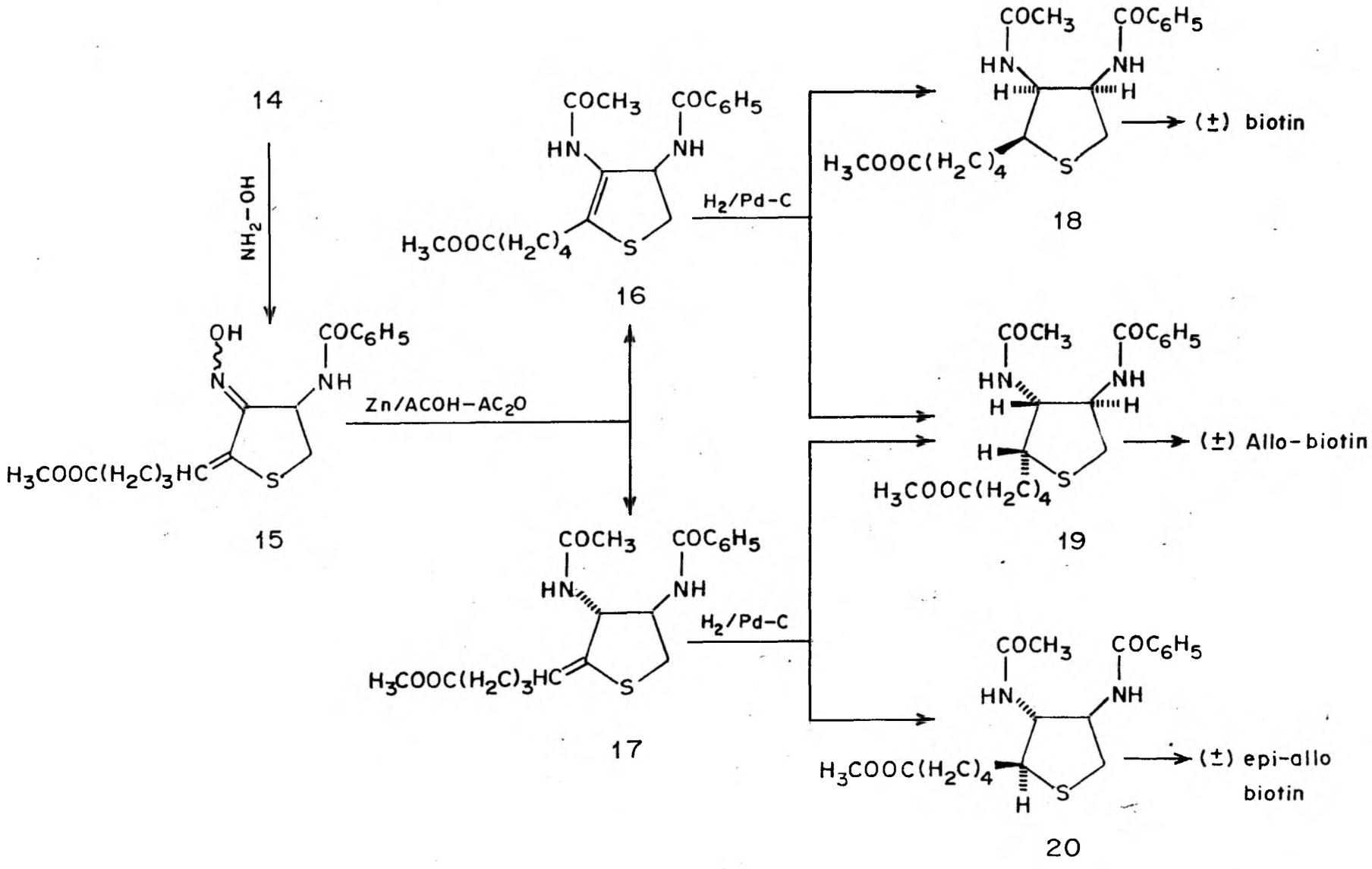


CHART – 1·4·1 (contd)

(±)allobiotin and (±)epi-allobiotin.

Baker et al.[11,12] reported the synthesis of (±)biotin from pimelic acid. Pimelic acid (21) was converted to a mixture of isomeric thiophane tricarboxylic acids as shown (Chart 1.4.2) in (25). The trans-isomer was taken for further reactions, which include esterification to (26), selective hydrolysis to the diester mono-acid (27). The acid chloride from (27) was converted to the azide (28), which furnished the isocyanate upon Curtius reaction. Treatment of isocyanate with aniline then gave the tri-anilide (29). The cyclic anilide (30) was obtained with inversion of trans configuration from (29) by the action of acetic anhydride in presence of catalytic amount of sodium acetate. The opening of the cyclic anilide (30) to give the cis-hydrazide (31) was done by the action of hydrazine hydrate. The compound (31) on Curtius rearrangement via azide (32) was converted to (33) which then produced (±)biotin in two simple steps.

Goldberg et al.[13] succeeded in the synthesis of biotin in a stereospecific manner starting from fumaric acid (Chart 1.4.3). This has become an industrial synthesis of (±)biotin. The key intermediate in this synthesis is the imidazolidone cis-dicarboxylic acid (37) obtained from fumaric acid (34) via the mesodibromide (35). Further the thiophane ring has built upon the imidazolidone ring through

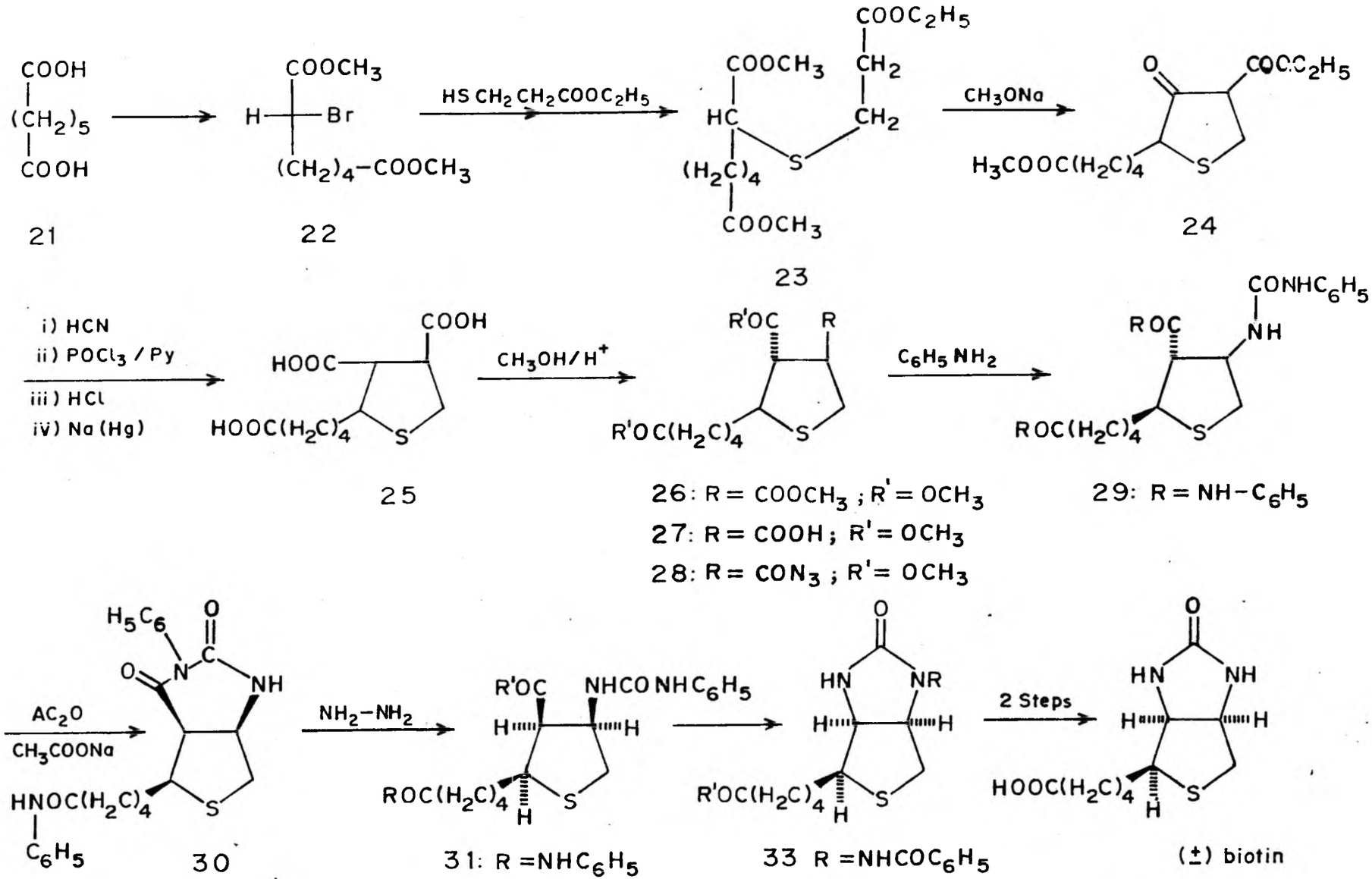
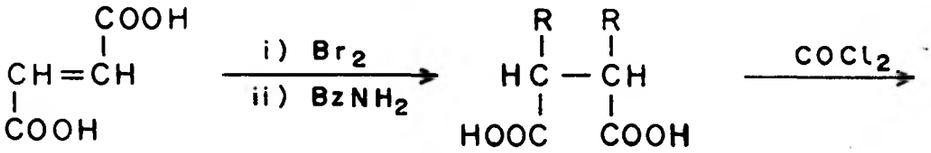

COOH
(CH2)5
COOH
21
COOCH3
H
Br
(CH2)4–COOCH3
22
HS CH2 CH2 COOC2H5
COOC2H5
COOCH3
CH2
HC
CH2
(H2C)4
S
COOCH3
23
CH3ONa
O
COOC2H5
H3COOC(H2C)4
S
24
i) HCN
ii) POCl3 / Py
iii) HCl
iv) Na (Hg)
COOH
HOOC
HOOC(H2C)4
S
25
CH3OH/H+
R'OC
R
R'O(H2C)4
S
26: R = COOCH3 ; R' = OCH3
27: R = COOH; R' = OCH3
28: R = CON3 ; R' = OCH3
C6H5NH2
CONHC6H5
ROC
NH
ROC(H2C)4
S
29: R = NH–C6H5
AC2O
CH3COONa
H5C6
O
N
C
NH
HNOC(H2C)4
C6H5
S
30
NH2–NH2
R'OC
NHCONHC6H5
ROC(H2C)4
S
31: R = NHC6H5
R' = NHNH2
32: R = NH–C6H5
R' = N3
HN
NR
R'O(H2C)4
S
33 R = NHCOC6H5
R' = NHC6H5
2 Steps
HN
NH
HOOC(H2C)4
S
(±) biotin

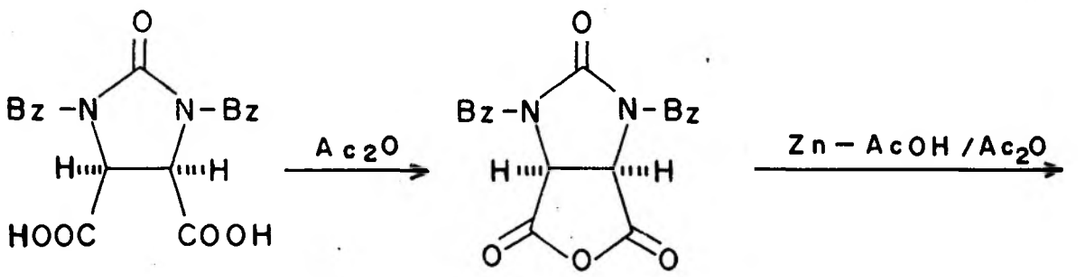
CHART – 1·4·2



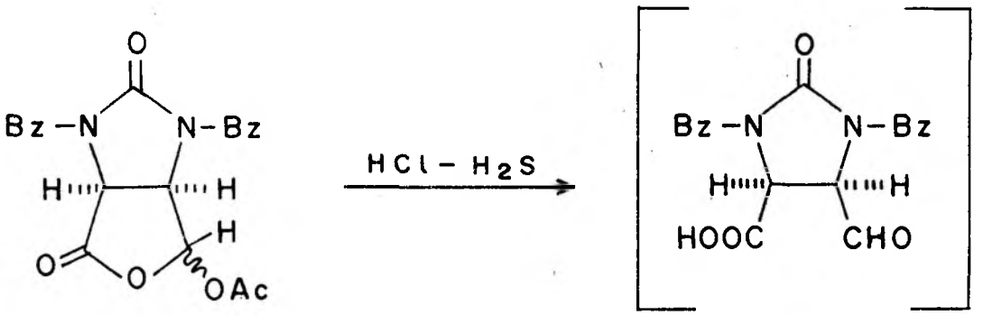
34

35 R = Br

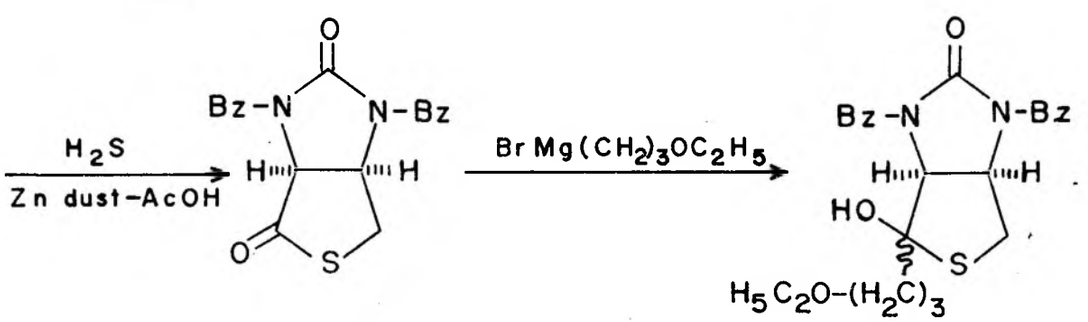
36 R = NHBz



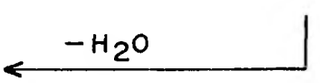
37 38



39 40

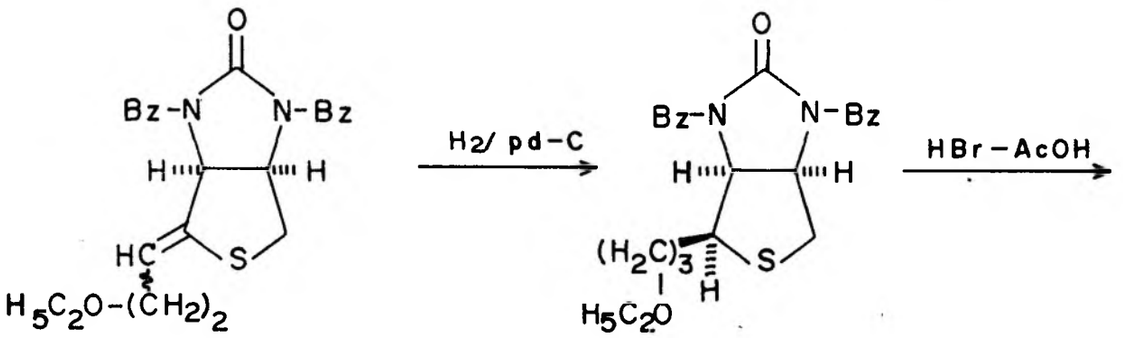


41 42

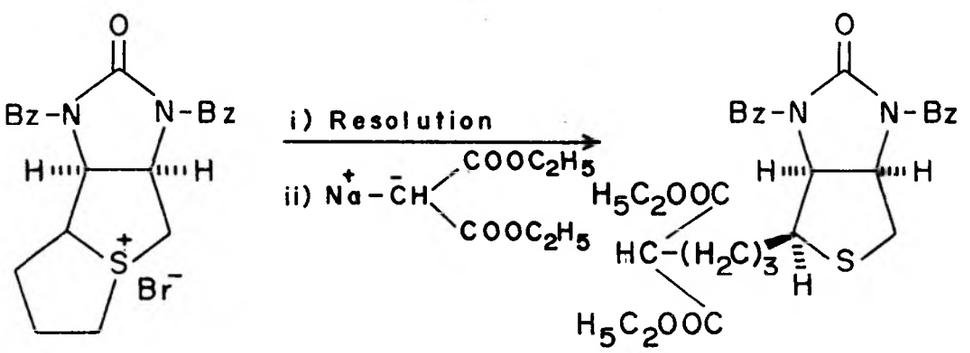


43

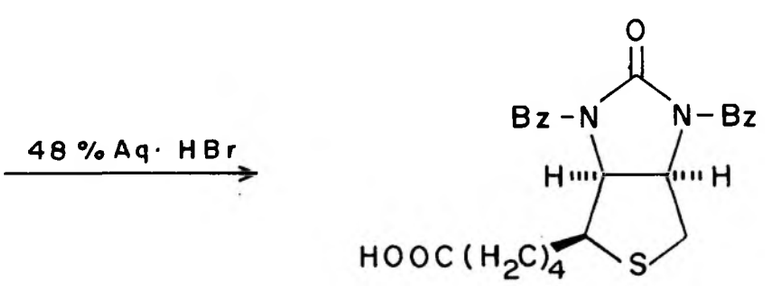
CHART—1·4·3



43 44



45 46



(+) biotin

CHART-1·4·3 (contd.)

a series of reactions on its anhydride (38) to obtain (41).

The aliphatic side chain was introduced by reacting (41) with 3-ethoxypropyl magnesium bromide. The resulting alcohol was dehydrated and hydrogenated to give (44) as a major isomer. Treatment with HBr in AcOH gave the tricyclic salt (45). Resolution of optical isomers was done at this stage with silver salt of d-camphor sulphonic acid. Further the right enantiomer was treated with sodio-malonic ester and the resulting compound (46) was boiled with 48% HBr. This resulted in the hydrolysis of the ester groups, mono-decarboxylation and elimination of the protective benzyl groups, thus affording (+)biotin.

Recently Zimmermann[14] and coworkers improved the Goldberg's method by modifying the key reaction in the formation of thiolactone (41) by a new method using potassium thioacetate in high boiling solvents. With this modification the synthesis became simpler and higher yielding.

In the synthesis of (±)biotin by Confalone *et al.*[15] (Chart 4) the starting material keto-thiophane (47) was converted into its oxime (48) and then transformed into an eight-membered carboxylactam (52) by aromatisation, hydrolysis of ester and lactamisation in refluxing xylene. The carboxylactam (52) was converted to all *cis* thiophane diurethane (56) by sequential reactions with (i) $ClCO_2C_2H_5/Et_3N$, (ii) NaN_3 and

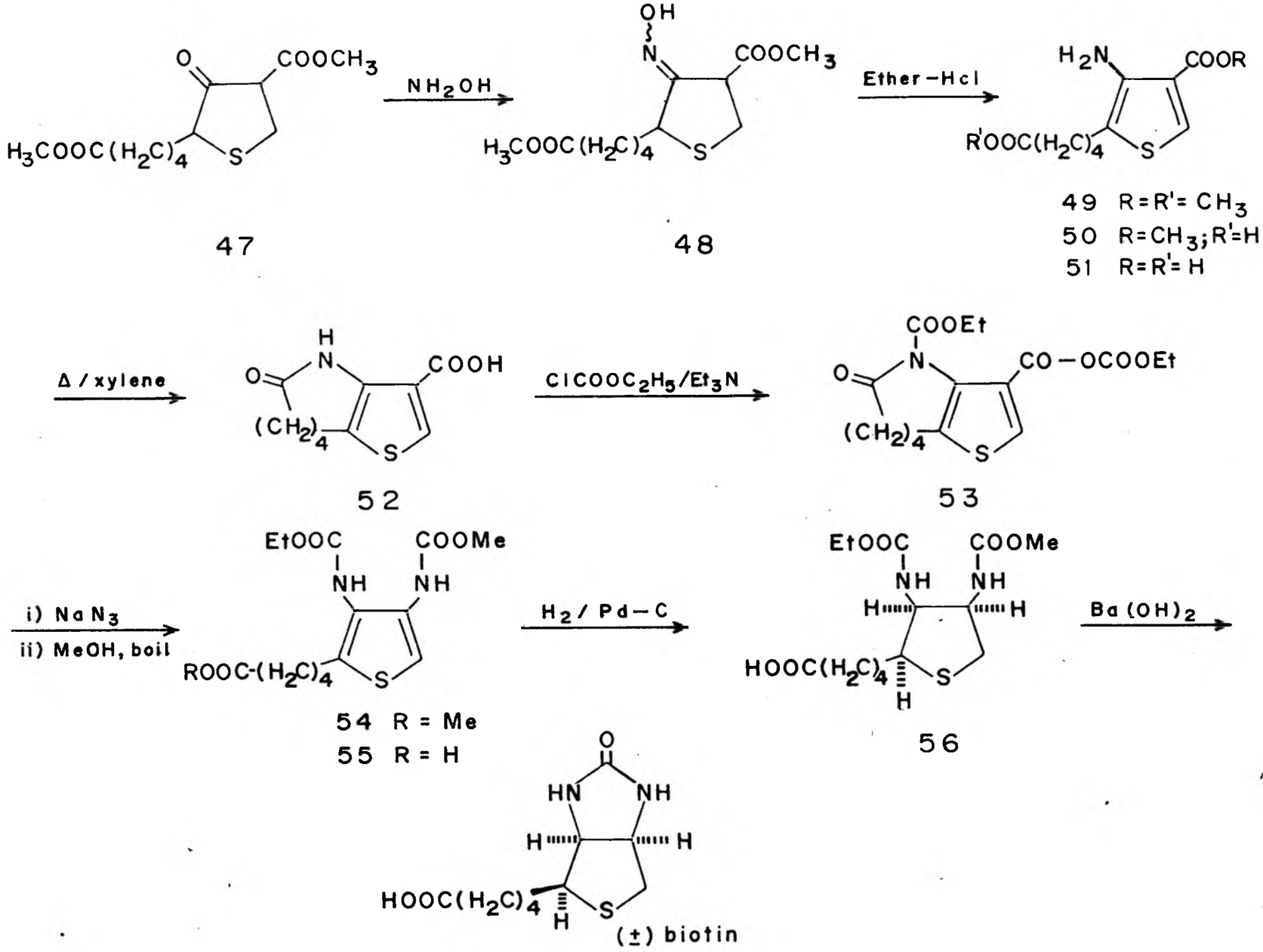

NH2OH
Ether–Hcl
Δ / xylene
ClCOOC2H5/Et3N
i) NaN3
ii) MeOH, boil
H2 / Pd–C
Ba(OH)2
47
48
49 R=R'= CH3
50 R=CH3; R'=H
51 R=R'= H
52
53
54 R = Me
55 R = H
56
(±) biotin

CHART – 1·4·4

(iii) MeOH/△ followed by catalytic hydrogenation at 50°C and 120 atm. for 10 h in acetic acid. The thiophane diurethane (56) was then hydrolysed with barium hydroxide to give (±)biotin.

Marx et al.[16] employed methyl ester of adipic acid semialdehyde (57) which was transformed into di(nitroethyl) sulfidic ester (61) as shown (Chart 1.4.5). This on treatment with phosphorus oxychloride-triethylamine in chloroform gave the intermediate bis-nitrile oxide (62), which then underwent spontaneous (3 + 2) intramolecular cycloaddition to furnish the thienofuroxane (63). When 63 was reduced with Zn-Ag couple in presence of trifluoroacetic anhydride in dimethoxy-ethane, an acylated enediamine (64) was obtained as the major product. Hydrogenation of (64) to all cis diamino thiophane derivative, hydrolysis and deacylation gave the diamine (66) which on treatment with phosgene yielded (±)biotin in 4.1% overall yield.

The synthesis of (+)biotin reported by G.F. Field[17] in 1978 (Chart 1.4.6) involved the resolution of an inter-mediate at an early stage in the synthetic sequence. The asymmetry in the resolved intermediate (69) a thioacid, controlled the development of the additional two chiral centres, via the amino alcohol (74) hydroxyimidazolidone (75) and the dehydrated products (76) and (77) through a stereo-controlled hydrogenation in the last step to give (+)biotin.

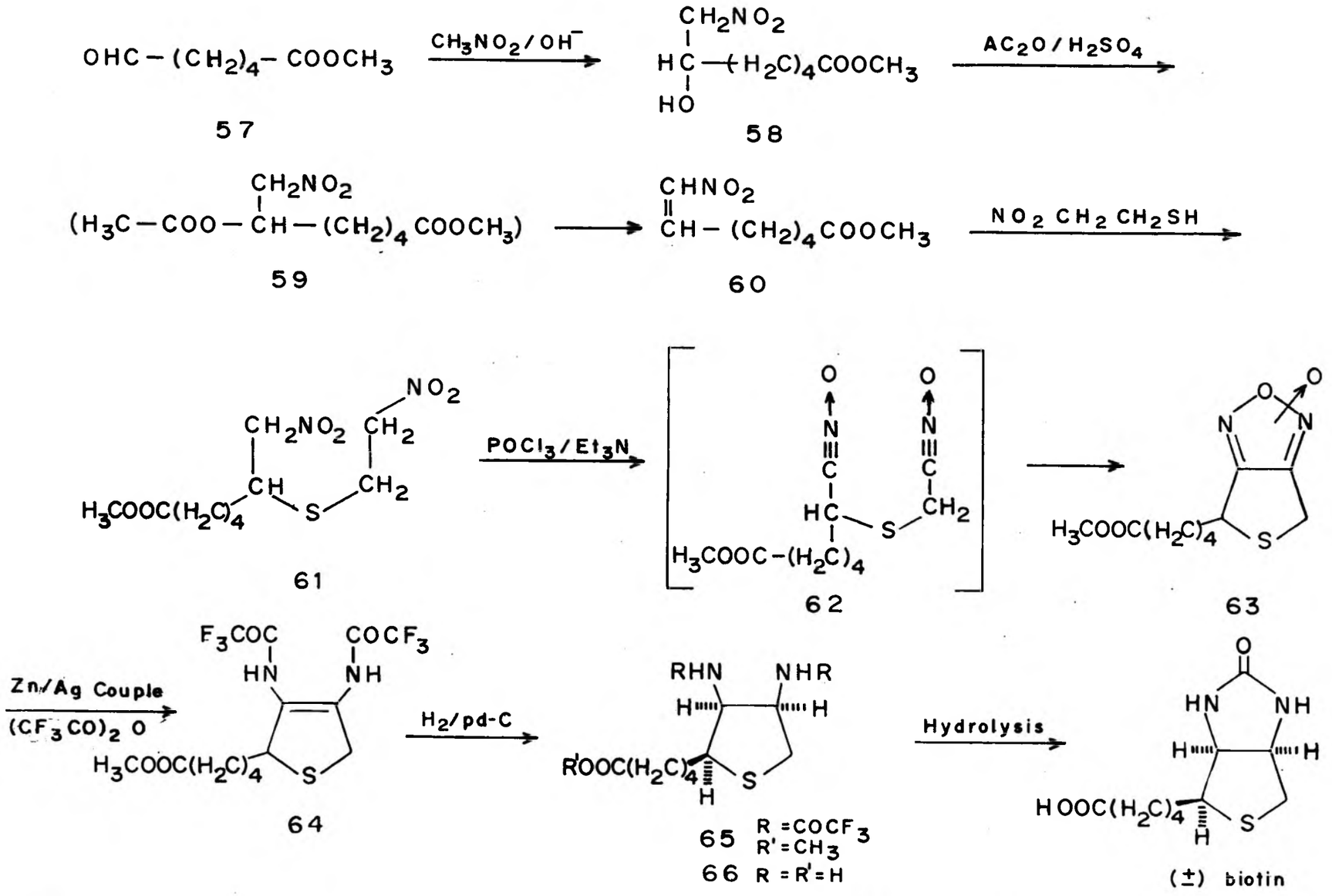

OHC – (CH2)4 – COOCH3
CH3NO2 / OH⁻
CH2NO2
HC
HO
(H2C)4COOCH3
AC2O / H2SO4
57
58
(H3C – COO – CH – (CH2)4 COOCH3)
CHNO2
CH – (CH2)4COOCH3
NO2 CH2 CH2SH
59
60
NO2
CH2NO2
CH2
CH
S
H3COOC(H2C)4
POCl3 / Et3N
O
N
C
HC
CH2
H3COOC – (H2C)4
61
62
63
Zn/Ag Couple
(CF3CO)2 O
F3COC
COCF3
HN
NH
H2/pd-C
RHN
NHR
R'OOC(H2C)4
Hydrolysis
HOOC(H2C)4
64
65 R = COCF3 R' = CH3
66 R = R' = H
(±) biotin

CHART – 1 · 4 · 5

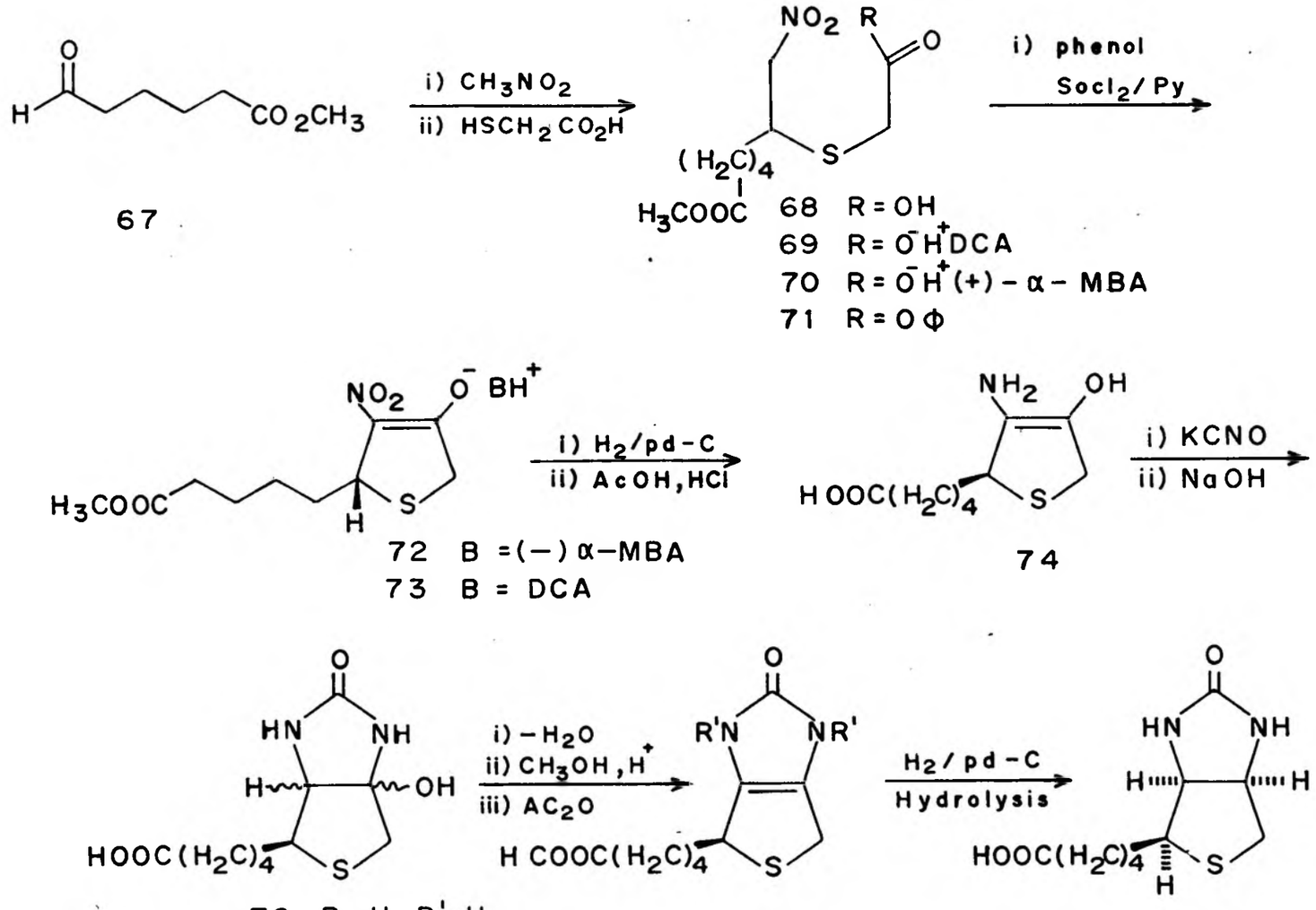
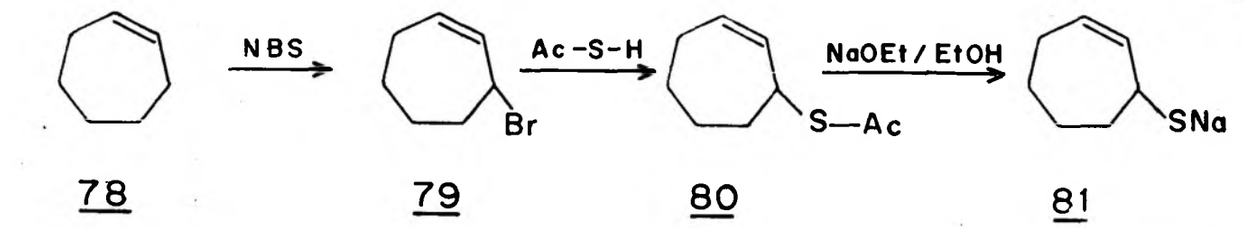

i) CH_3NO_2
ii) $HSCH_2CO_2H$
i) phenol
$SocI_2$/ Py
67
68 R = OH
69 R = O^-H^+DCA
70 R = O^-H^+(+) – α – MBA
71 R = OΦ
i) H_2/pd-C
ii) AcOH, HCl
72 B = (–) α–MBA
73 B = DCA
74
i) KCNO
ii) NaOH
i) $-H_2O$
ii) CH_3OH, H^+
iii) AC_2O
H_2/ pd-C
Hydrolysis
76 R = H; R' = H
77 R = CH_3; R' = $COCH_3$

CHART – 1·4·6

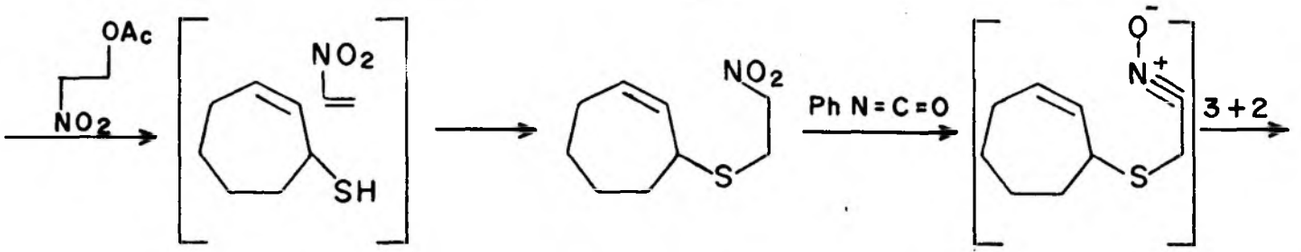
A novel synthesis of (±)biotin was reported by Confalone et al.[18] starting from cycloheptene (78) (Chart 1.4.7). This synthesis was based on intramolecular nitrone-olefin (3+2)cycloaddition to generate the crucial intermediate, an isooxazoline (85). Reduction with LAH followed by oxime formation was effected by conventional reactions and then oxime was allowed to undergo Beckmann transformation to yield eight-membered lactam (90). Hydrolysis of 90 produced the all cis diaminothiophane derivative (91) with the required side chain. Treatment with phosgene gave (±)biotin.

The synthesis by Volkmann[19] was based on adding an ester enolate of specific geometry bearing a masked α-amino functionality to a suitably substituted imine containing the valeric acid side chain of biotin as shown in (Chart 1.4.8). All the required asymmetric centres in biotin were fixed elegantly in this single reaction to give finally the all cis geometry of the biotin skeleton.

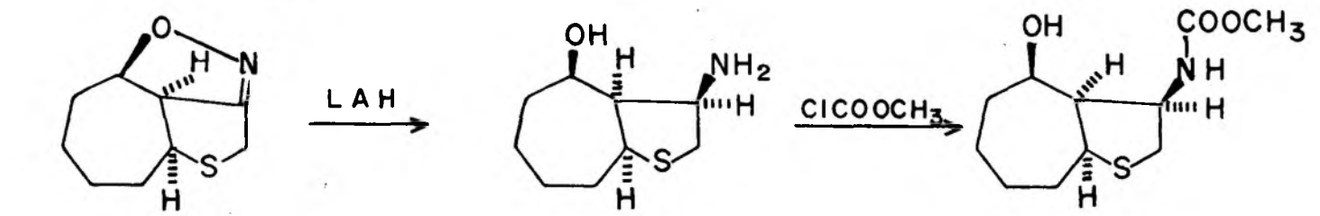
Ethyl 7-oxoheptanoate (92) was subjected to bromination to afford bromoaldehyde (93), which on treatment with sodium sulfide, cyclohexanone and ammonia gave directly the imine (94). 94 was added to ethyl isothiocyanate acetate catalysed by BF_3 to afford the diester (95). The diester (95) was reduced to monoalcohol (96) and then racemic alcohol was resolved as their d-camphor sulfonates. Treatment of the required diastereomer with trifluoroacetic acid gave d-2-thio-



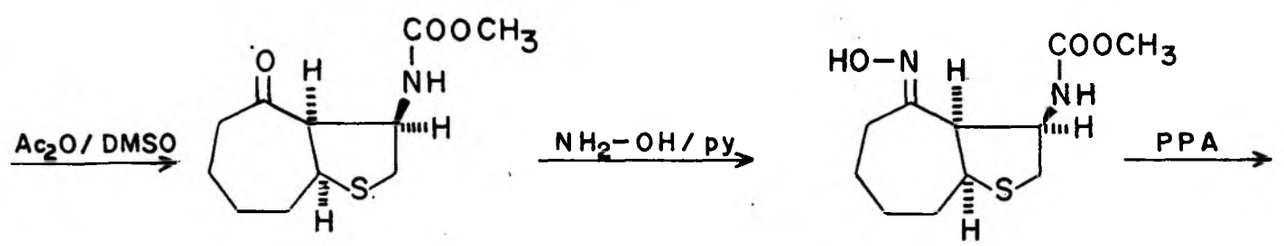
78 79 80 81



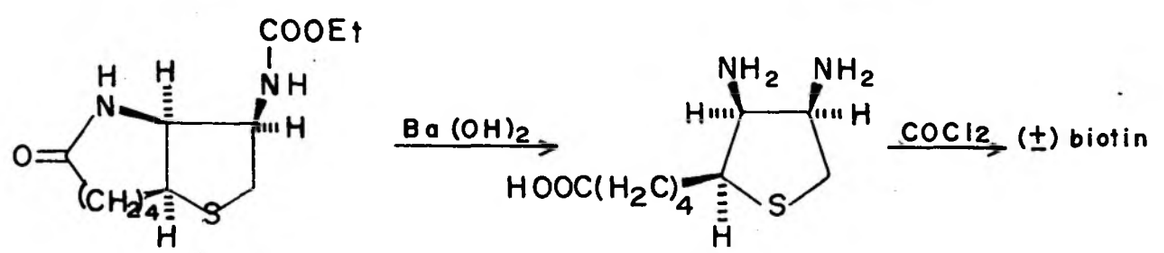
82 83 84



85 86 87



88 89



90 91

CHART-1·4·7

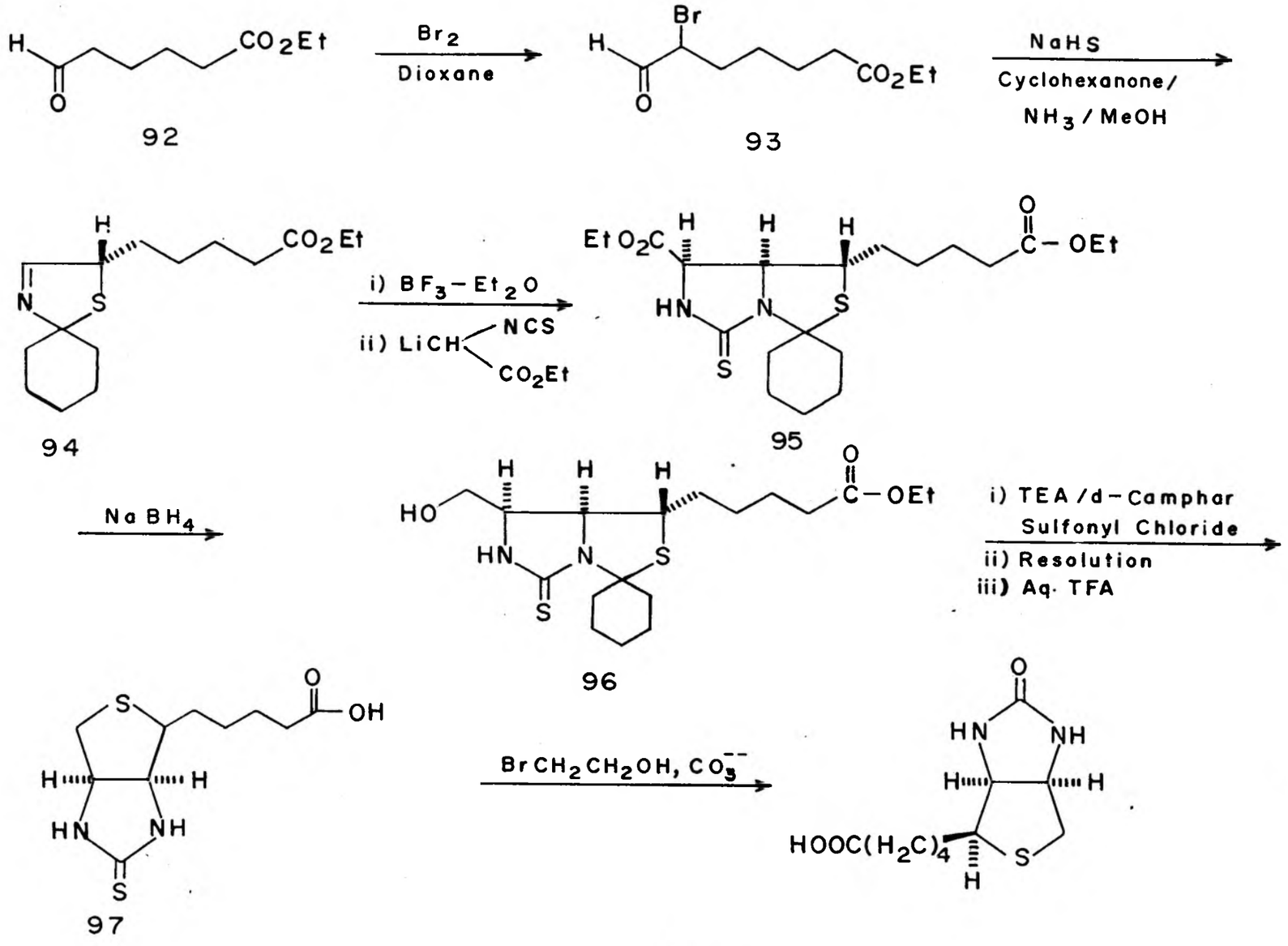

92
Br2
Dioxane
93
NaHS
Cyclohexanone/
NH3 / MeOH
94
i) BF3 – Et2O
ii) LiCH
NCS
CO2Et
95
NaBH4
96
i) TEA /d-Camphar
Sulfonyl Chloride
ii) Resolution
iii) Aq. TFA
97
BrCH2CH2OH, CO3--

CHART –1·4·8

biotin (97) which was then converted into d-biotin with bromoethanol in N-methylpyrrolidinone followed by treatment with sodium carbonate.

The synthesis of (±)biotin by Bory et al.[20,21] (Chart 1.4.9) took advantage of the high selectivity of the alkylation of sulfoxides (103, 104). Dibenzyl-cis-dicarboxyl-imidazolidone (98) was prepared from fumaric acid (34) in three steps, and was esterified and reduced to the diol (101). The mesylate of 101 was treated with sodium sulfide in ethanol to form the key intermediate (102) in 95% yield. Oxidation of this bicyclic compound (102) with sodium metaperiodate gave a mixture of two sulfoxides[21] (103) and (104) in the ratio of 10:90 (endo:exo). Stereoselective alkylation of the cis-sulfoxide (104) via the lithium derivative (105) led to (106). The sulfoxide group in (106) was reduced by $TiCl_3$ and the resulting compound (107) was hydrolysed and debenzylated to give (±)biotin.

Stereospecific synthesis of (±)biotin due to Fliri et al.[22] was based on cycloaddition of chlorosulfonyl-isocyanate on chromene (108) (Chart 1.4.10). Nucleophilic attack of azide ion on (109) followed by Curtius degradation and removal of the azido sulfonyl group by boiling aqueous sodium sulfite gave the imidazolidone (112). By Benkeser reduction of imidazole (112) was transformed into enol ether (113). Treating the compound (113) successively with metachloroperbenzoic acid and aqueous sodiumperiodate resulted in the formation of the keto lactone (114) which was stereo-specifically reduced with sodium borohydride-methanol with

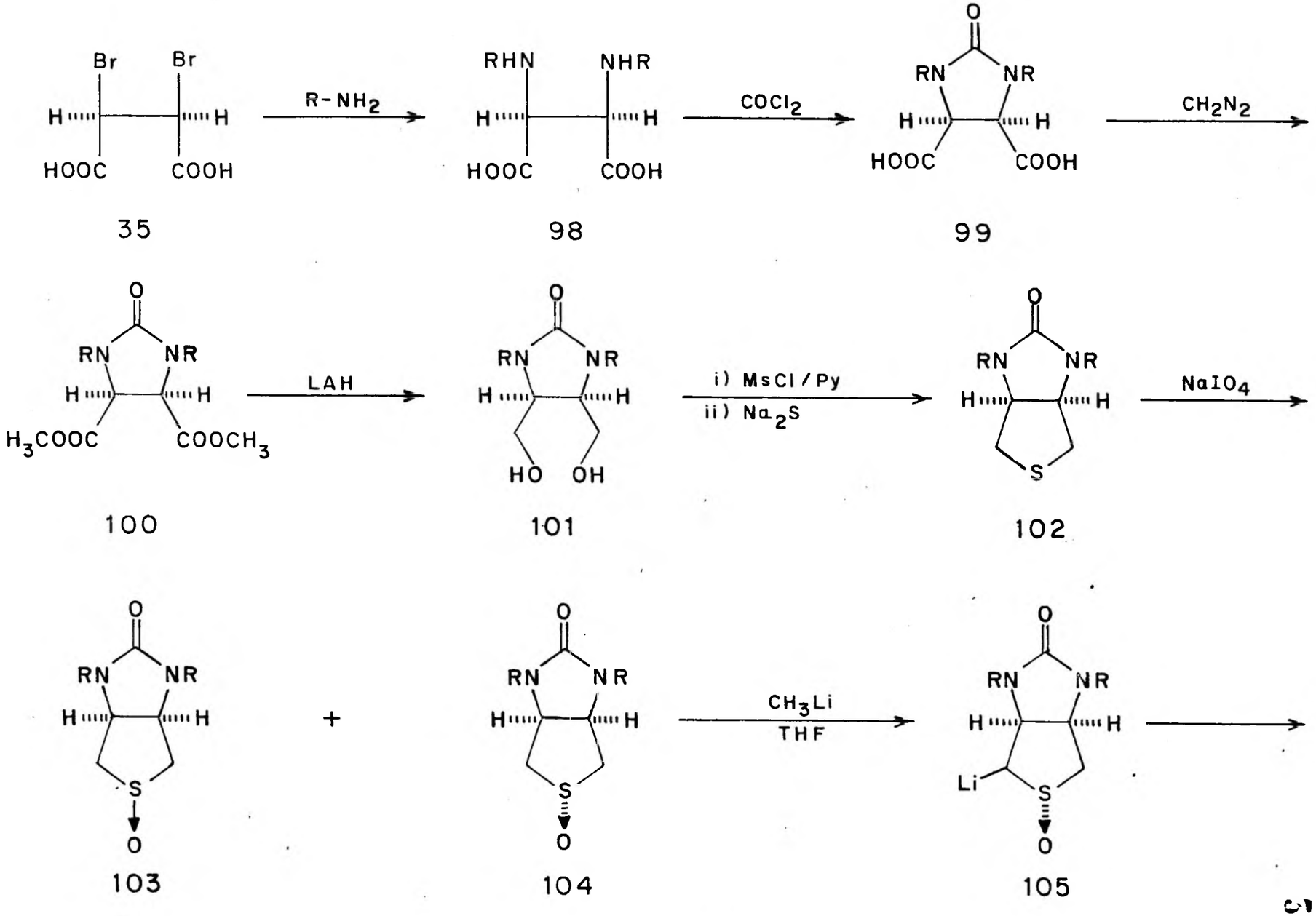

Br
Br
H
H
HOOC
COOH
R-NH2
RHN
NHR
H
H
HOOC
COOH
COCl2
O
RN
NR
H
H
HOOC
COOH
CH2N2
35
98
99
O
RN
NR
H
H
H3COOC
COOCH3
LAH
O
RN
NR
H
H
HO
OH
i) MsCl / Py
ii) Na2S
O
RN
NR
H
H
S
NaIO4
100
101
102
O
RN
NR
H
H
S
O
+
O
RN
NR
H
H
S
O
CH3Li
THF
O
RN
NR
H
H
Li
S
O
103
104
105

CHART - 1.4.9

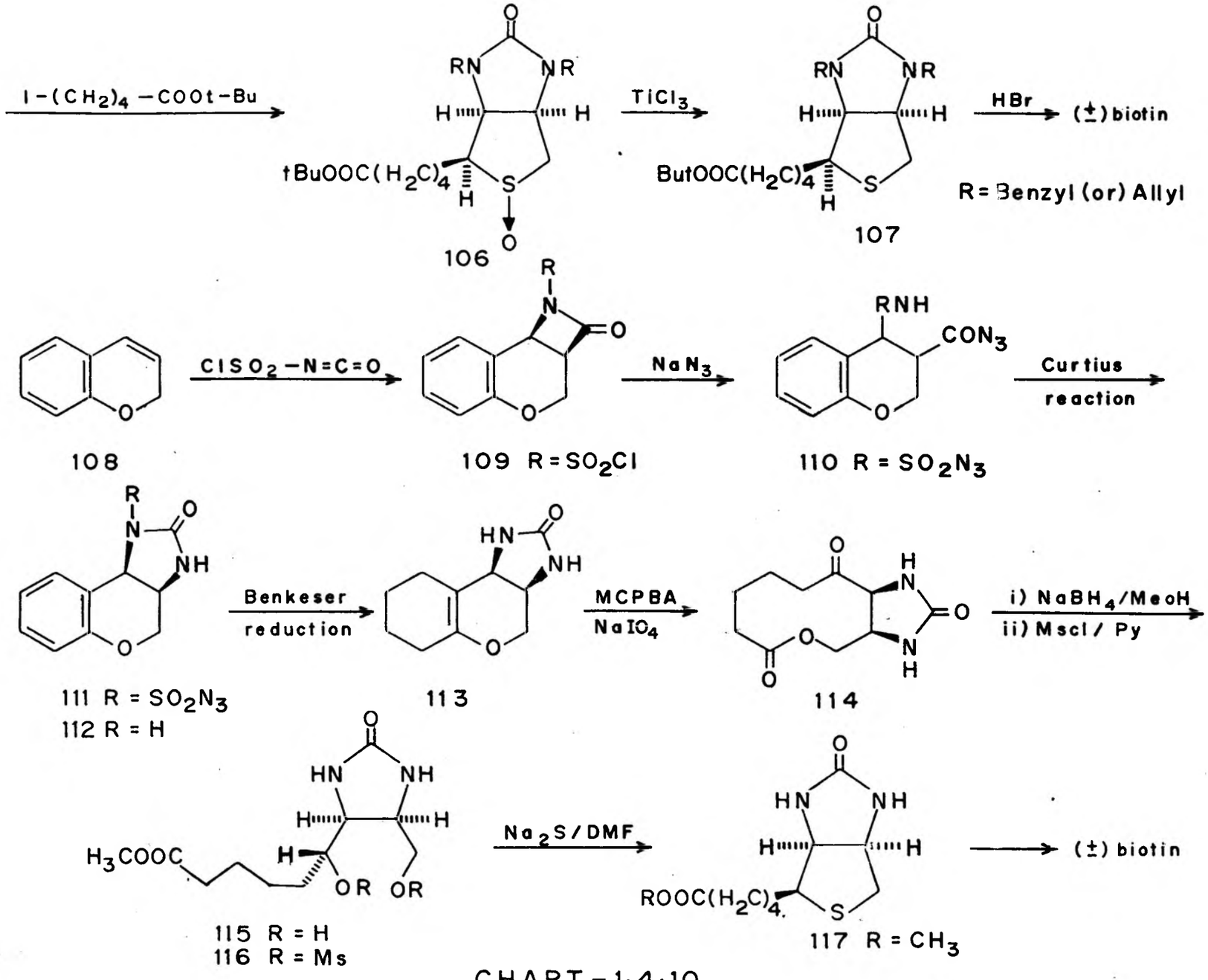

I-(CH2)4-COOt-Bu
TiCl3
HBr
(±) biotin
R = Benzyl (or) Allyl
106
107
ClSO2-N=C=O
NaN3
Curtius reaction
108
109 R = SO2Cl
110 R = SO2N3
Benkeser reduction
MCPBA NaIO4
i) NaBH4/MeOH
ii) Mscl / Py
111 R = SO2N3
112 R = H
113
114
Na2S/DMF
115 R = H
116 R = Ms
117 R = CH3

CHART-1·4·10

concomitant trans esterification to the dihydroxymethyl ester (115). Ring closure by treating the corresponding dimesylate (116) with sodium sulfide gave (±)biotin after saponification.

The important feature in the photochemical approach to the synthesis of (±)biotin by R.A. Whitney[23] was the cycloaddition reaction of 1,3-diacetylimidazolidone-2-one-(118) with3,4-dihydro-2-methoxy-2H-pyran (119) (Chart 1.4.11). The photo adduct was converted into the lactone (122), which had the complete carbon framework with all the requisite stereochemical features, by employing a sequence of reactions, e.g. hydrolysis, Wittig olefination and catalytic hydrogenation to the cyclobutanol (121). The latter was oxidized to the lactone (122) which was subsequently converted to (±)biotin in three steps as shown.

Zay'yalov et al.[24] reported the synthesis of (±)biotin from the key intermediate 4-methyl-imidazolidone (128) which was obtained from acetoacetic ester (125) (Chart 1.4.12). The compound (128) is converted to (129) by Friedel-Crafts acylation. The amino groups in 129 were protected by acetylation and the resulting compound (130) was brominated (NBS) to 4-bromoethyl derivative (131). Bromide group in compound (131) was replaced by thiourea to give (132) which was hydrolysed with 10% caustic soda and the resulting thiol (133) was cyclised with hydrochloric acid to give thiophene derivative (135).

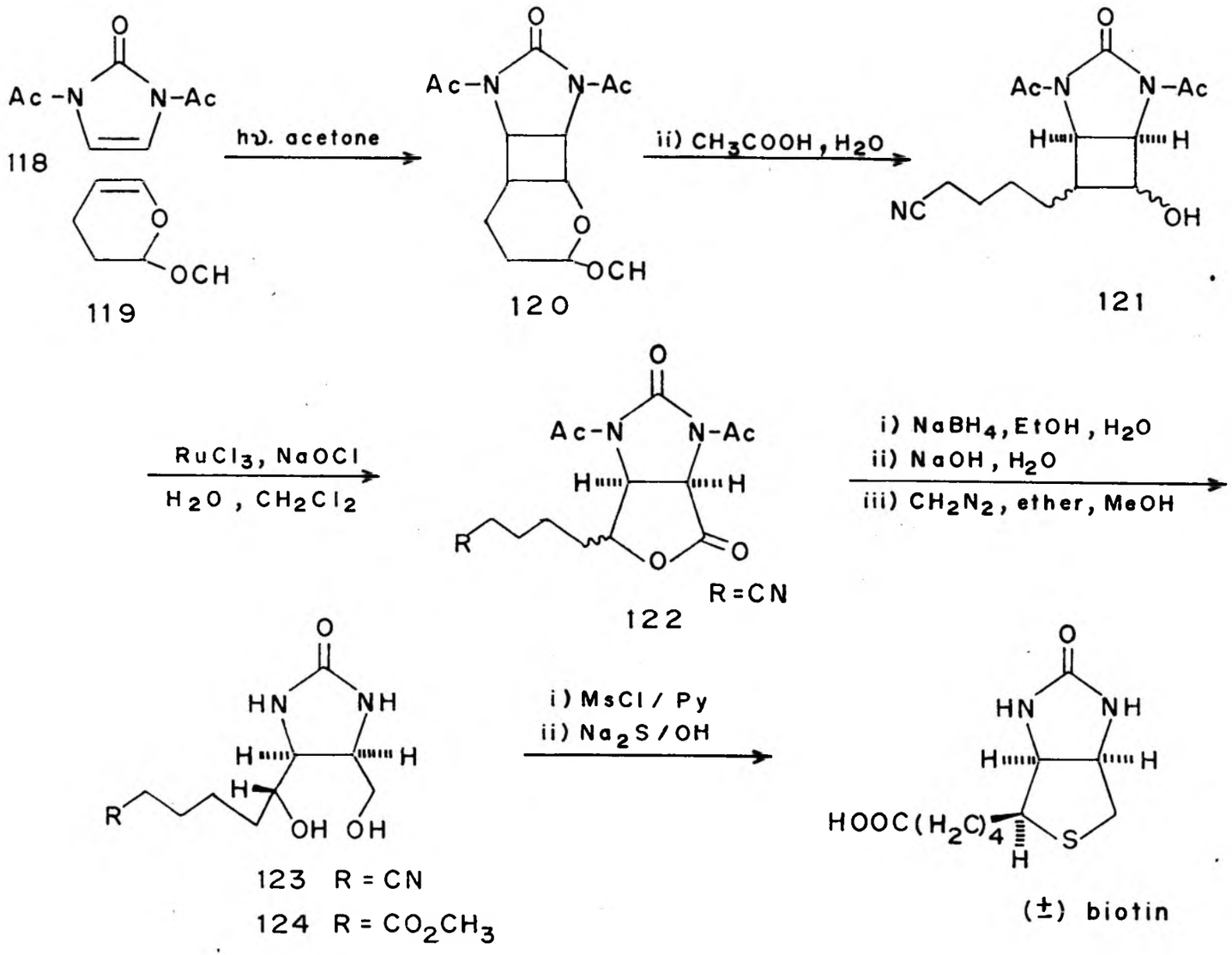

Ac-N
N-Ac
118
119
hν. acetone
120
ii) CH3COOH, H2O
NC
OH
121
RuCl3, NaOCl
H2O, CH2Cl2
R=CN
122
i) NaBH4, EtOH, H2O
ii) NaOH, H2O
iii) CH2N2, ether, MeOH
HN
NH
OH OH
123 R = CN
124 R = CO2CH3
i) MsCl / Py
ii) Na2S / OH
HOOC(H2C)4
S
(±) biotin

CHART – 1·4·11

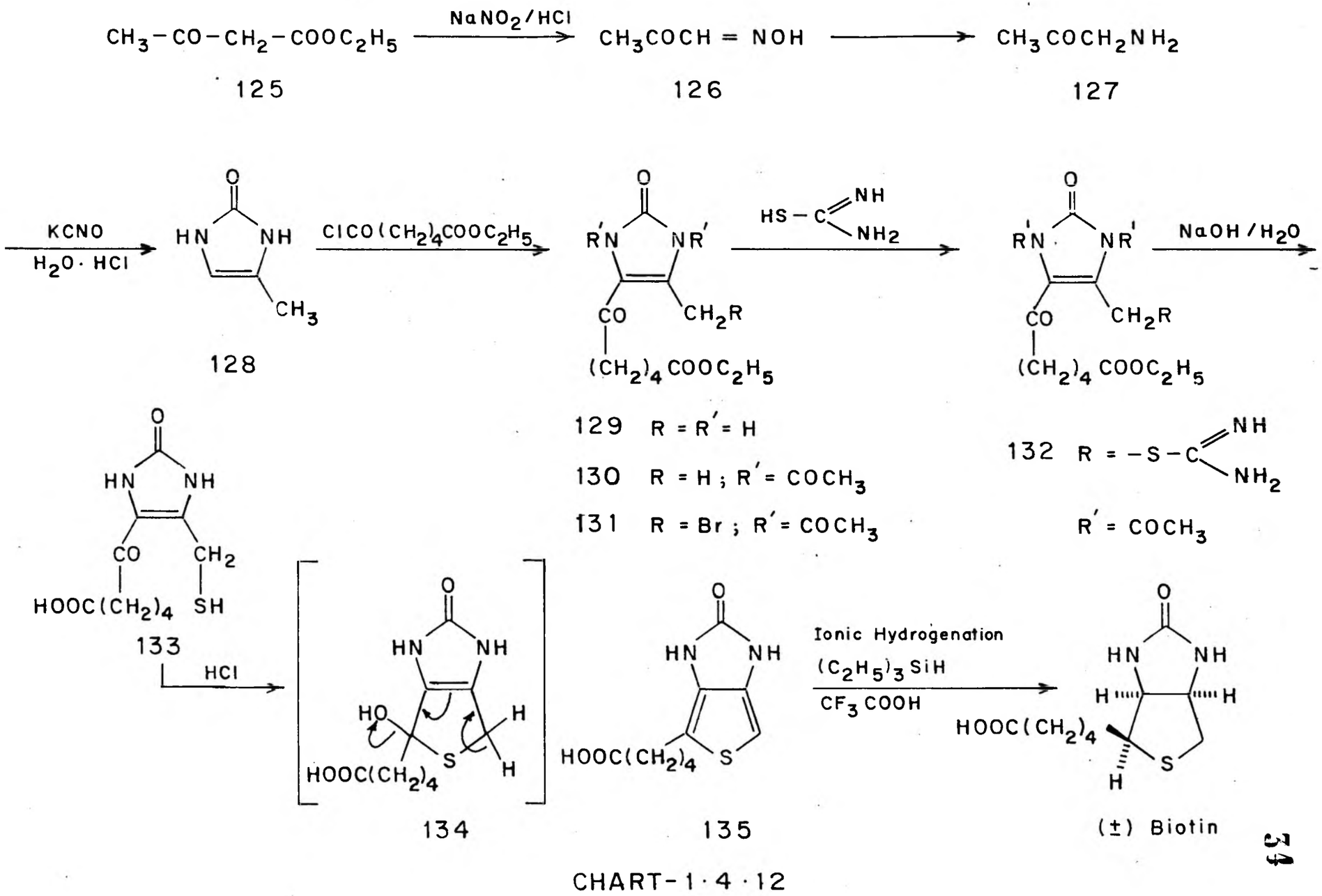

CH3-CO-CH2-COOC2H5
NaNO2/HCl
CH3COCH=NOH
CH3COCH2NH2
125
126
127
KCNO
H2O·HCl
ClCO(CH2)4COOC2H5
HS-C(=NH)-NH2
NaOH/H2O
128
129 R = R′ = H
130 R = H ; R′ = COCH3
131 R = Br ; R′ = COCH3
132 R = -S-C(=NH)-NH2
R′ = COCH3
HOOC(CH2)4 SH
133
HCl
134
135
Ionic Hydrogenation
(C2H5)3SiH
CF3COOH
(±) Biotin

CHART-1·4·12

The thiophene (135) on ionic hydrogenation with triethylsilanetrifluoroacetic acid furnished (±)biotin in 10% yield.

In Emoto and Nishimura[25] synthesis (Chart 1.4.13), thiophene (136) was acylated with glutaric diacid chloride in the presence of stannic chloride to result 2-substituted thiophene (137). The introduction of nitro group at position 3 of the thiophene molecule was achieved via 5-formyl thiophene derivative (141). The second nitro group was introduced at C-4 via bromothiophene derivative (144). The nitro groups were reduced with tin in HCl to give the diamine (146) which was further elaborated to give (±)biotin.

The Goldfarb[26] synthesis was similar to that of Emoto and Nishimura except for the introduction of the amino substitution. For instance, the acylated thiophene derivative (140) was cyclised to (148). Oximation followed by Beckmann rearrangement gave the lactam derivative (150). Hydrolysis followed by bromination and nitration resulted in nitroamine which was converted into (±)biotin (Chart 1.4.13).

Four syntheses of (+)biotin have been reported based on the transfer of the dextrorotatory optical activity of the sugars into the optically active molecule of natural biotin, through a series of stereospecific transformations.

In the first synthesis of this kind by Ohrui and Emoto[27], the use of cis diol grouping at C-2 and C-3 position of D-Mannose in the construction of imidazolidone ring was an

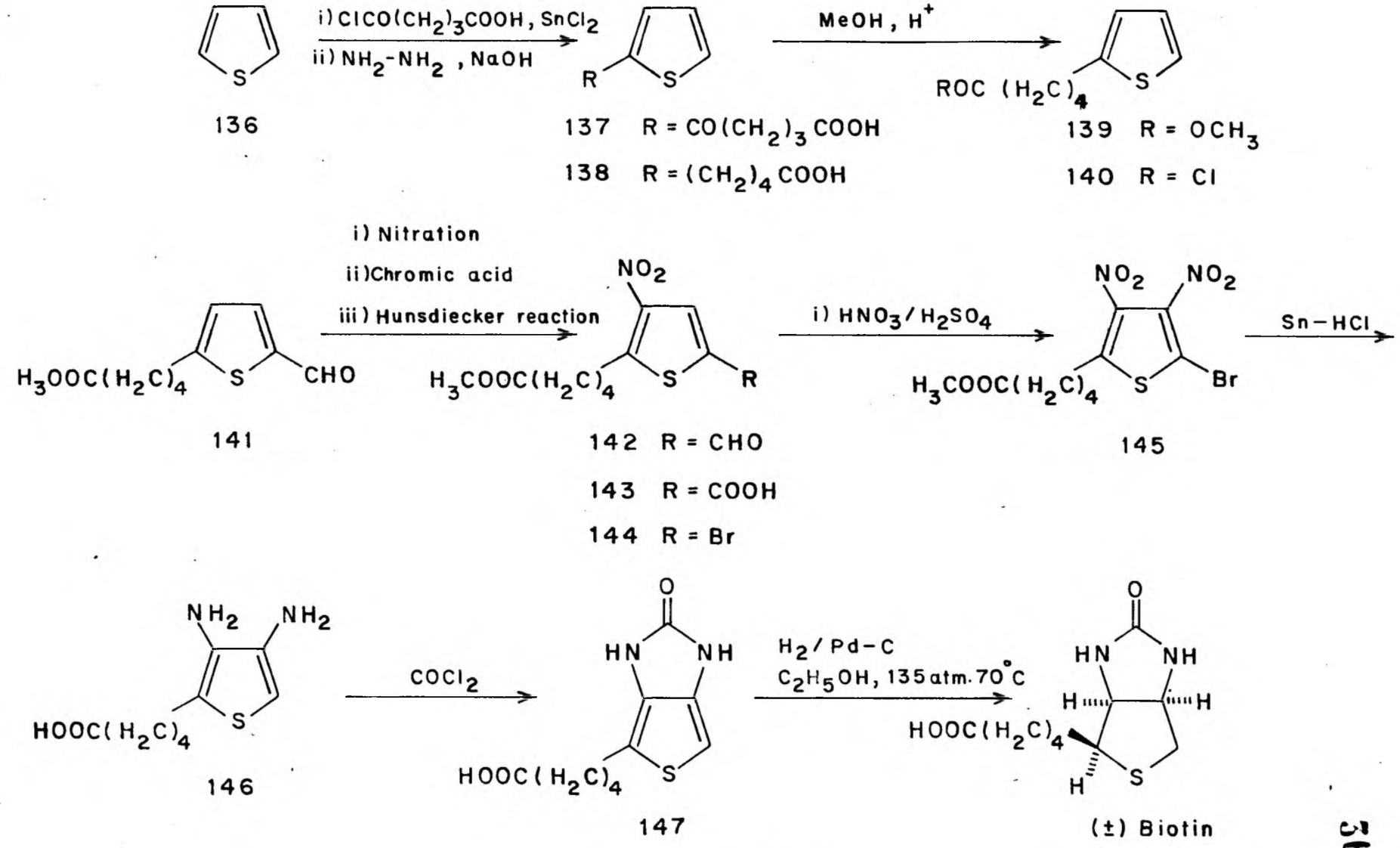

i) ClCO(CH2)3COOH, SnCl2
ii) NH2-NH2, NaOH
MeOH, H+
136
137 R = CO(CH2)3COOH
138 R = (CH2)4COOH
139 R = OCH3
140 R = Cl
i) Nitration
ii) Chromic acid
iii) Hunsdiecker reaction
i) HNO3/H2SO4
Sn-HCl
141
142 R = CHO
143 R = COOH
144 R = Br
145
146
COCl2
H2/Pd-C
C2H5OH, 135 atm. 70°C
147
(±) Biotin

CHART - 1·4·13

important feature. D-Mannose (154) was converted to the aldehyde (158) in four steps (Chart 1.4.14). Then the aliphatic side chain characteristic of biotin molecule was introduced by Wittig reaction with 3-methoxycarbonyl (prop-2-en-1-ylidene)triphenyl phosphorane followed by reduction to give (162). In the subsequent reactions thiophane ring was built up with the inversion at C-4 to obtain (163). Removal of the 2,3-isopropylidene and subsequent mesylation, and introduction of azido group with inversion of configuration at C-2 and C-3 gave the required cis diazide (165). Reduction of diazide followed by the reaction with phosgene gave natural biotin.

The synthesis of (+)biotin by Ogawa et al.[28] made use of the easily accessible 1,6:2,3 dianhydro-4-O-benzyl-β-D-mannopyranoside (168) (Chart 1.4.15) and involves the preparation of the key intermediate with the imidazolidone moiety (181). Ring opening of (168) with sodium azide gave the corresponding 2-azido derivative (169). O-mesylation followed by ring opening of the 1,6-anhydride (170) and the reduction of the resulting product gave the alditol (172). Protection of the diol with isopropylidene group and the SN_2 displacement of the mesylate gave the cis-diazide (174). Catalytic reduction of the cis-diazide to the diamine (175) followed by treatment with phosgene gave rise to imidazolidone (178). The introduction of the side chain, followed by closure to the tetrahydrothiophene ring with inversion at C-4 (181) gave the naturally occurring (+)biotin.

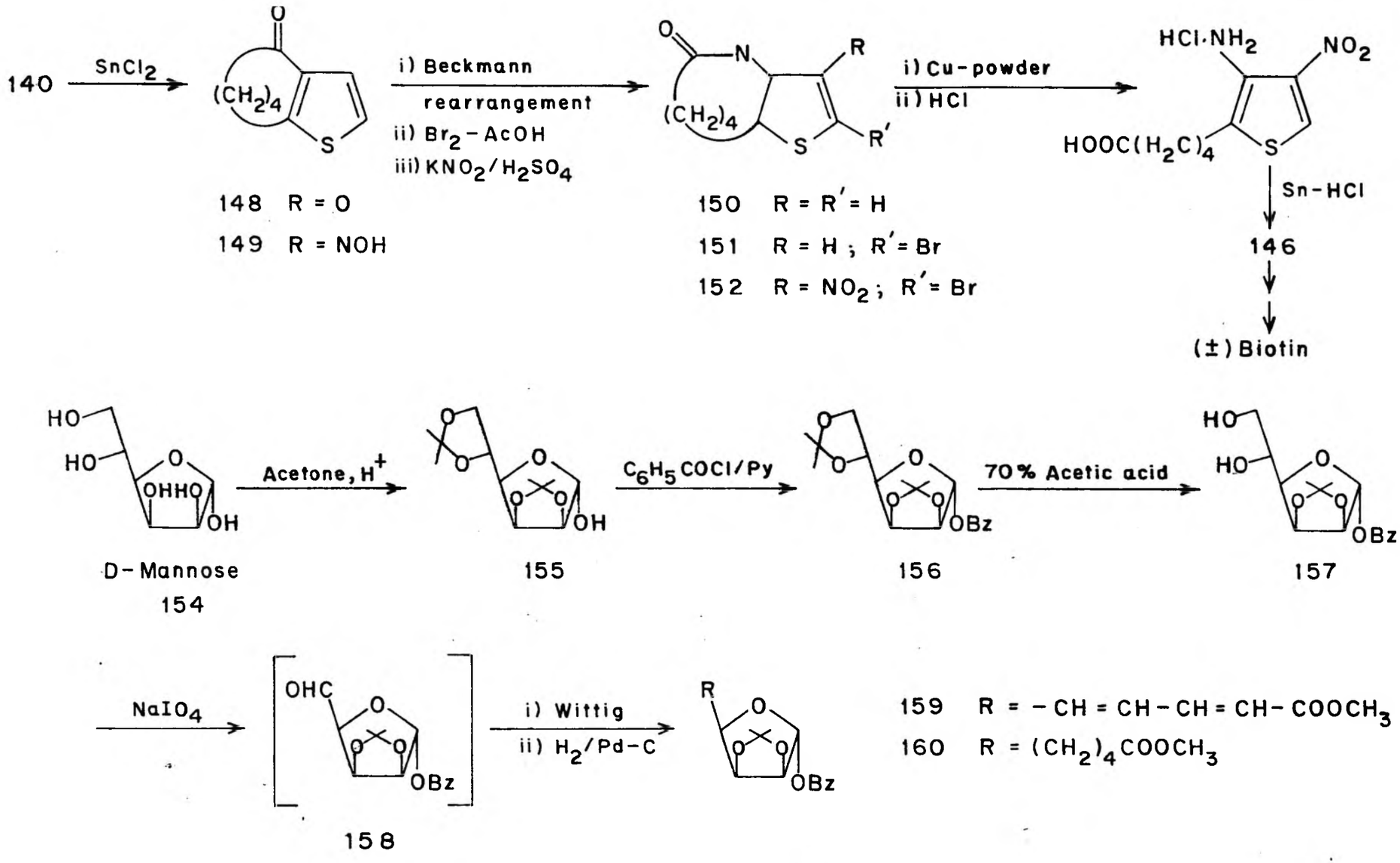

140
SnCl2
148 R = O
149 R = NOH
i) Beckmann
rearrangement
ii) Br2 – AcOH
iii) KNO2/H2SO4
150 R = R′ = H
151 R = H ; R′ = Br
152 R = NO2 ; R′ = Br
i) Cu-powder
ii) HCl
Sn-HCl
146
(±) Biotin
D-Mannose
154
Acetone, H+
155
C6H5COCl/Py
156
70% Acetic acid
157
NaIO4
158
i) Wittig
ii) H2/Pd-C
159 R = – CH = CH – CH = CH – COOCH3
160 R = (CH2)4COOCH3

CHART-1·4·14

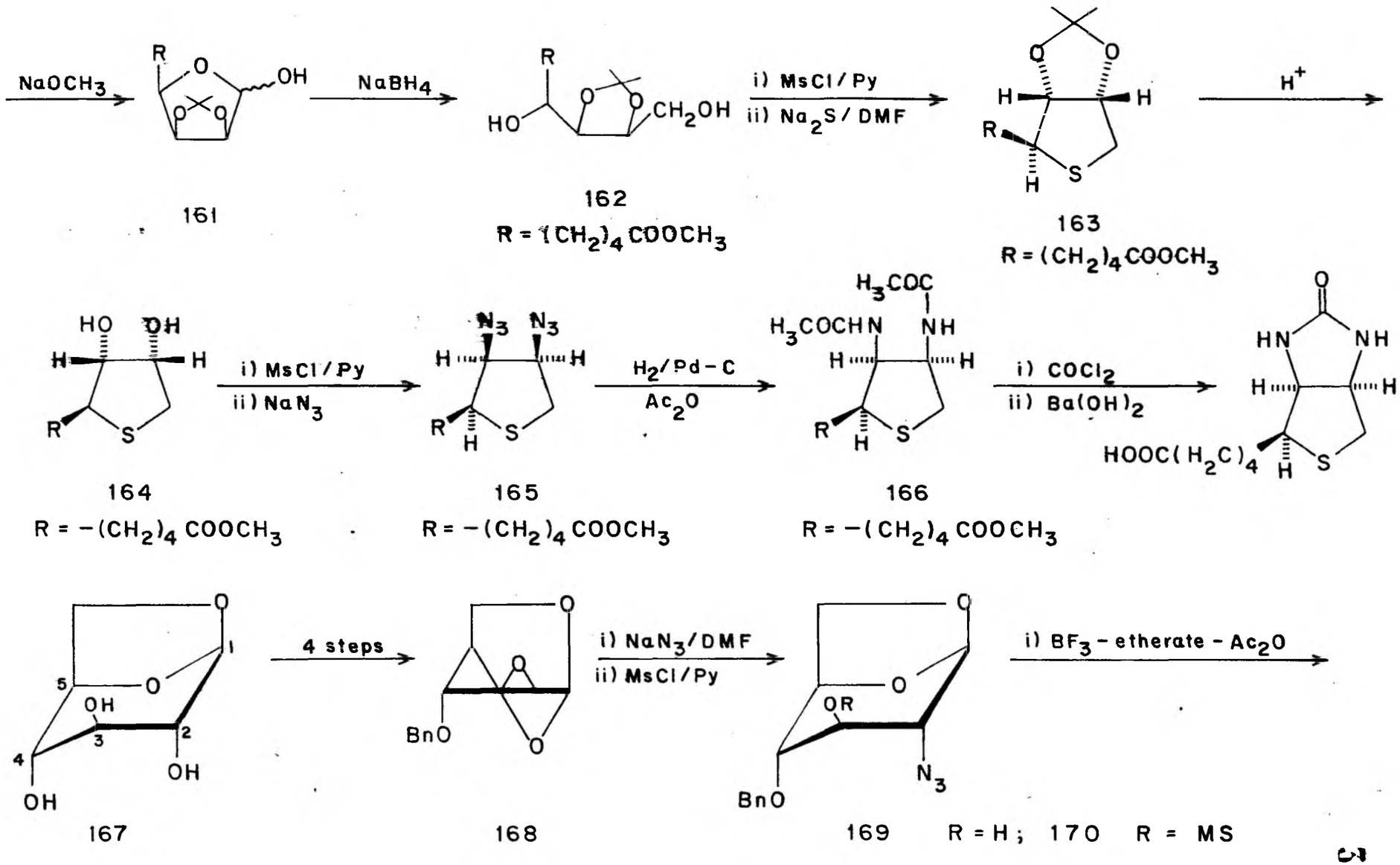
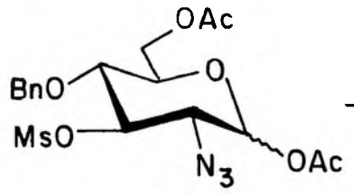
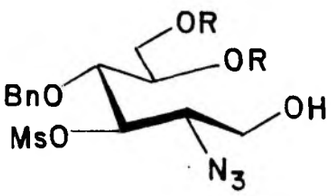

NaOCH3
NaBH4
i) MsCl / Py
ii) Na2S / DMF
H+
161
162
R = (CH2)4COOCH3
163
R = (CH2)4COOCH3
i) MsCl / Py
ii) NaN3
H2 / Pd - C
Ac2O
i) COCl2
ii) Ba(OH)2
HOOC(H2C)4
164
R = -(CH2)4COOCH3
165
R = -(CH2)4COOCH3
166
R = -(CH2)4COOCH3
4 steps
i) NaN3 / DMF
ii) MsCl / Py
i) BF3 - etherate - Ac2O
167
168
169 R = H; 170 R = MS

CHART-1·4·15



171

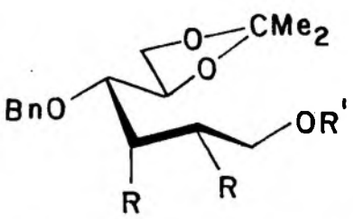
i) 1 NHCl
ii) $NaBH_4$



172 R = H

173 R, R = CMe_2

i) 2,2-dimethoxypropane in DMF, PTsA
ii) LiN_3/DMF
iii) H_2/Lindlar catalyst
iv) $COCl_2$, Na_2CO_3
v) Ac_2O-Py



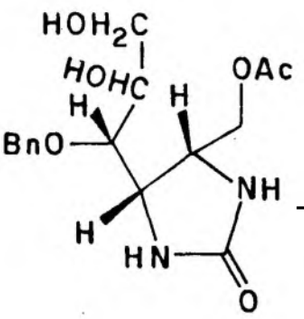
174 R = N_3, R' = H

175 R = NH_2, R' = H

176 R, R = $(NH)_2CO$, R' = H

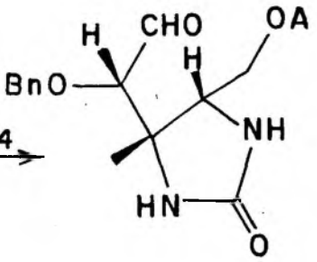
177 R, R = $(NH)_2CO$, R' = Ac

Aq. AcOH



178

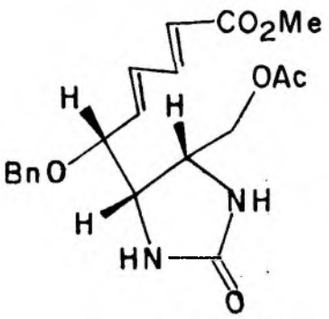
$NaIO_4$



179

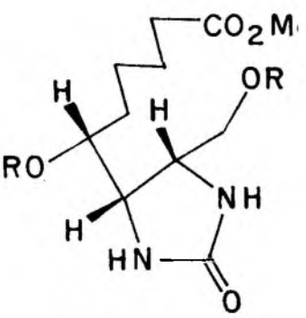
Th. 6920.

Wittig



180

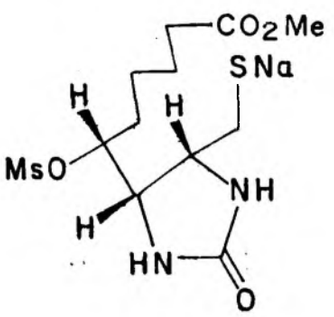
i) H_2/Pd-C
ii) MeONa
iii) MsCl/Py



181 R = H

182 R = Ms

Na_2S/DMF



183

(+) Biotin

Th. 6920.

CHART-1.4.15 (contd.)

Ohrui et al.[29] reported the synthesis of the key intermediate (181) from D-glucosamine (184) in ten steps (Chart 1.4.16).

The crucial intermediate diol (162) prepared by Ohrui et al. from mannose, was also synthesised from D-arabinose by Schmidt et al.[30] as shown in (Chart 1.4.17).

The synthesis of (+)biotin from L(+)cysteine (197) by Confolone et al.[31] (Chart 1.4.18) involved its condensation with benzaldehyde to give the thiozolidene (198). The imino group in (198) was protected and further transformed to (202) through a series of reactions, viz. reduction with diborane, oxidation with Cr_2O_3/pyridine and Grignard with vinylmagnesium bromide. Imidazolidone (202) on Claisen rearrangement with trimethyl orthoacetate in benzene in presence of propionic acid catalyst gives (203) which was further subjected to stereospecific oxidative cyclisation under the influence of pyridinium hydrobromide-perbromide furnishing the thiophene derivative (205). This was subsequently converted to the lactam (208) which on treatment with LiN_3/DMF at 130° brings about the inversion of configuration at C-4 to give the azido lactam (209). The lactam on catalytic hydrogenation led to the cis-aminolactam (210). Hydrolysis of this and subsequent treatment of the product with phosgene gave (+)bis-norbiotin (211) which is then converted to (+)biotin in 5 steps. The overall yield of (+)biotin is 3.6% based on the initial L(+)-cysteine.

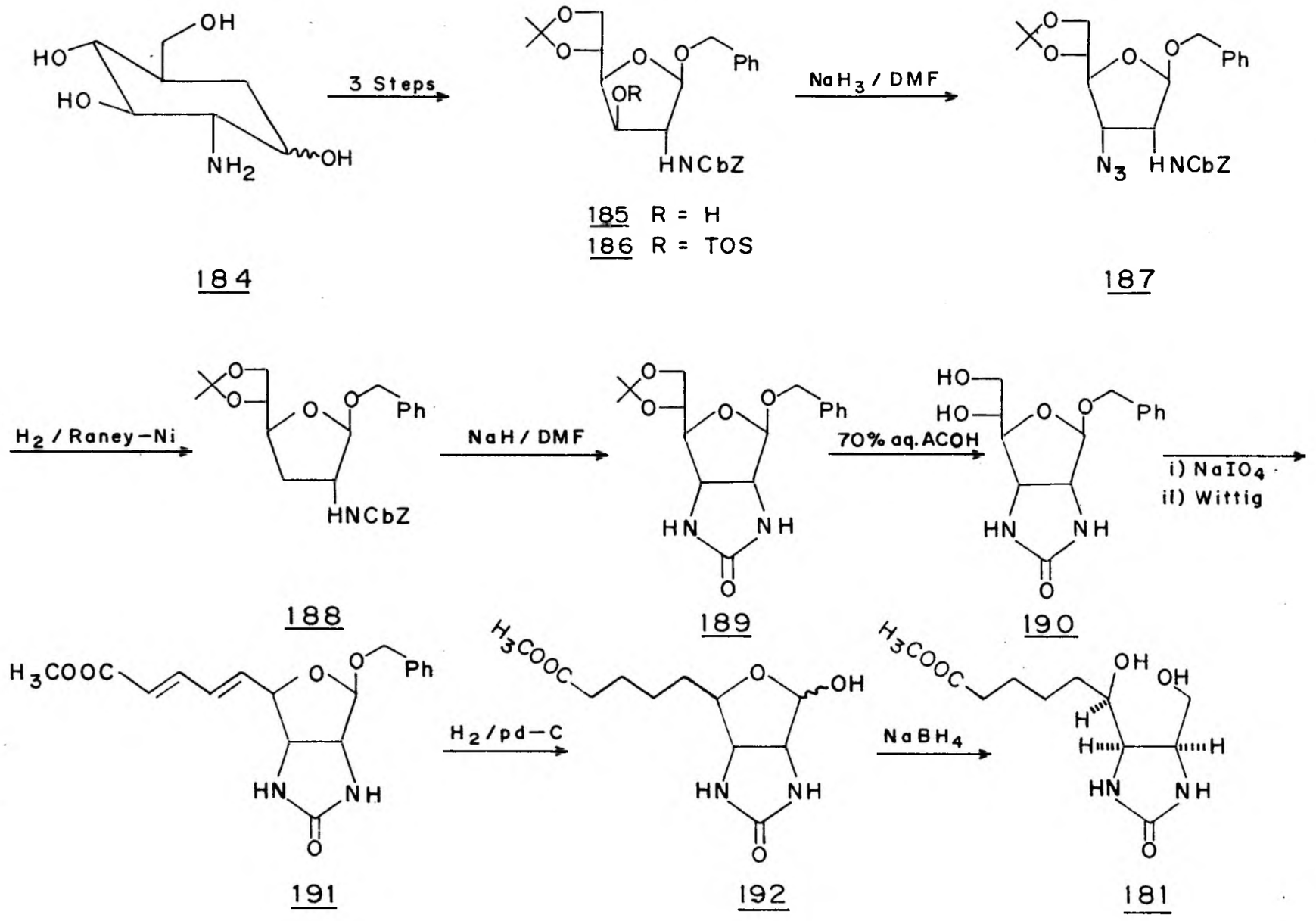
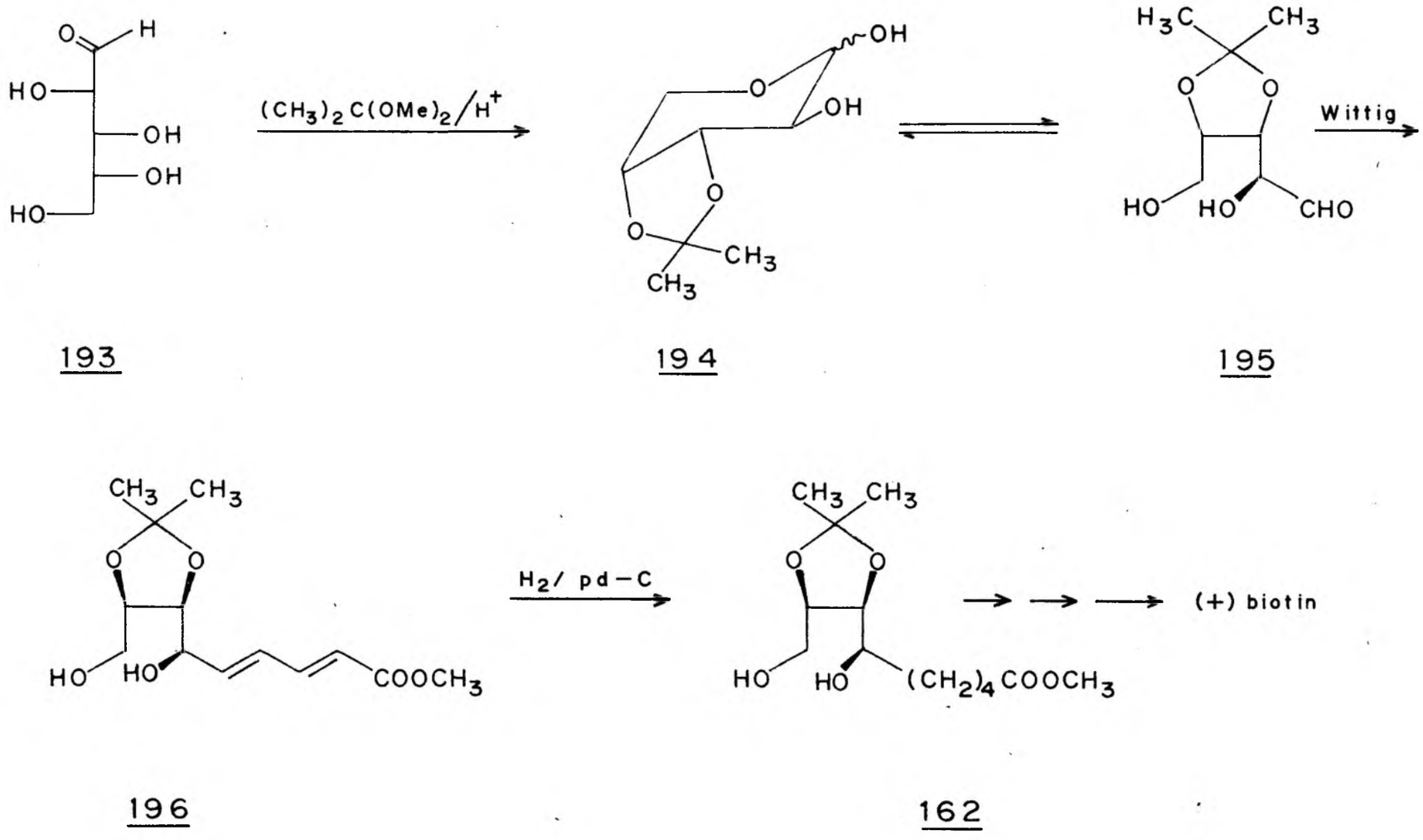

OH
HO
HO
NH2
OH
3 Steps
O
O
O
O
Ph
OR
HNCbZ
NaH3 / DMF
N3
HNCbZ
185 R = H
186 R = TOS
184
187
H2 / Raney–Ni
HNCbZ
NaH / DMF
HN
NH
O
70% aq. ACOH
HO
i) NaIO4
ii) Wittig
188
189
190
H3COOC
191
H2/pd–C
OH
192
NaBH4
181

CHART – 1·4·16



193 194 195

196 162

CHART – 1.4.17

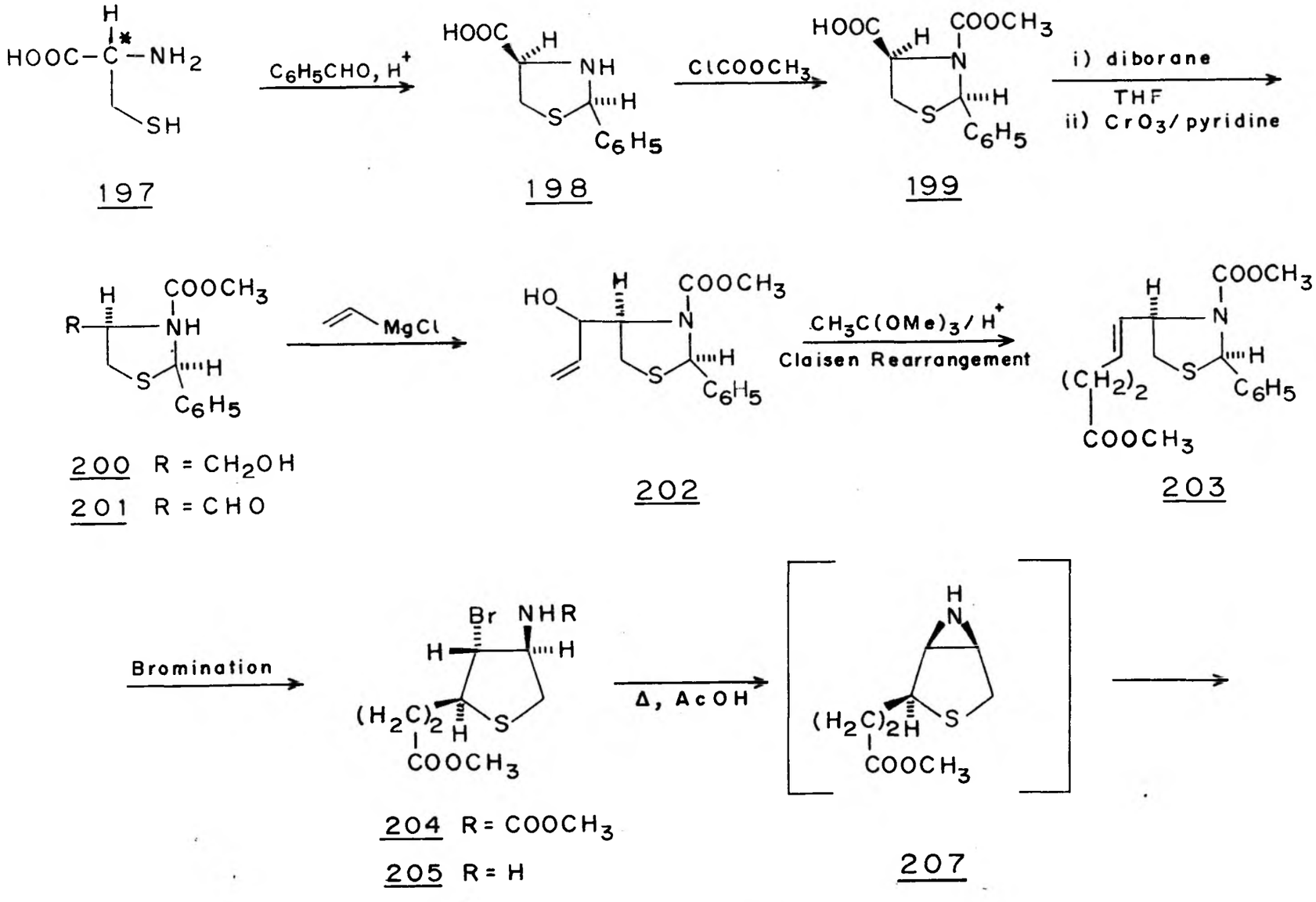

HOOC–C*–NH2
SH
C6H5CHO, H+
HOOC
NH
S
H
C6H5
ClCOOCH3
COOCH3
N
i) diborane
THF
ii) CrO3/ pyridine
197
198
199
R
MgCl
HO
CH3C(OMe)3 / H+
Claisen Rearrangement
(CH2)2
200 R = CH2OH
201 R = CHO
202
203
Bromination
Br
NHR
Δ, AcOH
204 R = COOCH3
205 R = H
207

CHART-1·4·18

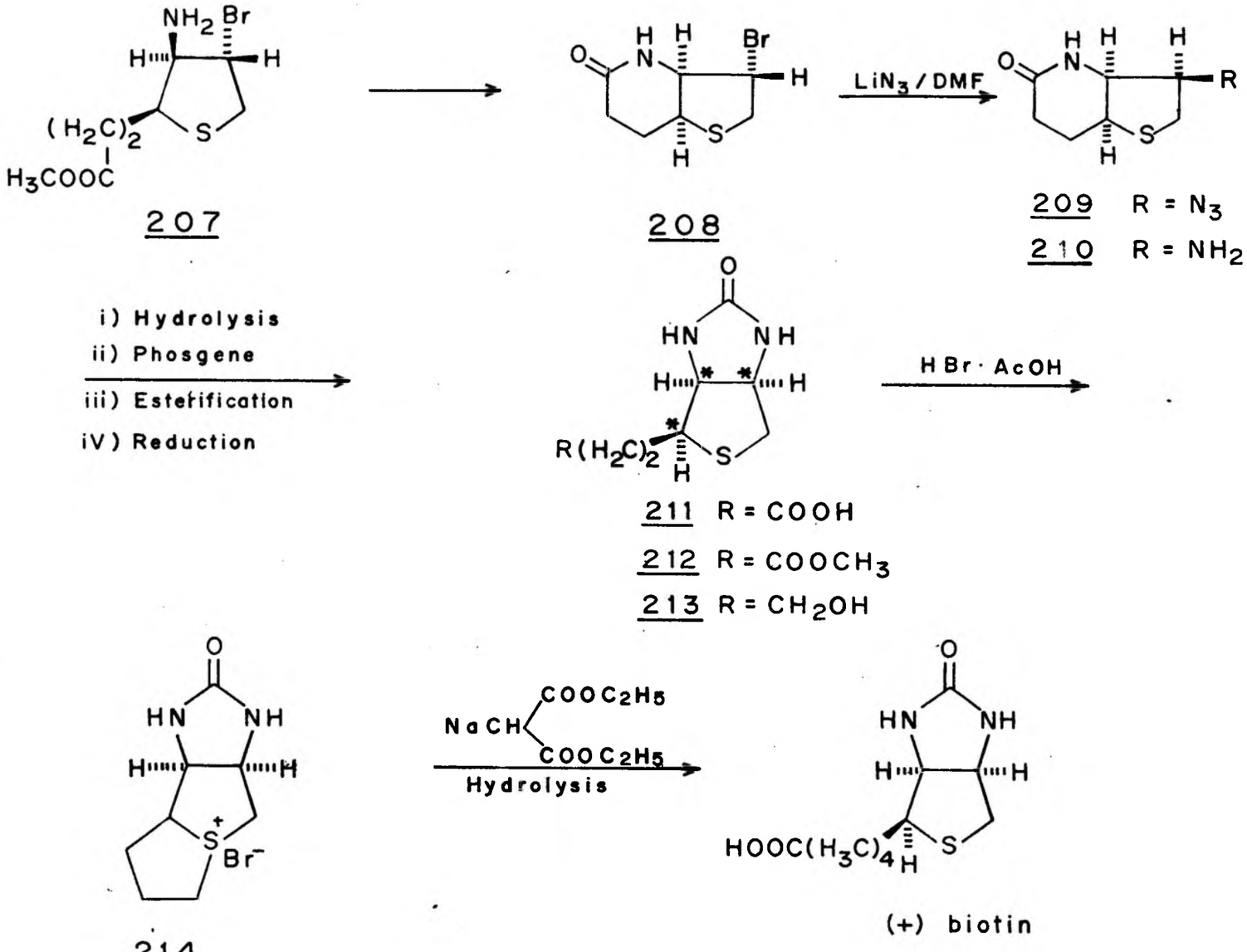
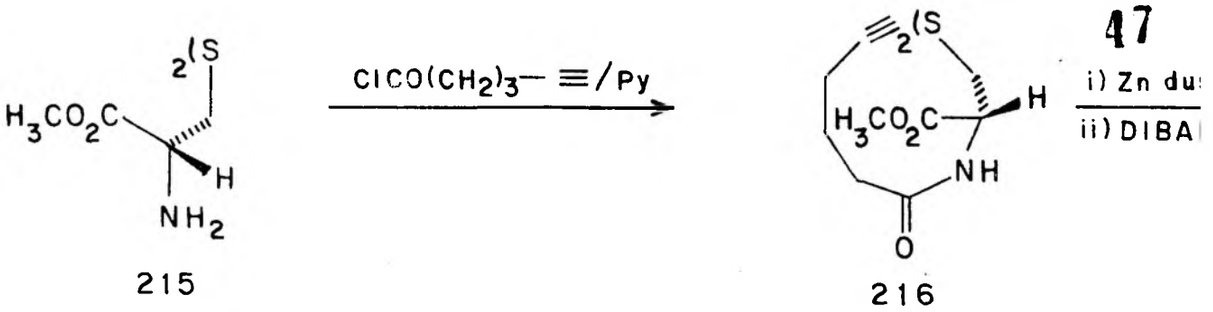


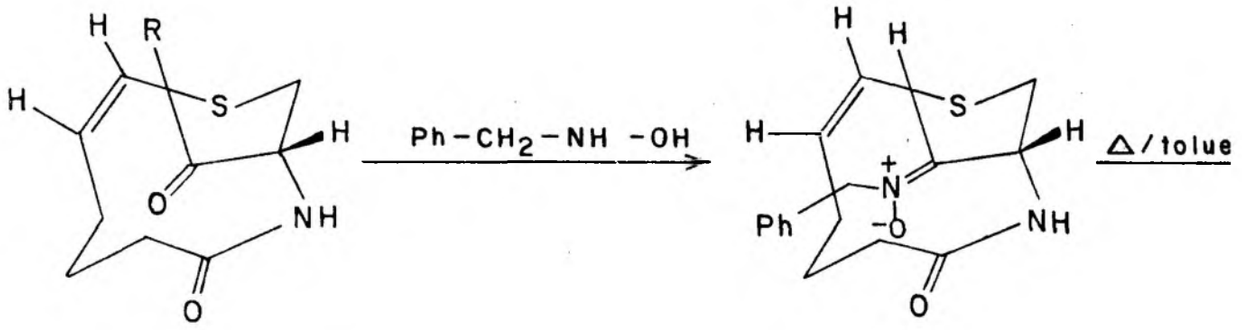
CHART – 1·4·18 (contd.)

The synthesis of (+)biotin from cysteine by G. Baggiolini et al.[32] is based on the intramolecular (3+2) cycloaddition of an olefinic nitrile oxide to thio-enolether double bond (Chart 1.4.19). This addition was effected in a single step with the formation of the additional two out of three chiral centres with proper absolute stereochemistry required for d-biotin.

L-cysteine dimethyl ester (215) was acylated at the nitrogen with 5-hexynoylchloride to give (216) which was treated with zinc dust in presence of air to produce a 9:1 mixture of Z/E olefinic products. The compound (217) was reduced with Diisobutylaluminium hydride followed by reacting with benzylhydroxylamine to afford stereospecifically the Z-nitrone (219). Nitrone (219) on refluxing in toluene underwent cycloaddition to afford tricyclic intermediate (220). The compound (220) on treatment with zinc dust in acetic acid and the simultaneous acylation of the amine with methylchloroformate afforded the bicyclic intermediate (221). Hydrolysis of lactone moiety of (221) and concomitant cyclisation with barium hydroxide gave imidazolidone (222). The compound on treatment with thionyl chloride gave (223). Dechlorination was effected with excess of sodium borohydride in dimethyl-formamide to furnish (224). Subsequent hydrolysis of (224) with hydrobromic acid leads to (+)biotin.



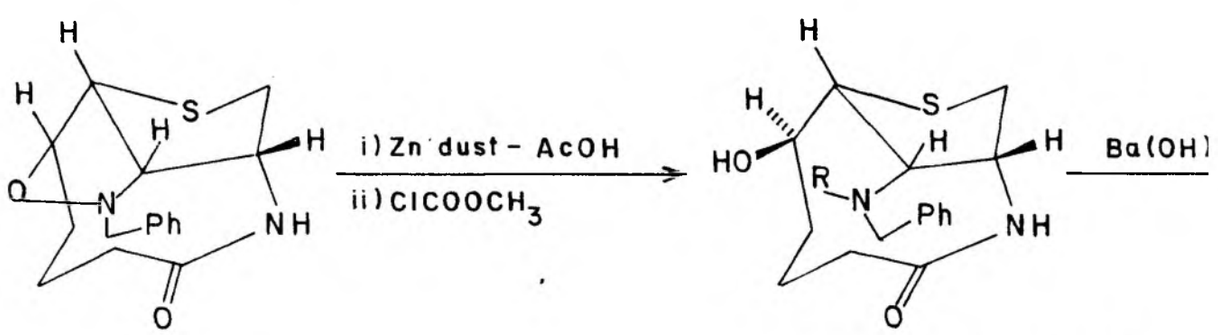
215 216



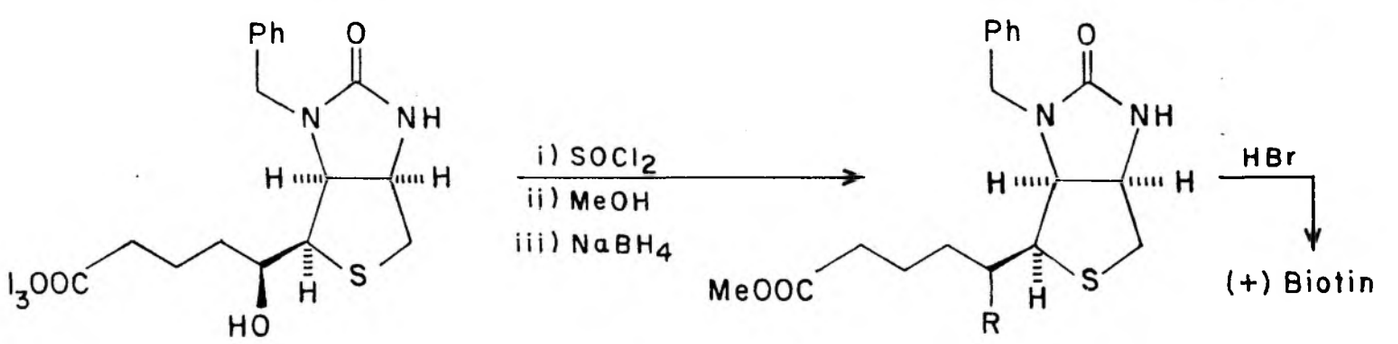
217 R = OCH_3

218 R = H

219



220 221 R = $-CO_2CH_3$



222 223 R = Cl

224 R = H

CHART—1·4·19

1.5.0 REFERENCES

1 F. Kogl and B. Tonnis
Z. physiol. chem., 193, 125 (1936).

2 D.B.Melville, A.W.Moyer, K. Hofmann and V. Du-Vigneaud
J. Biol. Chem., 146, 487-492 (1942).

3 S.A. Harris, D.E. Wolf, R.Mozingo, R.C.Anderson, G.E. Arth, N.R. Easton, D. Heyl, A.N. Wilson and K. Folkers
J. Am. chem. Soc., 66,1756 (1944).

4 W. Traub
Nature (London), 178, 647-650 (1956).

5 J. Trotler and J.A. Hamilton
Biochemistry, 5, 713-714 (1966).

6 G.T. de Titta, J.W. Edmonds, W. Stallings and J. Donohue
J. Am. Chem. Soc., 98, 1920 (1976).

7 a) J.A. Glassel
Biochemistry, 5, 1851-1855 (1966).

b) R. Lett and A. Marquet
Tetrahedron, 30, 3365-3367 (1974).

8 References concerning the biochemistry of biotin and biotin enzymes can be found in several review articles.

a) J. Knappe
in Ann. Rev. Biochemistry, 39, 757-776 (1970)

b) J. Moss and D. Lane
in Adv. in Enzymology, 35, 321-441 (1971).

c) A.W. Alberts and P.R. Vagelos
in the enzymes (3rd ed.) P.D. Boyer, Academic Press, N.Y., 37-82 (1972).

9 A. Marquet
Pure and Appl. Chem., 49, 183 (1977).

10 S.A. Harris, D.E. Wolf, R. Mozingo, G.E. Arth, R.C. Anderson, N.R.Easton and K. Folkers
J.Am. Chem. Soc., 67, 2096-2106 (1945).

11 B.R. Baker, W.L. McEwen and W.N. Kinley
J. Org. Chem., 12, 322 (1947).

12 B.R. Baker, W.L.McEwen and W.N. Kinley
J. Org. Chem., 12, 322 (1947).

13 M.W. Goldberg and L.H. Sternbach
U.S. Patent 2,489,236; Chem. Abstr., 45, 187 (1951).

M.W. Goldberg and L.H. Sternbach
U.S. Patent 2,489,232 (1949); Chem.Abstr., 45, 186 (1951).

M.W. Goldberg and L.H. Sternbach
U.S. Patent 2,489,234 (1949); Chem.Abstr., 45, 186 (1951).

14 M. Geneke, J.P. Zimmerman and W. Aschwanden
Helv. Chim. Acta, 53, 991 (1970).

15 P.N. Confalone, G. Pizzalato and M.R. Uskokovic
J. Org. Chem., 42, 135 (1977).

16 M. Marx, F. Marti, J. Residorff, R. Sandmeier and
S. Clark
J. Am. Chem. Soc., 99, 6754 (1977).

17 a)G.F. Fild and W. Caldwell, G.F.R. Patent
2,558,356. Cl. C07D495/04 (1976); Chem.Abstr., 86,
29,809 (1977).

b)G.F. Fild and W. Caldwell
U.S. Patent 4,054,740. Cl. 548-303 (1977).

c)J.Varelevskis, J.A. Gualtieri, S.D. Hutchings,
R.C. West, J.W. Scott, D.R. Parrish, F.T. Bizzarrao,
G.F. Field
J. Am. Chem.Soc., 100, 6291 (1978).

18 P.N. Confalone, E.D. Lollar, G. Pizzolato and
M.R. Uskokovic
J. Am.Chem. Soc., 100, 6291 (1978).

19 R.A. Volkmann, J.T. Davis and C.N. Meltz
J. Am.Chem.Soc., 105, 5946-5948 (1983).

20 S. Bory,M.J. Luche, B. Moreau, S. Lavielle and
A. Marquet
Tetrahedron Lett., 827 (1975).

21 S. Lavielle, S. Bory, B. Moreau, M.J. Luche and
A. Marquet
J. Am. Chem.Soc., 100, 1558 (1978).

22 A. Fliri and K. Hohenlohe-Oehringen
Chem. Ber., 113, 607-613 (1980).

23 R.A. Whitney
Can. J. Chem., 61, 1158 (1983).

24 S.I. Zay'yalov, I.A. Radionova, L.L. Zheleznaya, G.I. Bolestova, V.V. Fillippova, Z.I. Parner and D.N. Kursanov
Izv. Akad. Nauk SSSR. Ser. Khim. 1643 (1975).

25 S. Nishimura and E. Imoto
Bull. Chem. Soc.Japan, 35, 432 (1962).

26 B.P. Fabrichnyi, I.F. Shalavina and Ya.L.Gol'dfarb
Zh. Obshch. Khim., 31, 1244 (1961).

27 H. Ohrui and S. Emoto
Tetrahedron Lett., 32, 2765-2766 (1975).

28 T. Ogawa, T. Kawano and M. Modsui
Carbohydr. Res. 57 C_{31}-C_{35} (1977).

29 H. Ohrui N. Sueda and S. Emolo
Agric. Biol. Chem., 42, 865-868 (1978).

30 R.R. Schmidt and M. Maier
Synthesis, 9, 747-748 (1982).

31 P.N. Confalone, G. Pizzalato, E.G. Baggiolinc, D. Lollar and M.R. Uskokovic
J. Am. Chem. Soc., 97, 5936 (1975);
99, 7020 (1977).

32 E.G. Baggiolini, H.L. Lee, G. Pizzolato and M.R. Uskokovic
J. Am. Chem. Soc., 104, 6460-6462 (1982).

CHAPTER - 2.0.0

SYNTHESIS OF (±) BIOTIN

FOREWORD

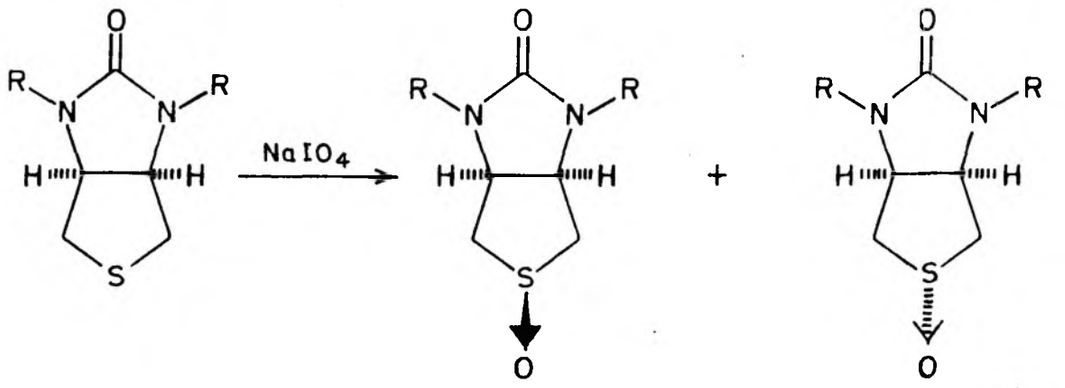
The key intermediate, 3,4-(1,3-dibenzyl-2-oxo-imidazolido)thiophane (2) for the synthesis of biotin (1) has been prepared starting from cis-but-2-ene-1,4 diol (21). During the preparation of the above mentioned sulfide (2), a new methodology has been developed for the efficient conversion of vicinal diamine (26) to imidazolidone (28) via the diurethane (27).

Our efforts in the preparation of optically-active cis-tetrahydro-2-oxofurano[3,4-d]1,3-dibenzylimidazolidone (51), and also a shorter synthesis of (2) are described in this chapter.

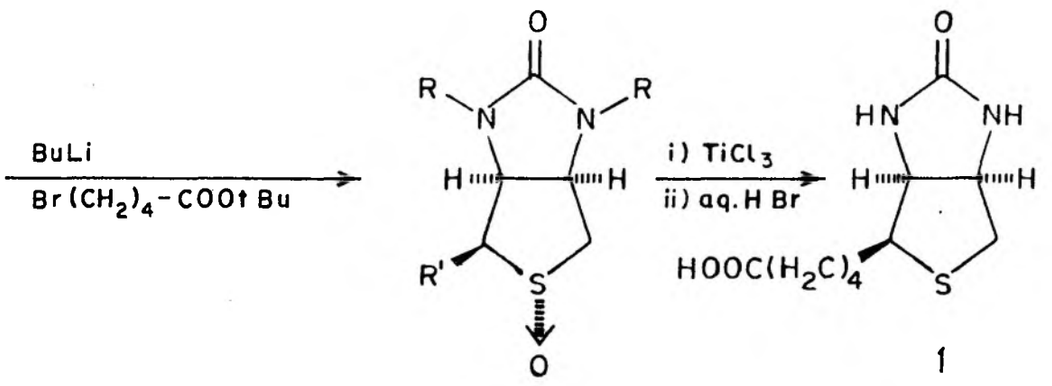
2.1.0 INTRODUCTION

In the first chapter of this thesis various syntheses of biotin (1) reported in the literature, were reviewed. It is evident that some of these syntheses are of industrial significance. The strategies involved in these, if necessary with suitable modifications can be exploited for developing a commercial synthesis of biotion. One such synthesis is by French workers[1] which involves stereoselective alkylation of cyclic sulfoxide (4) for the introduction of the valeric acid side chain characteristic of biotin molecule (Chart 2.1.1). This approach is versatile for the preparation of other biotin analogues, some of which are biologically active[2], because the same intermediate can be alkylated to introduce different substituents.

The crucial intermediate sulfide (2) required in this synthesis was earlier obtained by three different routes. The French workers obtained the compound (2) from fumaric acid (6) in 7 steps (Chart 2.1.2). The yields in all the steps, except for the conversion of the diester (10) into the diol (11) are good. Some drawbacks of this synthesis are (i) the use of poisonous phosgene gas and diazomethane for construction of imidazolidone system and esterification respectively, (ii) the costly



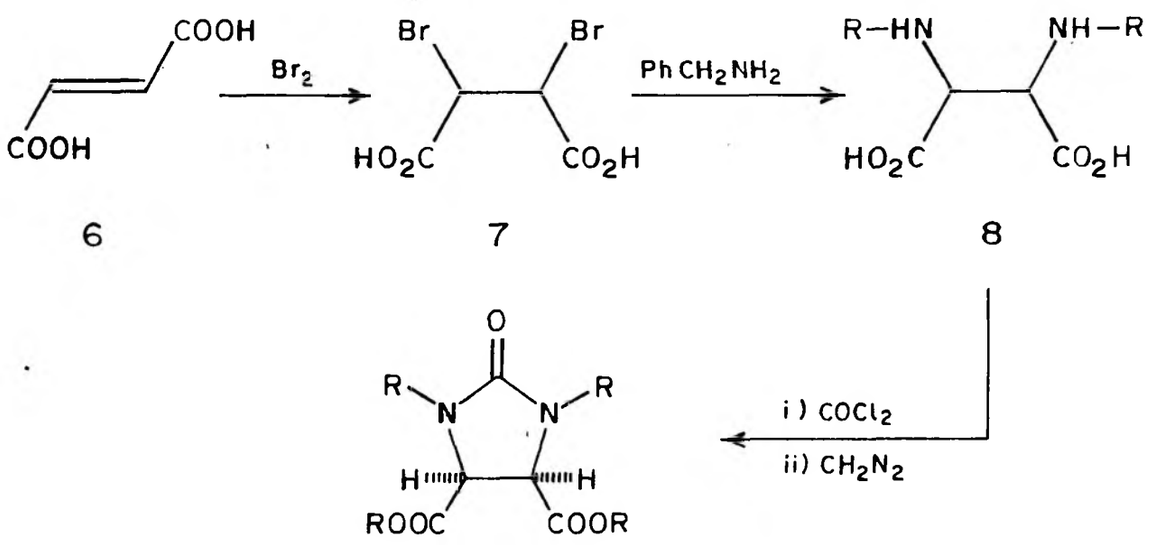
2: R = CH_2-Ph 3: R = CH_2-Ph 4: R = CH_2-Ph



5: R = CH_2-Ph
R' = $-(CH_2)_4COOt\,Bu$

1
(±) biotin

CHART – 2·1·1

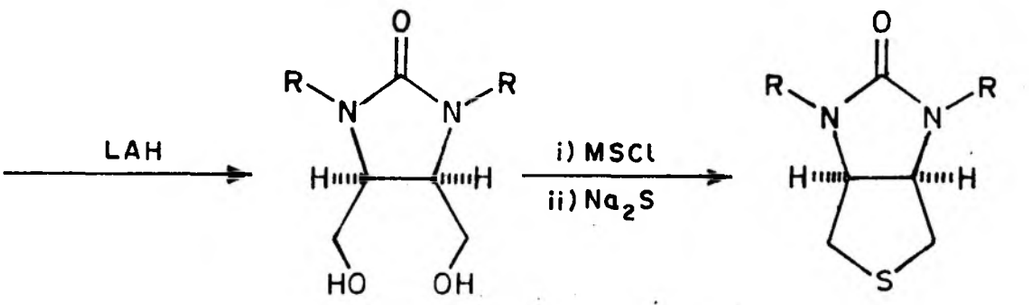


6 7 8

9: R = H
10: R = CH_3

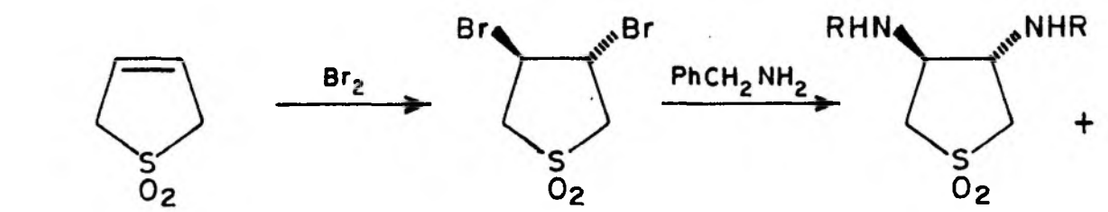
LAH reduction step of converting the diester to diol.

The other two syntheses of (2) are by the Japanese workers[3,4], and starts from 3-sulpholene (12). In the first synthesis (Chart 2.1.3), the trans 3,4-dibromosulfolane (13) is treated with benzylamine to give a mixture of cis and trans diaminosulfolane derivatives (15 and 14 respectively). Further the cis-derivatives are treated with phosgene to give (16) which on LAH reduction afforded the desired sulfide (2). This route to (2) is unsatisfactory, since the reaction of dibromo-sulfolane (13) with benzylamine provides the desired cis-diamino derivative (15) only as a minor product. To overcome this difficulty, the Japanese workers[4] have come up with alternative synthesis of (2) in which 3-sulfolene (12) is treated with sulfurylchloride in acetonitrile to get the imidoylchloride (17). The compound (17) was allowed to react with benzylamine in presence of TEA to give (18), which was further treated with basic alumina in acetonitrile to afford the cyclisation product (19). On treatment of (19) with alkali in refluxing ethanol the amino group was effectively transformed to amido group giving ureylene derivative (20). Further the N-benzylation of (20) using BuLi-$PhCH_2Br$/THF-HMPA and LAH reduction of the resulting (16) at -15° to -10° gave the required sulfide (2) as shown in Chart 2.1.4.

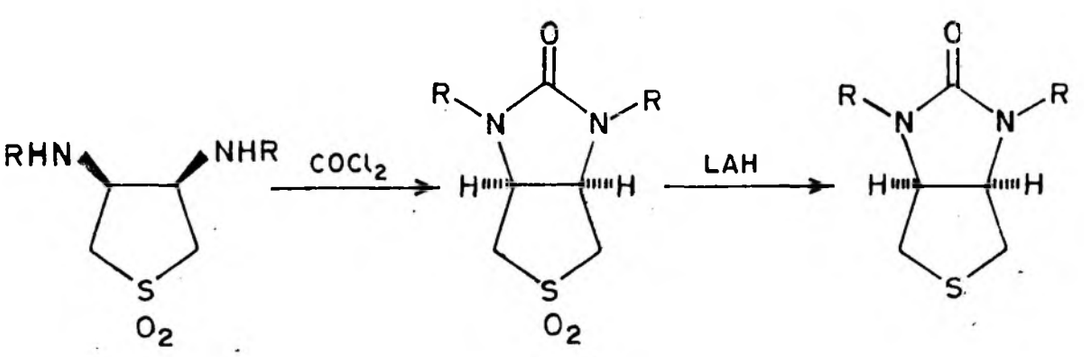


11: R = CH_2–Ph 2: R = CH_2–Ph

CHART-2·1·2

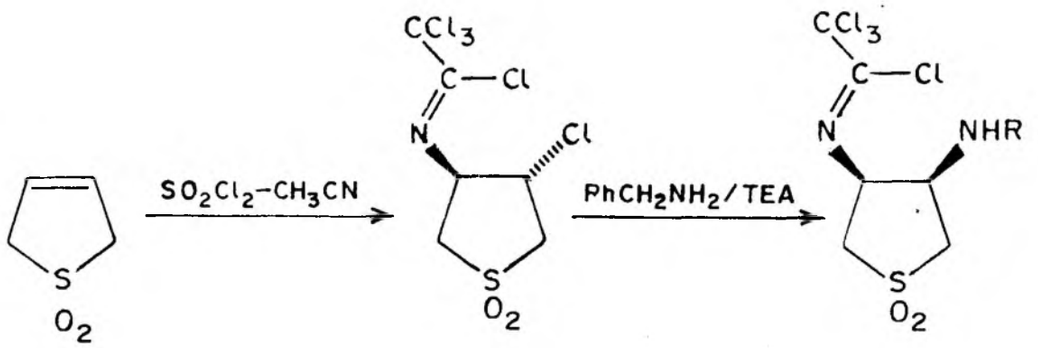


12 13 14: R = CH_2–Ph

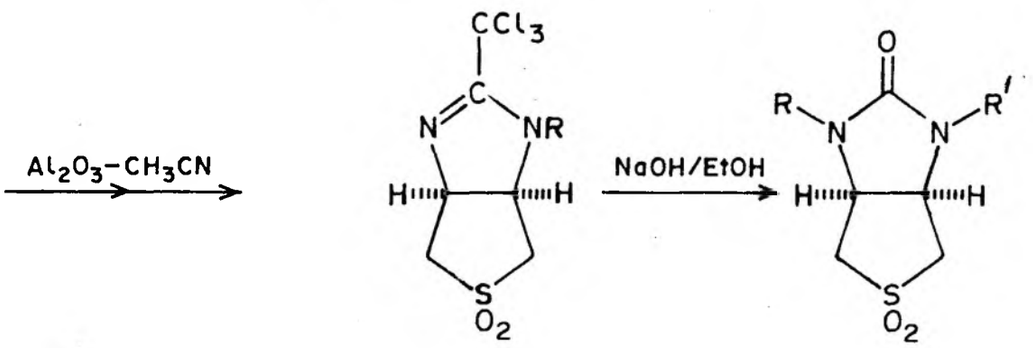


15 16: R = CH_2–Ph 2: R = Ch_2–Ph

CHART 2·1·3



12 17 18

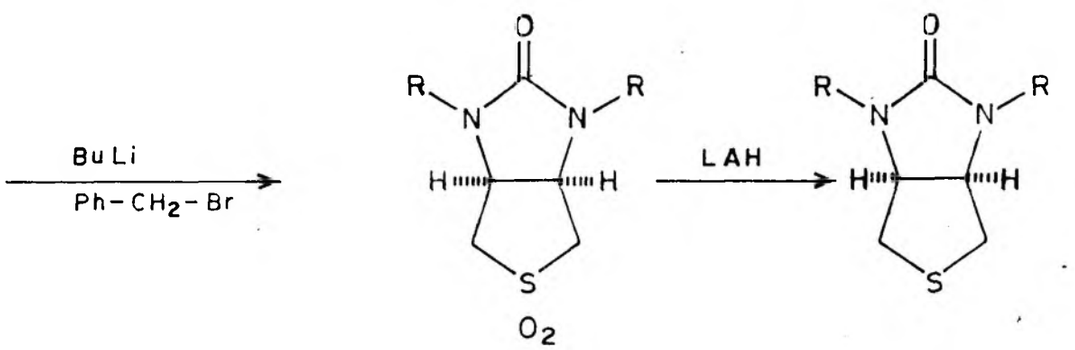


19

R = H

R' = CH_2Ph

20



R = CH_2Ph

16 2

CHART – 2·1·4

2.2.0 PRESENT WORK

The present work mainly describes two alternate syntheses of the sulfide (2) starting from the inexpensive and abundantly available cis-butene-1,4-diol (21) (Chart 2.2.1). The significance of these two approaches is a new methodology whereby a one-step efficient conversion of the diurethane (27) to the imidazolidone (28) or the dibenzyl imidazolidone (33) as desired can be effected. The method is hopefully of general utility for the conversion of vicinal diamines to imidazolidones.

1,3-Dioxepin (22) was prepared in 85% yield from cis-butene-1,4-diol (21) by reported procedure[5]. Controlled oxidation of (22) with aqueous $KMnO_4$ at 0° for 6 hr followed by continuous ether extraction of the reaction product furnished the cis diol (23) as a viscous oil in 50% yield, (IR, cm^{-1} 3450). Methanesulfonylation (CH_3SO_2Cl-pyridine-dichloromethane) of (23) gave a crystalline dimesylate (24), m.p. 129-31° (90% yield). The dimesylate was then heated with excess of sodiumazide in DMF at 90° for 5 hr to furnish the cis-diazide (25) as a pale yellow oil (85% yield), IR (Film: cm^{-1}) 2230 ($-N_3$). Catalytic hydrogenation of (25) in methanol at atmospheric pressure and room temperature using 10% Pd/C gave the diamine (26), a thick brown liquid in almost quantitative yield. The diamine (26) was treated with ethylchloroformate in aqueous

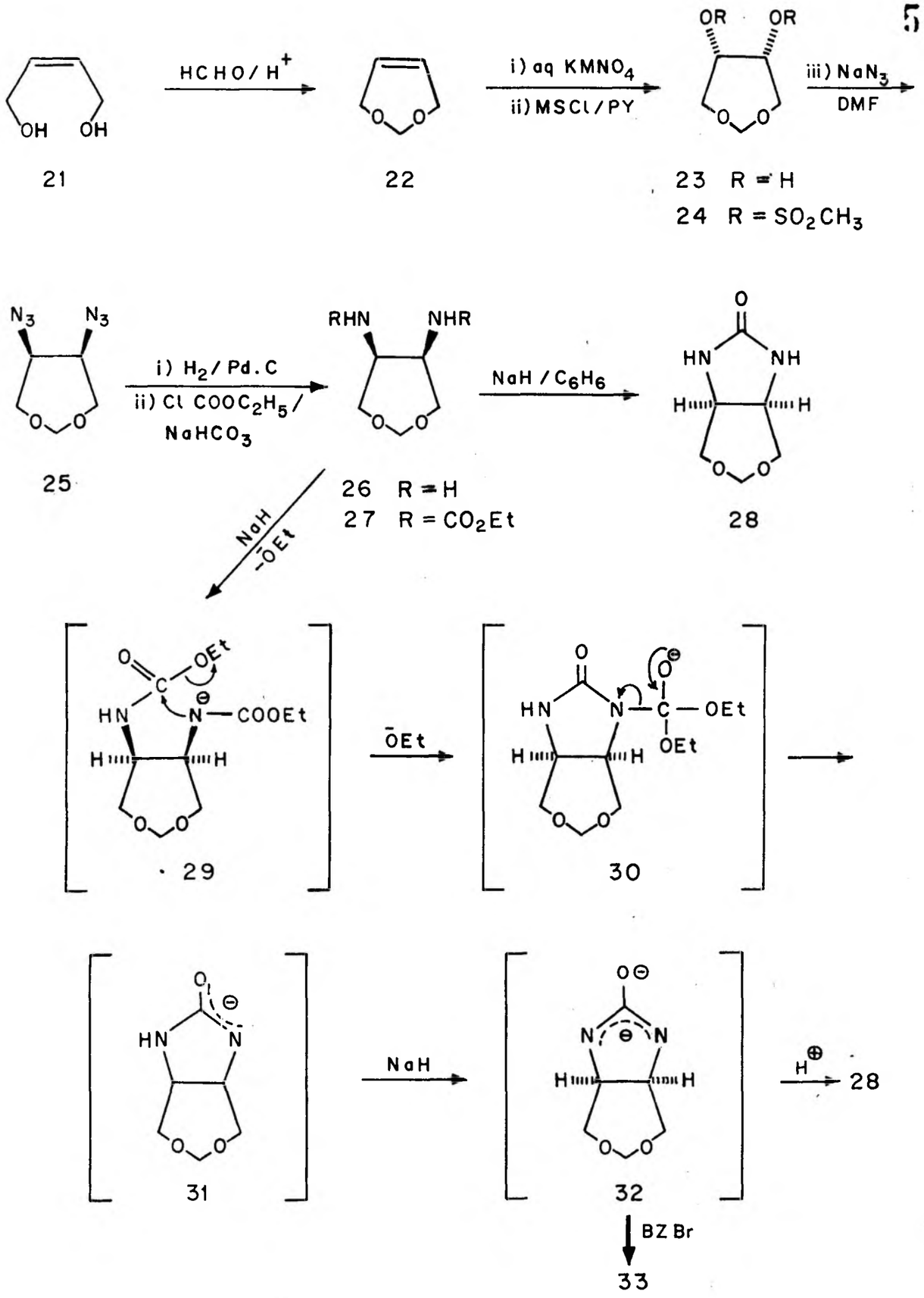

HCHO / H+
i) aq KMnO4
ii) MSCl / PY
iii) NaN3
DMF
21
22
23 R = H
24 R = SO2CH3
i) H2 / Pd.C
ii) Cl COOC2H5 / NaHCO3
NaH / C6H6
25
26 R = H
27 R = CO2Et
28
NaH
-OEt
29
OEt
30
NaH
31
32
BZ Br
33

CHART - 2·2·1

alcoholic bicarbonate at room temperature for 4 hr and was converted to the crystalline diurethane (27) which was characterised by spectral analysis, m.p. 75°; IR (Nujol, cm^{-1}) 3460 & 1695 (N-H & NH-C(=O)-).

The diamine (26) on treatment with phosgene gave a resinous mass from which the desired imidazolidone (12) m.p. 245-250°C (decomp.) M^+ 158 was isolated in very poor yields (8%). The imidazolidone is highly soluble in water and sparingly soluble in most of the commonly used organic solvents and hence posed the problem of isolation and purification from the reaction mixture.

As the efforts to convert the diamine (26) to the imidazolidone (28) did not result in good yields, the cyclisation of the diurethane (27) with sodium hydride in dry benzene with a hope to get (30) which could be easily hydrolysed and decarboxylated to the imidazolidone (28). Interestingly however, aqueous work up of this reaction resulted exclusively in formation of (28) and not (30) as anticipated. The imidazolidone (28) on treatment with benzylbromide in presence of NaH in dry DMF furnished N,N'-dibenzyl imidazolidone (33) in 80% yield; m.p. 132°; M^+ 338.

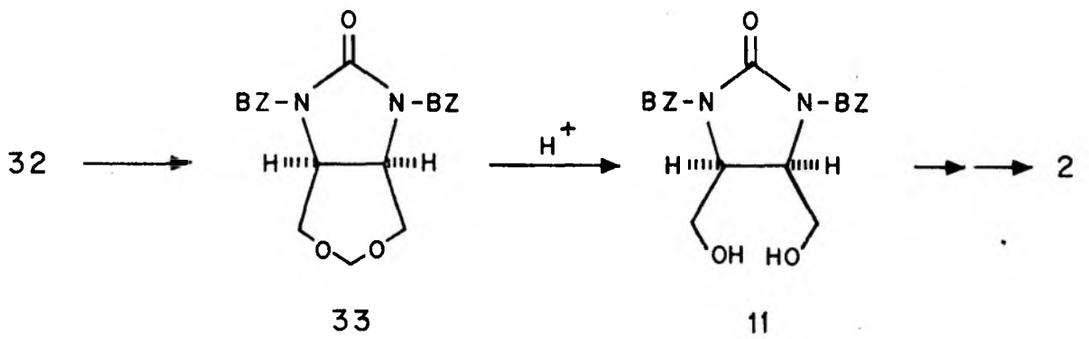
Alternatively, the diurethane (27) was smoothly converted to (33) directly in one-pot reaction by reacting

(27) with benzylbromide in dry benzene in presence of excess of sodium hydride in (80%) yield. The mechanism of formation of (28) and (33) from 27 is schematically represented in Chart 2.2.1.

Hydrolysis of (33) with ethanolic hydrochloric acid furnished the diol (18), in 73.6% yield, m.p. 129-130° (reported 130°)[1].

Conversion of the diol to the desired sulfide (2) was achieved by methanesulfonylation and treatment with sodium sulfide in ethanol. Compound (2) was identical in all its properties with those reported earlier[1]. Since, in this route the overall yield of the diol (23) from the dioxepin (22) is not very satisfactory, an alternate method of preparing the sulfide *via* the epoxide (34) was investigated (Chart 2.2.2).

The dioxepin on oxidation with MCPBA in dichloromethane gave the epoxide (34) in 76% yield, m.p. 55°[6]. Ammonolysis of (34) with methanolic-ammonia in a sealed tube at 100-120° furnished the *trans* aminoalcohol (35) as a dark brown liquid. This on treatment with ethyl chloroformate in ethanol afforded the crystalline urethane alcohol (36) m.p. 110-112° (70% yield on epoxide), M^+ 205, ^1H NMR in D_2O showed a triplet at 1.13 (3H) and quartet at 4.0 (2H) due to methyl and methylene protons ($-O-CH_2-CH_3$)



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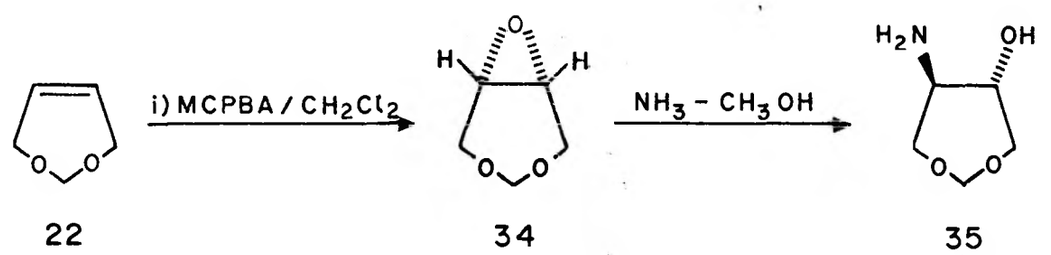
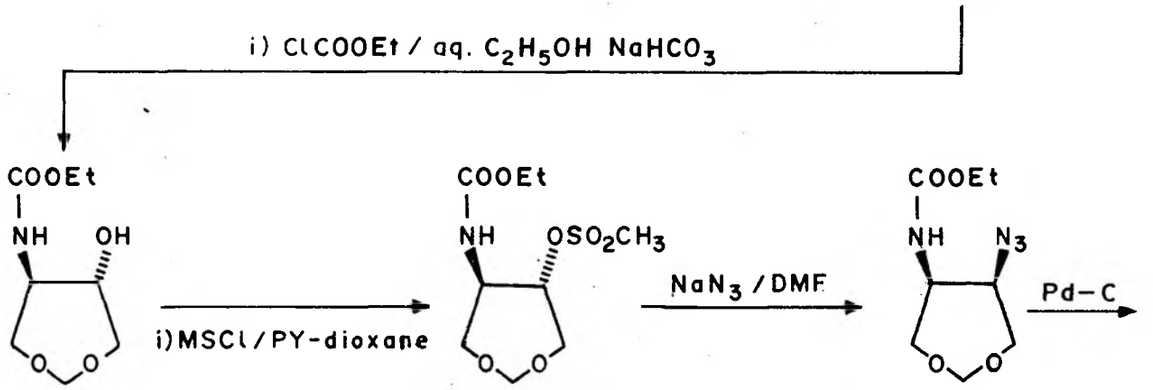
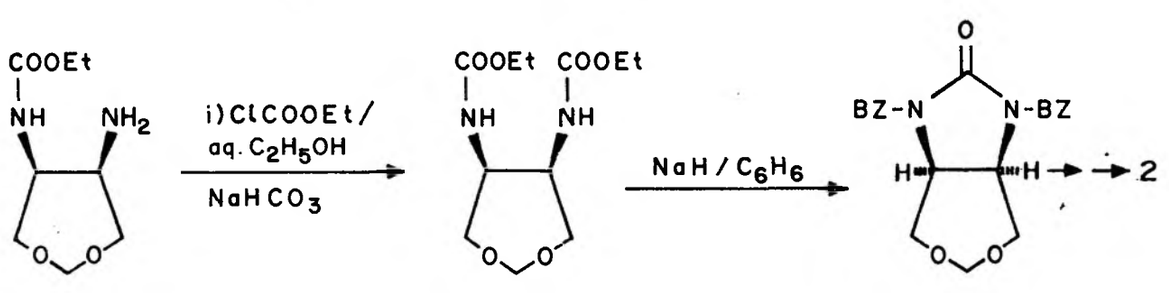


22 34 35



36 37 38



39 27 33

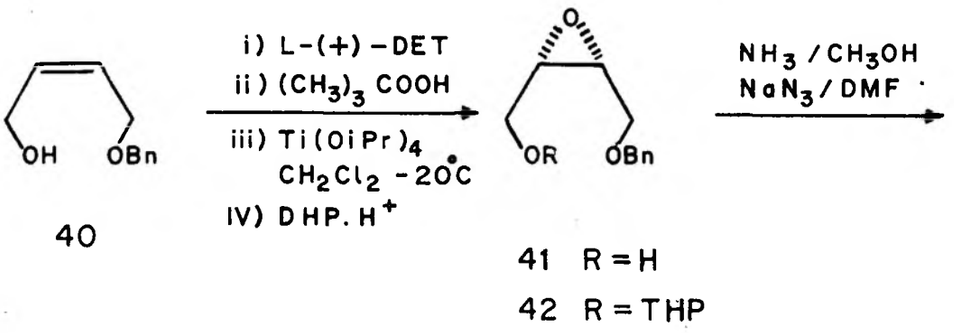
CHART-2·2·2

and 4.63 (s, 2H, -O-CH_2-O-). The urethane alcohol (36) on mesylation (MsCl-pyridine-dioxane) gave crystalline (37) in 90% yield, m.p. 91-92°, M^+ 283. Reacting the mesylate (37) with excess of sodium azide in HMPA for 48 hr at 50° furnished the cis azide (38) as a pale yellow oil (76%). The IR spectrum of (38) showed a strong band at 2110 cm^{-1} due to $-N_3$ stretching vibrations. The azide (38) was smoothly reduced to the amine (39) by catalytic hydrogenation over 10% Pd/C catalyst. The amine (39) on reacting with ethyl chloroformate furnished a diurethane which was identical with (27) in all respects.

Since the conversion of the sulfide to (±)biotin is already reported[1] this work also constituted a new total synthesis of (±)biotin from cis-butene-1,4-diol.

Attempted synthesis of optically active cis-tetrahydro-2-oxofurano[3,4-d] 1,3-dibenzyl imidazolidone (51)

Since a new approach has been developed for the construction of imidazolidone system on epoxide, it was envisaged that the Sharpless epoxidation[7] on cis-but-2-ene-1,4-diol mono-benzyl ether (40) would give the required asymmetric epoxide (41) which can be easily transformed to imidazolidone (48) and the latter can be converted to optically active lactone (51) (Chart 2.2.3). The lactone on further elaboration using reported procedure would give (+)biotin, as shown in (Chart 2.2.4). A derivative of the same lactone



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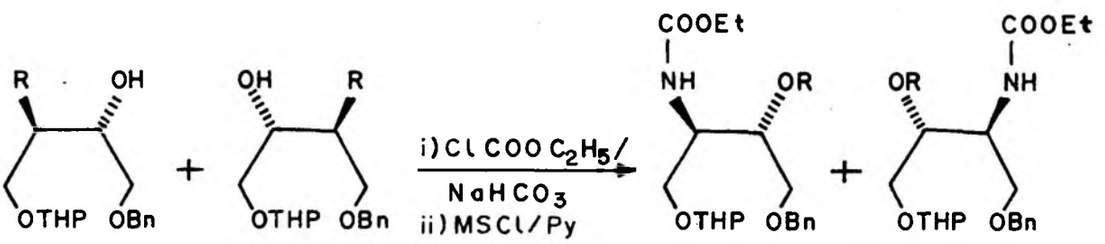
41 R = H

42 R = THP

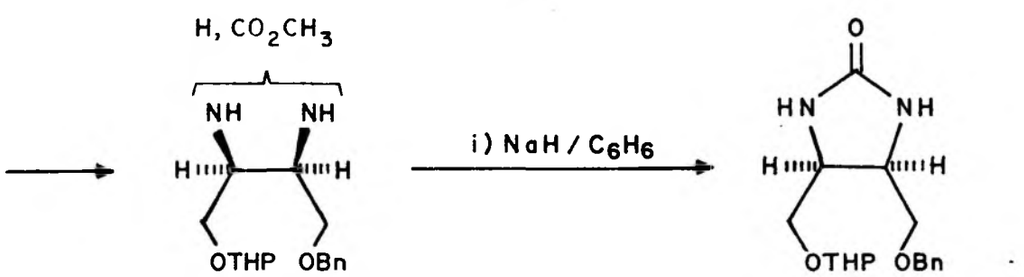


43 R = N_3

44 R = NH_2

45 R = H

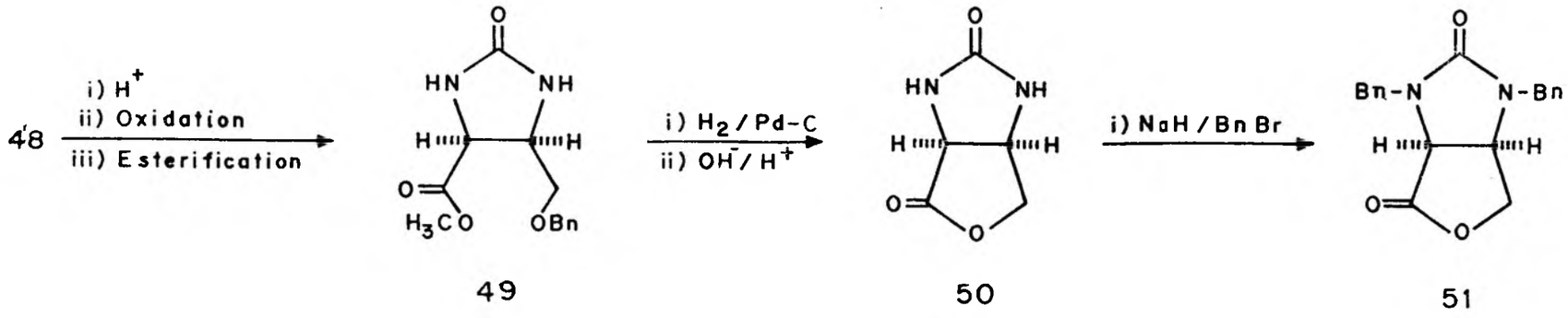
46 R = MS



47

48

Chart 2·2·3



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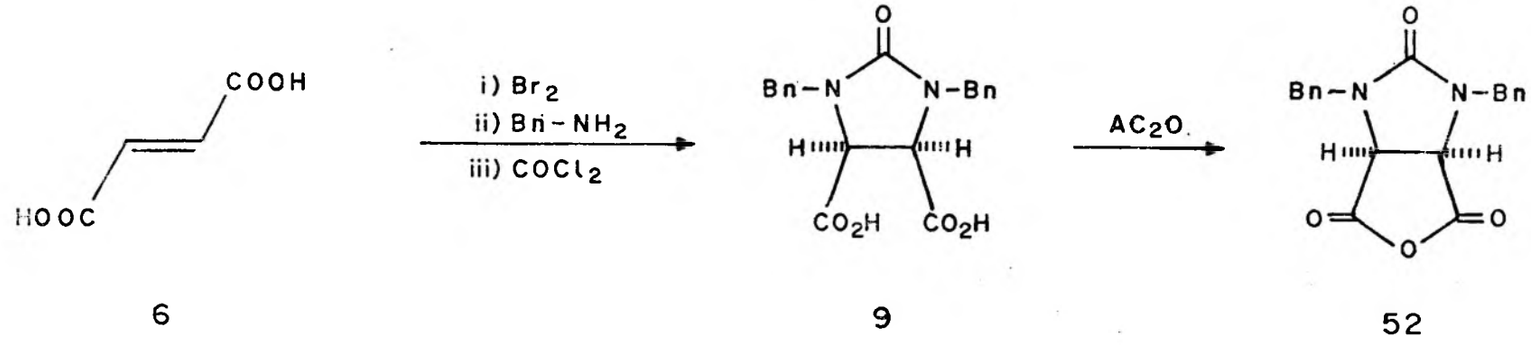

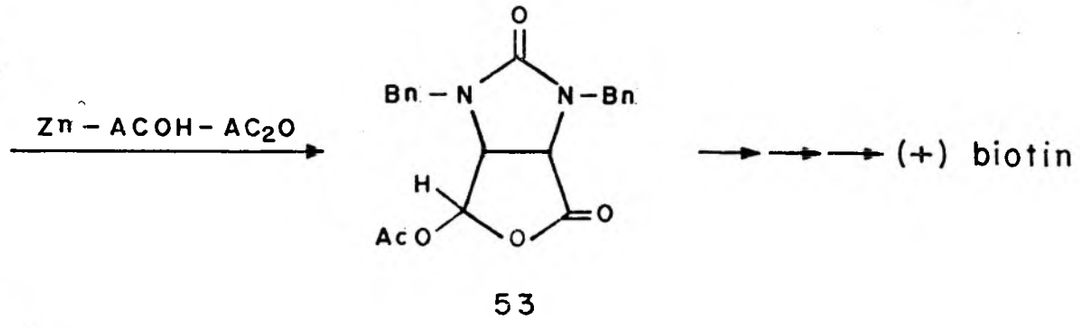

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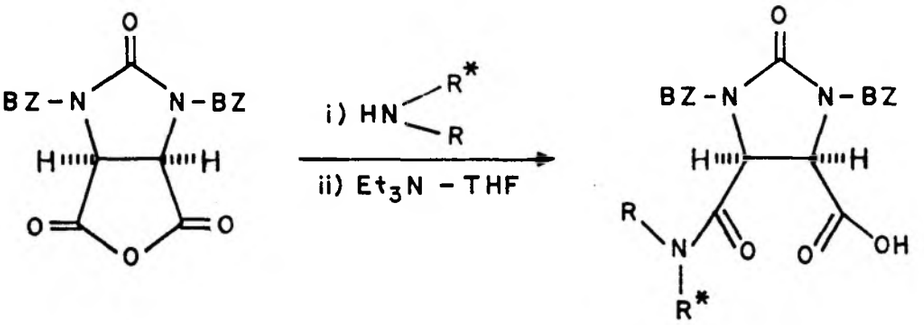
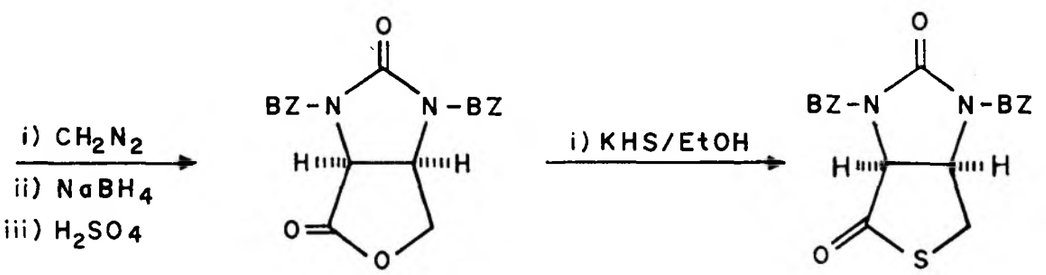
in the racemic form (53) was the intermediate in the preparation of (+)biotin as reported by Hofmann La Roche group[8] who started from fumaric acid and introduced a resolution step at an intermediate stage to get natural biotin. Preparation of the lactone in the optically active form (51) was also reported later by Japanese workers[9] which was based on the reaction of an optically active amine with the Hofmann La Roche anhydride (52) (Chart 2.2.5). Thus the reaction of (52) with an optically active secondary amine in presence of triethylamine proceeded enantioselectively to produce a diastereomeric mixture of half amide salt (54), whose esterification followed by reduction and hydrolysis gave optically active lactone (55).

Compound (55) could be further elaborated to (+)biotin by the reactions reported in literature[8]. This avoided chemical resolution. Our scheme for the asymmetric synthesis of (51) started with the chemical differentiation of allyl alcohol group in cis-butenediol by monoprotection. The reported procedure[10] for the conversion of cis-butenediol (21) to its monobenzyl ether (40) is to reduce its benzylidene (52) derivative with LAH. However, it was observed by us that compound (40) could also be obtained in excellent yields in one shot by heating diol (21) with benzyl bromide in presence of excess of anhydrous K_2CO_3 in refluxing acetone. Sharpless epoxidation



52 54



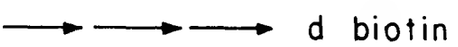


CHART-2·2·5

of (40) using one equivalent of titanium tetraisopropoxide at -20° gave the epoxide (41) in 80% yield which showed specific rotation of -6° (lit.[11] -27°). However, when the same reaction was carried with two equivalents of titanium tetraisopropoxide at -20° the rotation improved to -21.5°. The epoxide with $[\alpha]_D$ of -21.5 was converted to its THP derivative (42) which on heating with saturated solution of methanolic ammonia led to the formation of amino alcohol (44). This compound was characterised as its urethane alcohol (45). Its IR spectrum (film) showed bands at 3340 (b, NH, OH) and 1730 cm^{-1} (urethane carbonyl). Our next plan was to mesylate the OH functionality in (45) and then do a catalytic hydrogenation to obtain the amino urethane (47). However all attempts to prepare (46) by known methods were unsuccessful. The reasons for failure could not be ascertained.

As an alternative, the azido alcohol (43) was prepared from the epoxide (42) and attempts to mesylate the alcohol (43), however, resulted in a mixture of several products (TLC) from which the desired product could not be identified.

Attempts at the synthesis of the thieno imidazolidone (2)

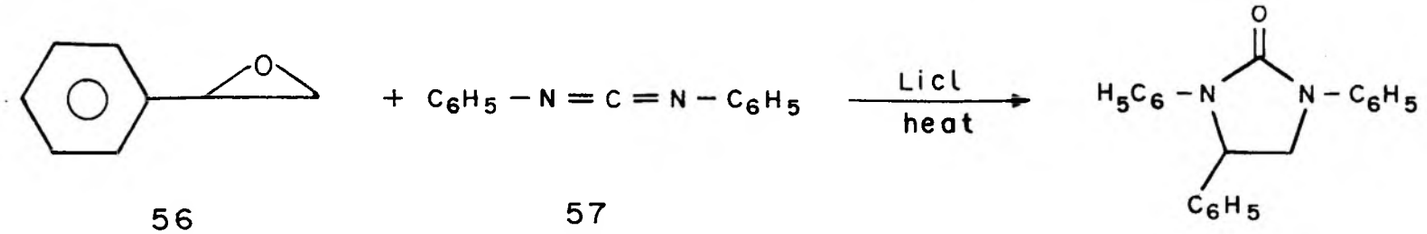
i) By reaction between epoxides and carbodiimides

It is reported by Gulbis and Hamann[12] that styreneoxide (56) on heating with diphenylcarbodiimide (57) furnished the imidazolidone (58) (Chart 2.2.6). In order to ascertain whether the reaction is of general utility and can be extended to the synthesis of (2) a model experiment was carried out in which styreneoxide was heated with the readily available dicyclohexylcarbodiimide (60) in presence of LiCl with and without BF_3 etherate. There was no reaction. The reactants recovered were almost unchanged. Similarly the epoxide (34) failed to furnish (62) on heating with dicyclohexylcarbodiimide (60).

ii) By cycloaddition reactions

The cycloaddition reaction of cyclohexene (63) with dichloro dimethyl ether[13] (64) in presence of MeLi has been shown to yield cis fused bicyclic system of the type (65) (Chart 2.2.7). Similar type of intramolecular cycloadditions have been studied by Huisgen and coworkers[14] leading to the formation of the five-membered heterocyclic compounds. Although these reactions may be closely related to 6 π -electron cyclisation reactions, the mechanism is not very clear and has been presented as shown in (Chart 2.2.7).

In analogy with the above reactions it was thought



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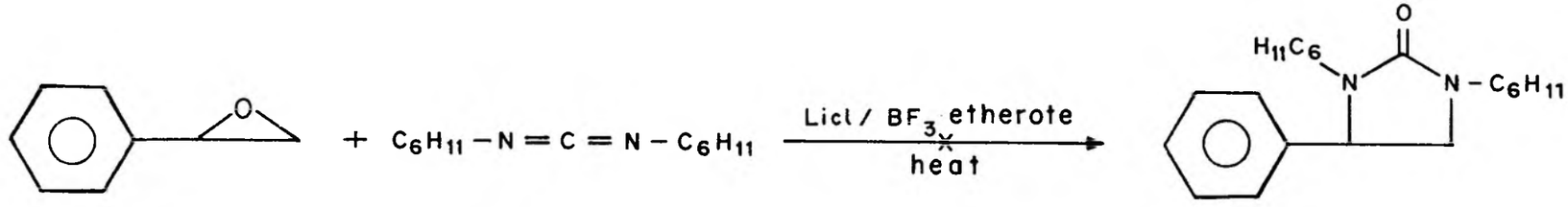

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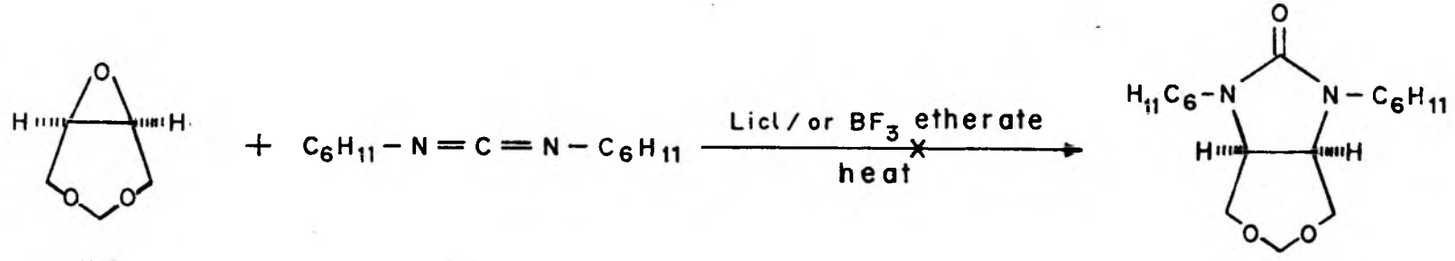

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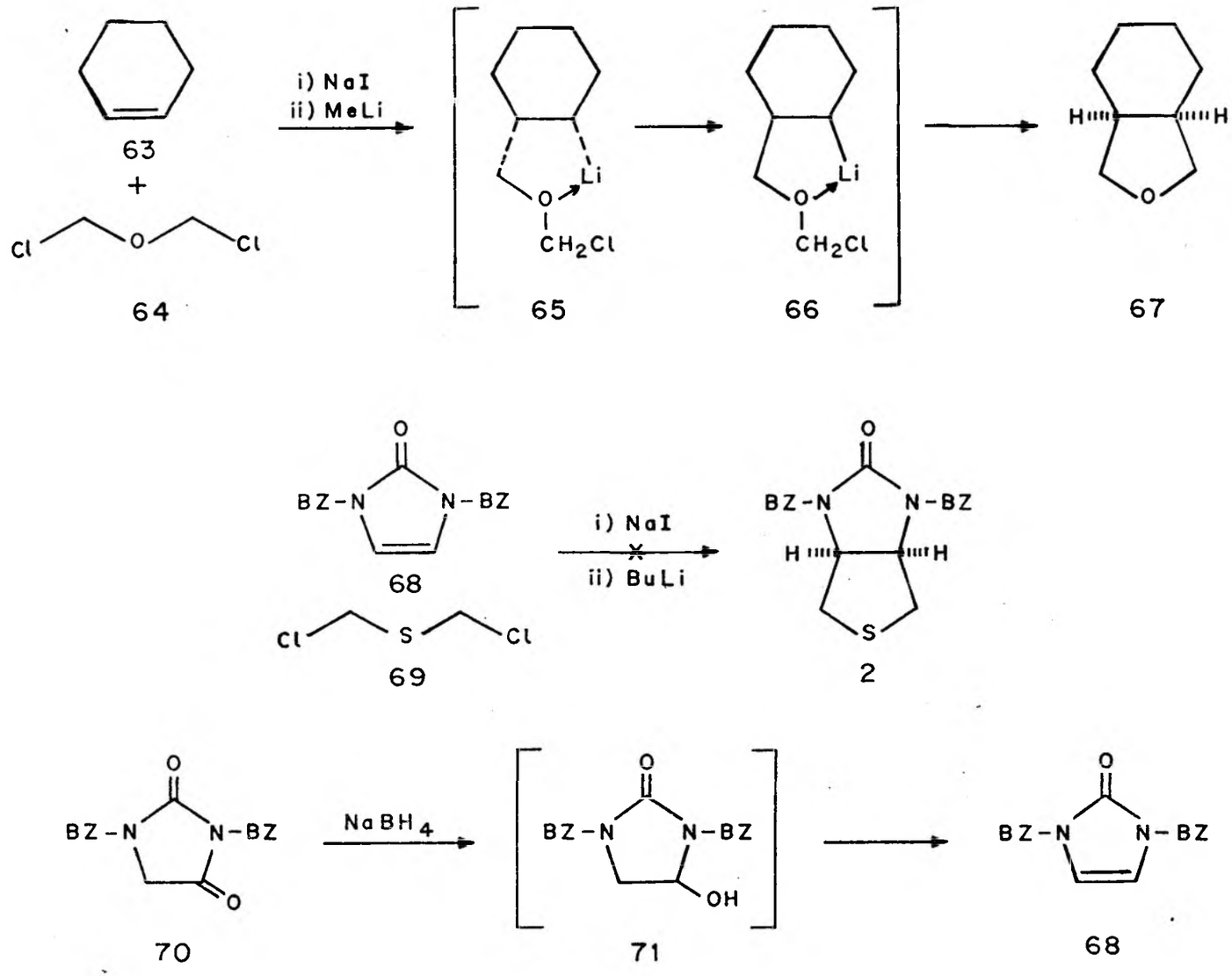

i) NaI
ii) MeLi
63
+
Cl
O
Cl
64
Li
O
CH2Cl
65
66
H
H
O
67
BZ-N
N-BZ
O
68
i) NaI
ii) BuLi
Cl
S
Cl
69
2
NaBH4
OH
70
71

CHART - 2·2·7

worthwhile to explore cycloaddition reaction between 1,3-dibenzyl imidazoline-2-one (68) bis dichlorodimethyl sulfide (69) in order to obtain the thienoimidazolidone (2), a precursor of biotin.

Compound (68) was prepared from N,N'-dibenzyl-hydantoin (70)[15] by reduction with sodium borohydride which instantly gets dehydrated to result in (68). Bis-dichlorodimethyl sulfide (69) was prepared as per literature procedure[16]. A mixture of equimolar quantities of (68) and (69) containing sodiumiodide in ether was cooled to 0°C. N-BuLi was then added under N_2 atmosphere and after 1 hr at 0°C (TLC) indicated that there was no reaction; unreacted (68) was recovered after working up the reaction mixture.

2.3.0 EXPERIMENTAL

Experiments requiring anhydrous ethanol, methanol dichloromethane, were prepared by procedure given in the Text Book of Practical Organic Chemistry by Vogel.

Preparation of n-butyl lithium

Prepared according to the reported procedure[17] from lithium (15.4 g, 2.2 moles) and n-butyl chloride (92.5 g, 1 mole) in petroleum ether at reflux or lithium (7.7 g, 1.1 mole) and butyl bromide (68.5 g, 0.5 mole) in ether at -10° and estimated by the double titration method of Gilman.

Cis-1,3 dioxepin (22) was prepared by the known procedure[5] from cis-butene 1,4-diol (21), b.p. 110°C. Reported 110°C[5].

Preparation of 5,6-dihydroxy tetrahydro-1,3-dioxepin (23)

To an ice cold mixture of dioxepin (22), 10g and water (100 ml) an aqueous solution of $KMnO_4$ (16 g in 150 ml of water) was added slowly with vigorous stirring during an hour. The reaction mixture was stirred for additional 4.0 hr at 0°C. It was filtered, the filtrate was treated with 100 g of potassium carbonate and extracted with ether using liquid-liquid extractor. The ether extract was dried and evaporated to furnish almost pure (TLC) diol 6.7 g (50% yield), b.p. 120-122°/4 mm Hg. IR (Film) 3450 cm^{-1} (-OH). Fig.2.3.1.

Preparation of cis-5,6-dimesyl tetrahydro-1,3 dioxepin (24)

To an ice-cold solution of the diol (23), 12.1 g in pyridine (35 ml) and methylene chloride (50 ml) methanesulfonylchloride (28 ml) was added dropwise with stirring. The reaction mixture was allowed to stand at R.T. for 15 hr. It was poured in 200 ml ice-cold water and extracted successively with 3 x 300 ml methylene chloride. The combined extract was washed with hydrochloric acid (10%) then with water and dried. Evaporation of methylene chloride and crystallisation of the resulting product from ethyl acetate furnished the dimesylate (24), 24 g (89.5% yield), m.p. 129-131°C. IR (Nujol) cm^{-1} 1183 and 1357 ($-O-SO_2CH_3$). ^1H NMR ($CDCl_3$) δ 3.2 (S, 6H, 2 X SO_3CH_3) 4.03, m, 4H, 2 X $-OCH_2$); 4.85 (S, 2H, $-O-CH_2-O-$); 5.03 (m, 2H, 2 X $-CH-OSO_2-$). Fig. 2.3.2.

Preparation of cis-5,6-diazidotetrahydro-1,3-dioxepin (25)

A mixture of dimesylate (24) (5.3 g, 0.018 mol) and sodium azide (7.8 g, 0.12 mole) in DMF (30 ml) was heated to 80-90°C for 4 hr with stirring. The reaction product was cooled, diluted with water and extracted with hexane, washed with water and dried. Evaporation of the solvent furnished the diazide 2.8 g as a pale yellow oil (83.3% yield). IR (Film) 2137 cm^{-1} ($-N_3$). Fig. 2.3.3. ^1H NMR ($CDCl_3$) δ 4.0 (m, 6H); 4.86 (s, 2H).

Preparation of 5,6 diamino-tetrahydro 1,3 dioxepin (26)

A solution of the diazide (25) (2 g) in 50 ml of methanol

was hydrogenated at R.T. for 6 hr at 15 psi in presence of 10% Pd-C catalyst. Catalyst was filtered and the solvent evaporated to furnish the diamine (2 g) as a thick brownish liquid. The TLC and IR of the product showed absence of the starting material. The product without further purification was used for the preparation of the diurethane (27).

Preparation of cis 5,6-carboethoxyamino tetrahydro 1,3-dioxepin (27)

The diamine (26) (1.32 g, 0.01 mole) in 200 ml of ethanol was treated with ethyl chloroformate (5.4 g, 0.025 mole) at R.T. The pH of the reaction media was maintained between 8 and 9 by addition of 10% sodium bicarbonate. After 4.0 hr the reaction product was extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated to afford the crystalline diurethane 2.35 g (85% yield), m.p. 76-76°C; IR (Nujol) 3460 cm^{-1} (-NH), 1695 amide carbonyl (-NH-CO). ^1H NMR (CCl_4) δ 2.6 (t, 6H, 2 x CH_3) 3.83 (m, 10H), 4.7 (s, 2H, -O-CH_2-O-); 5.40 (bd, 2H, 2 X NH-C=O). Fig. 2.3.4.

Analysis: Calculated for $C_{11}H_{20}N_2O_6$: C, 47.8; H, 7.2; N, 10.15. Found: C, 47.87; H, 7.4; N, 10.45%.

Preparation of imidazolidone (28) from diamine (26)

To an ice cold solution of the diamine (1 g) in ether (25 ml), containing 2 g of sodium carbonate, a 2% solution of phosgene in toluene (100 ml) was added dropwise

in about an hour. Excess of phosgene was removed by bubbling nitrogen. The product was filtered and the filtrate was evaporated under reduced pressure to give resinous mass which was successively extracted with methanol. The extract was evaporated and the residue was crystallised from water to furnish crystalline product (28) in 8% yield. M.p. 245-250°C (decomp.); IR (Nujol) 1690 cm^{-1}. Fig. 2.3.5.

Analysis: Calculated for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.32; N, 17.72. Found: C, 45.36; H, 6.57; N, 17.79%.

Imidazolidone (28) from the diurethane (27)

To a solution of diurethane (1.38 g, 0.005 mole) in dry benzene (25 ml), NaH (0.360 g, 0.015 mole) was added and the reaction product was stirred for 12 hr at R.T. It was poured in 50 ml of cold water aqueous layer was separated. Aqueous layer was acidified with 10% HCl and was evaporated to dryness under reduced pressure. The residue 1.6 g was a mixture of imidazolidone and sodium chloride. The mixture was directly used for the preparation of dibenzyl derivative.

Dibenzylimidazolidone (33)

The residue (1.6 g) from the above experiment was taken in DMF (25 ml) and was stirred at R.T. with NaH (0.360 g) and benzyl bromide 2 ml (0.016 mole) for 12 hr and at 80°C for 2 hr. The product was cooled and extracted with 3 x 50 ml of hexane. The combined organic layer was dried and evaporated. The solid residue was crystallised to give imidazolidone (33)

1.33 g (79% yield), m.p.132°C, M^+ 338. IR (Nujol) 1680 cm^{-1} (-N-C-). ^1H NMR ($CDCl_3$) δ 3.69 (d, 4H, 2X -O-CH_2), 3.88 (m, 2H, 2X CH-N-C-), 4.08 & 4.96 (d, AB, 4H, J = 15 Hz, 2X CH_2-φ), 4.61 & 4.84 (d, AB, 2H, J = 6 Hz, -O-CH_2-O) and 7.24 (s, 10H, Ar-H). Fig. 2.3.6.

Analysis: Calculated for $C_{20}H_{22}N_2O_3$: C, 71.00; H, 6.5 and N, 8.68. Found: C, 70.84; H, 6.77 and N, 8.37%.

One pot preparation of N,N-dibenzylimidazolidone (33) from (27)

To a solution of diurethane (1.38 g, 0.005 mole) in dry benzene (30 ml), sodium hydride (0.720 g; 0.03 mole) was added. The reaction mixture was stirred for 4.0 hr at R.T. when most of the diurethane in the reaction mixture disappeared. Benzyl bromide (2 ml) was added and the stirring continued for 12.0 hr at R.T.and 2.0 hr at 80°. The product was cooled and was poured in ice cold water (50 ml). Benzene layer was separated, aqueous layer was acidified (10% HCl) and was extracted with benzene (3 x 25 ml). Organic layers were pooled and washed with water and evaporated to give (33) 1.35 g(80% yield), m.p. 132°C. ^1H NMR and IR were identical with the spectra of N,N-dibenzylimidazolidone (33) prepared earlier.

Preparation of diol (11)

A solution of dibenzyl imidazolidone (33) 1.7 g in ethanol, containing 1 ml of conc. HCl was refluxed on steam bath

for 8.0 hr. Solvent was distilled off and the residue was crystallised from methylene chloride to furnish the diol 1.2 g (73.6%) m.p. 129-130°C (reported 130°C), M^+ 326. IR (Nujol, cm^{-1}) 3200 (-OH) 1670 (amide -C(=O)-NH). Fig.2.3.8. ^1H NMR (d_6 DMSO) δ 3.44 (m, 2H), 3.7 (m, 4H), 4.16 & 4.71 (AB, 4H, J = 15 Hz) and 7.4 (s, 10H, Ar-H). Fig.2.3.7.

The dimesylate and the sulfide were prepared according to the procedure reported by French workers.

The dimesylate: m.p. 144°C; M^+ 482; ^1H NMR ($CDCl_3$) δ 2.9 (s, 2H, 2X $-OCH_3$); 3.76 (m, 4H, 2X $-O-CH_2-$), 4.36 (m, 2H, 2X -CH), 3.93 & 4.78 (AB: 4H, J = 15 Hz, 2X OCH_2), 7.2 (s, 10H, Ar-H).

The sulfide: m.p. 124-125°C; ^1H NMR ($CDCl_3$) δ 2.73 (4H, 2X 2 CH_2), 4.60 (2H, 2X -CH), 4.2 and 4.66 (AB, 4H, J = 15 Hz, 2X $-CH_2-\phi$) 7.3 (s, 10H, Ar-H). Fig.2.3.9.

Preparation of epoxide (34)

A solution of m-chloroperbenzoic acid (85% 10.5 g, 0.052 mole) in chloroform (30 ml) was stirred magnetically in an ice bath. Dioxepin (22) (5 g, 0.05 mole) was added dropwise over a period of 1 hr. Stirring was continued for 1 hr at 0°C and then at R.T. for 3 hr. The reaction mixture was filtered and the filterate was washed with 0.1N NaOH solution and brine, dried and solvent distilled off to give the epoxide 4.4 g in 76% yield, m.p. 55°C; ^1H NMR (CCl_4) 3.06 (m, 2H, 2X -O-CH), 4.03 (d, 4H, 2X $-O-CH_2-$) and 4.6

(q, 2H, -O-CH_2-O-).

Preparation of 6-amino 5-hydroxy tetrahydro 1,3-dioxepin (35)

A solution of the epoxide (3.58 g) in methanol ammonia (25 ml) was heated to 120°C in a steel bomb for 6 hr. The reaction product was cooled and the solvent was distilled off to give the amino alcohol (4 g) as a viscous brownish oil which without further purification was directly used for the preparation of urethane alcohol (36).

Preparation of urethane alcohol (36)

To a solution of amino alcohol (35, 4g) in ethanol (25 ml) ethyl chloroformate (4.9 g) was added with stirring at R.T. the pH of the reaction mixture was maintained between 8-9 by addition of 10% $NaHCO_3$ solution to the reaction mixture. After 4 hr, the product was extracted with methylene chloride (3 x 30 ml). The extracts were combined, washed with brine and evaporated. The resulting product was crystallised from ethyl acetate to give a crystalline urethane-alcohol (36) in 70% yield on epoxide (34); m.p. 110-112°C. ^1H NMR (D_2O) δ 1.13 (t, 3H, $CH_2\underline{CH}_3$), 3.66 (m, 6H), 4 (q, 2H, -O-$\underline{CH}_2CH_3$), 4.63 (s, 2H, -O-CH_2-O-), Fig. 2.3.10.

Analysis: Calculated for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 47.85; H, 7.34; N, 7.08%.

5-Mesyl 6-carbethoxyaminotetrahydro-1,3-dioxepin (37)

To an ice cold solution of urethane alcohol (1g) in

a mixture of dioxane (10 ml) and pyridine (5 ml). Methanesulfonyl chloride (2 ml) was added dropwise with stirring in 30 min. After the addition, the reaction mixture was stirred for 48 hr, at R.T. The product was poured in 100 ml of water and was extracted with methylene chloride (3 x 25 ml). The combined organic extract was washed subsequently with water, dil. HCl (10%),water and dried. Evaporation of solvent furnished a solid which on crystallisation from actone-pet.ether gave urethane mesylate (37) 1.24 g (90% yield), m.p. 92°, M^+ 283. ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, $-CH_3$), 3.16 (s, 3H, $-O-SO_2-CH_3$), 4 (m, 8H), 4.76 (s, 2H, $-O-CH_2-O-$), 5.53 (d, 1H) (-NH-C-), Fig 2.3.11.

5-Azido-6-carbethoxyamino tetrahydro 1,3-dioxepin (38)

A mixture of the urethane mesylate (2.83 g, 0.01 mole) and sodium azide (3 g, 0.046 mole) in HMPA (25 ml) was heated to 50° with stirring for 24.0 hr. The mixture was cooled, diluted with water and was extracted with benzene (3 x 500 ml). Organic layer was washed with water and evaporated to furnish the azide (38) 1.75 g (76% yield) as a pale yellow oil. IR (Film) 2110 cm^{-1} ($-N_3$), Fig.2.3.12. ^1H NMR (CCl_4) δ 1.23 (t, 3H, CH_3), 3.70 (m, 6H), 4.0 (q, 2H, CH_2-CH_3), 4.63 (s, 2H, $-O-CH_2-O-$) and 4.93 (d, 1H, NH-C=O).

5-Amino-6-carbethoxyamino tetrahydro-1,3-dioxepin (39)

A solution of the azide (38) (1.15 g) in methanol (25 ml) was hydrogenated at R.T. for 6.0 hr at a pressure of

30 psi in presence of 10% pd/C catalyst. The catalyst was filtered and the filterate was evaporated to furnish the amino urethane (1 g) as a viscous brownish oil. The urethane amine (39) on treatment with ethyl chloroformate according to the procedure described earlier for the preparation of diurethane (27) gave the same diurethane in an overall yield of 82%.

Preparation of monobenzyl ether of cis-butene 1,4-diol (40)

The mixture of cis-butene 1,4 diol (21) 8.8 g (0.1 mole), potassium carbonate 6.9 g (0.1 mole) in dry acetone 150 ml was refluxed for 30 min. A solution of benzyl bromide 12 ml (0.1 mole) in 100 ml of acetone was added dropwise to the refluxing reaction mixture of butene diol. After the addition, the contents were further refluxed for 5 to 6 hrs. Potassium carbonate was filtered, acetone was removed by distillation. The crude product was dissolved in water,extracted with 3 x 20 ml of petroleum ether, the combined extracts were washed with water, dried, concentration of the solvent furnished, unreacted benzylbromide, with trace amount of dibenzyl cis-butene-1,4 diol.

The aqueous layer was further extracted with benzene (3 x 25 ml), the combined extracts were washed with water, dried. Removal of the benzene afforded monobenzyl cis-butene-1,4-diol (7.5 g, 42% yield). IR (film) 3400 cm^{-1} (-OH). ^1H NMR (CCl_4) δ 3.0 (s, 1H-OH), 3.75 (d, 4H), 4.15 (s,

2H), 5.3 (m, 2H), 7.0 (s, 5H, ArH).

Asymmetric epoxidation of Monobenzyl cis butene 1,4-diol (40) using Sharpless epoxidation technique[7]

A 100 ml single necked round bottomed flask equipped with a teflon-coated magnetic bar was oven dried, and then fitted with a serum-cap and flushed with nitrogen. The flask was charged with 50 ml of dry dichloromethane (distilled over CaH) and cooled by stirring in a -23°C bath (dry ice-CCl_4). Then the following liquids were added sequentially via syringe, with cooling, 8.9 mol (30 m.mole) of titanium tetraisopropoxide in 10 ml of CH_2Cl_2, 4.1 g (15 m.mole) of L(+)diisopropyl tartrate in 10 ml of CH_2Cl_2. The contents were stirred for minutes, then 2.7 g (15 m.mole) of alcohol (40) in 5 ml of methylene chloride and t-butyl hydroperoxide in ditertiary butyl peroxide 1.8 ml (15 m.mole) were added.

The resulting homogeneous solution was then stored in freezer at -20°C for 5 days. The progress of the epoxidation was monitored by TLC. The reaction was completed in about 5 days.

Then the flask was placed in a -23° bath (dry ice-CCl_4). To this a mixture of precooled 100 ml of acid free acetone containing 10 ml of distilled water was added slowly, with stirring. Then it was stirred for 1 hr at R.T. The precipitate of titanium dioxide was filtered,

acetone was removed under vacuum. To the aqueous part 150 ml of ether was added, it was cooled to 0°C and calculated amount of NaOH solution (to hydrolyse diethyl tartarate) was added dropwise. It was stirred vigorously for 40 min. at 0°. The organic layer was separated, aq. layer was extracted with ether (3 x 15 ml). The combined ether layer was washed with brine solution, dried. Evaporation of solvent furnished the epoxide (41), 2.2 g with trace of starting material. Product was purified by resolving in silica gel column. The epoxide (41) was isolated in pure form, 1.9 g, $[\alpha]_D$ -21.7°. Reported: -27°. IR (film): 3470 cm^{-1} (-OH). ^1H NMR (CCl_4): Fig.2.3.13.

Preparation of THP ether of the epoxide (41)

To a solution of epoxy alcohol (41) (3.8 g, 0.02 mole) in 20 ml of dry chloroform cooled to 0°C, catalytic amount of p-toluene sulfonic acid was added. A solution of 3.15 g (0.03 moles) dihydropyran in 10 ml of chloroform was added dropwise, after being stirred for 15-20 minutes at 0°C, it was allowed to stir at R.T. for 30 min. To the reaction mixture solid anhydrous potassium carbonate was added, the suspension formed was stirred vigorously for 30 min. and then filtered through a fluted filter paper to remove solid potassium carbonate. The clear filtrate was concentrated under vacuum, residue was purified by chromatography to give pure (42) 4.5 g.

^{1}H NMRδ1.60 (m, 6H), 3.15 (m, 2H), 3.60 (m, 7H), 4.60 (s, 2H), 7.40 (s, 5H, Ar-H).($CDCl_3$)

Preparation of urethane alcohol (45)

To a solution of THP ether of the epoxide (42) 2.78 g (0.01 mole) in 5 ml of methanol was added 15 ml of methanol containing 3 g of NH_3. The reaction mixture was heated in sealed steel tube at 120°C for 2 hrs. The tube was cooled to 0°C, the reaction mixture was transformed to a R.B. flask, and the solvent was removed under reduced pressure. The coloured residue containing (44) was dissolved in ethanol and to this ethyl chloroformate was added dropwise followed by the addition of $NaHCO_3$ solution intermittently to maintain the pH of the reaction mixture between 8-9. After the addition, stirring was continued for 2 hr. The reaction mixture was diluted with few cc of water, extracted with CH_2Cl_2, the combined organic extracts were washed with water, dried. Removal of the solvent furnished thick liquid which was purified by column chromatography to give (45) 2.5 g, IR (film) 3320 (-OH) 1730 cm^{-1}, -HN-C(=O). ^{1}H NMR ($CDCl_3$) Fig.2.3.14. Analysis: Calculated for $C_{19}H_{29}O_6N$: C, 62.1; H, 7.90; N, 3.8; Found: C, 62.0; H, 7.5; N, 4.20%.

Preparation of urethane mesylate (46)

To a mixture (7:3) of dioxane and pyridine containing excess (1.5 ml) of methane sulfonyl chloride, was cooled to 0°C. The urethane alcohol (66) (367 mg,

0.001 mole) was added slowly. After the addition, the reaction mixture was stirred for 12 hr at R.T. TLC indicated no change in the starting material. Then it was left for 2 days. No progress in the reaction was observed. The reaction was worked out by diluting with water, then extracting with methylene chloride. The starting urethane alcohol was recovered.

Preparation of azido alcohol (43)

To a solution of THP ether epoxide (42) (2.78 g, 0.01 mole) in 15 ml of DMSO was added 1 g sodium azide and the mixture was heated to 100°C for 4 hr. Reaction mixture was diluted with water, extracted with ethyl acetate. The organic extracts were washed with water, dried over sodium sulfate. Removal of the solvent furnished the azide alcohol (43) as a thick liquid, which was purified by column chromatography to give (2.5 g, pure compound). IR (film) 3320 (-OH), 2110 cm^{-1} ($-N_3-$). Fig.2.3.15. ^1H NMR ($CDCl_3$) δ 1.6 (s, 6H), 3.0 (s, 1H), 3.3 - 4.0 (m, 9H), 4.6 (d, 2H), 7.3 (s, 5H).

Reaction of epoxide (34) with Dicyclohexyl carbodiimide (60)

The mixture of epoxide (34) (570 mg, 5 m.mole) dicyclohexyl carbodiimide (60) (970 mg, 5 m.mole) and catalytic amount of lithium chloride was heated in sealed tube for 7 hr at 200°C. The starting epoxide was recovered.

Reaction of styrene oxide (56) with Dicyclohexyl Carbodiimide (60)

Heating at 200°/5 hr resulted only in the recovery of starting styrene oxide unchanged.

Preparation of 1,3-dibenzyl hydantoin (70)

Prepared according to the procedure reported in literature[15], m.p. 64°C, lit. 64-65°.

Preparation of 1,3-dibenzyl imidazoline-2-one (68)

2.80 g of (0.01 mole) 1,3 dibenzyl hydantoin was dissolved in 15 ml of dry methanol to this 740 mg (0.01 mole) of sodium borohydride was added in two to three portions. It was stirred for 1 hr at R.T. The reaction mixture was neutralised with acetic acid. Solvent was removed under vacuum residue was recrystallised in benzene pet.ether (1:1) to give (2.6 g, 98%), m.p. 68°. IR (film): 1680 cm^{-1} (amide carbonyl). ^1H NMR(CCl_4)δ4.60 (s, 4H, 2 X CH_2-Ph), 5.85 (s, 2H), 7.3 (s, 10H, Ar-H).

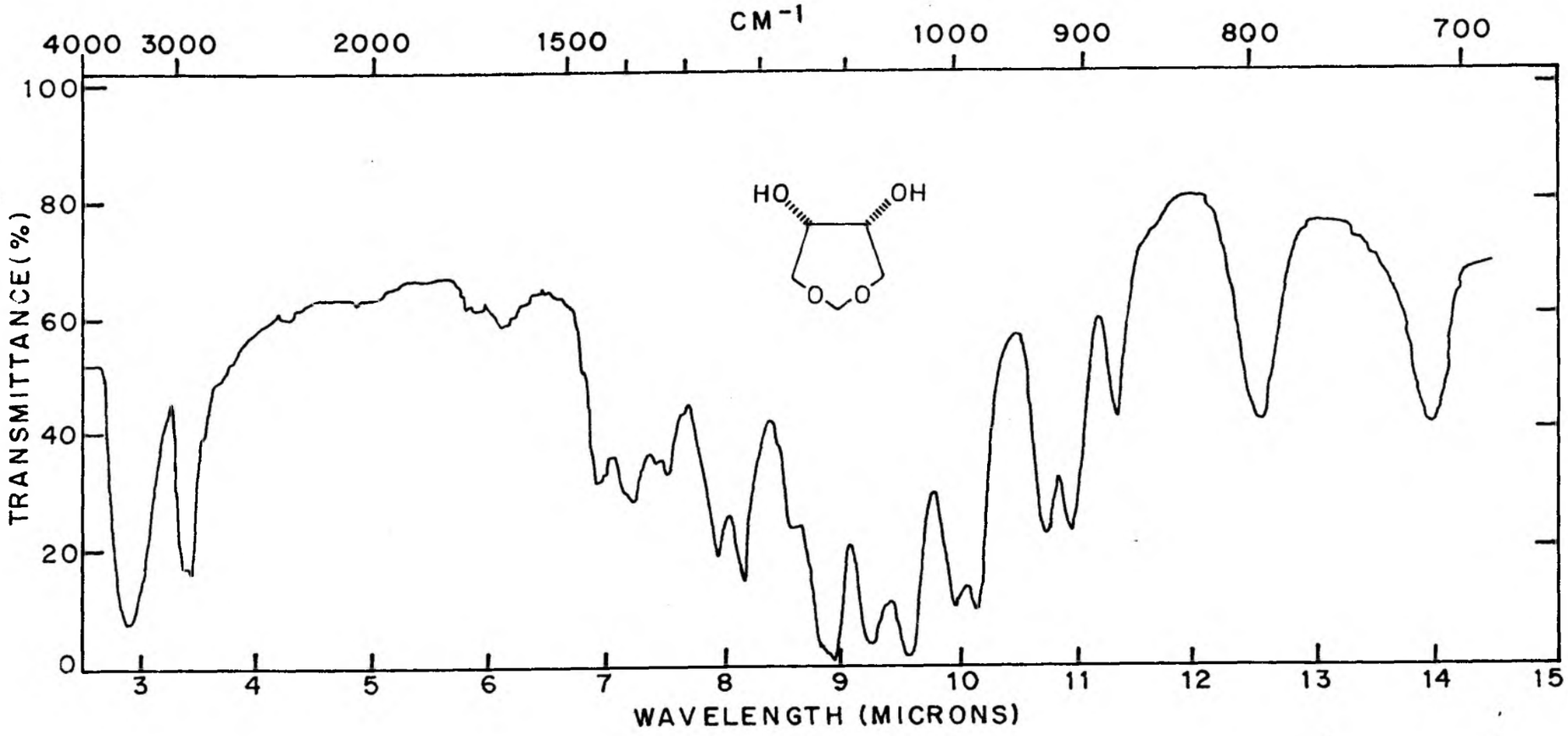
Preparation of bis-dichlorodimethyl sulfide (69)

69 was prepared by the reported procedure[16]. b.p. 156°C at atmospheric pressure. ^1H NMR (CCl_4)δ 4.75 (s, 4H).

Reaction of 1,3-dibenzyl imidazoline-2-one (68) with bis dichlorodimethyl sulfide (69)

A two necked R.B. flask of 25 ml capacity was fitted

with a three way stopcock and a small magnetic bar was introduced, the other neck was closed with septum and the flask was flushed with nitrogen. A solution of 578 mg (2 m.mole) of 1,3-dibenzyl imidazoline-2-one in 4 ml of dry ether was introduced in the flask with the help of syringe. The flask was cooled to 0°C with ice salt mixture. A solution of 260 mg (2 m.mole) of bisdichloro dimethyl sulfide (which was separately treated with 1 eq. of NaI (298 mg, 2 m.mole) in ether was introduced into the flask. A solution of 1 ml of 2N BuLi in pet.ether was added slowly with the help of syringe. After being stirred for 1 hr at 0°C, the reaction mixture was poured in water and the ether layer was separated. Concentration of the solvent resulted only in the recovery of starting 1,3-dibenzyl imidazoline-2-one (68).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100
80
60
40
20
0
TRANSMITTANCE(%)
HO
OH
O
O
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

FIG. 2·3·1

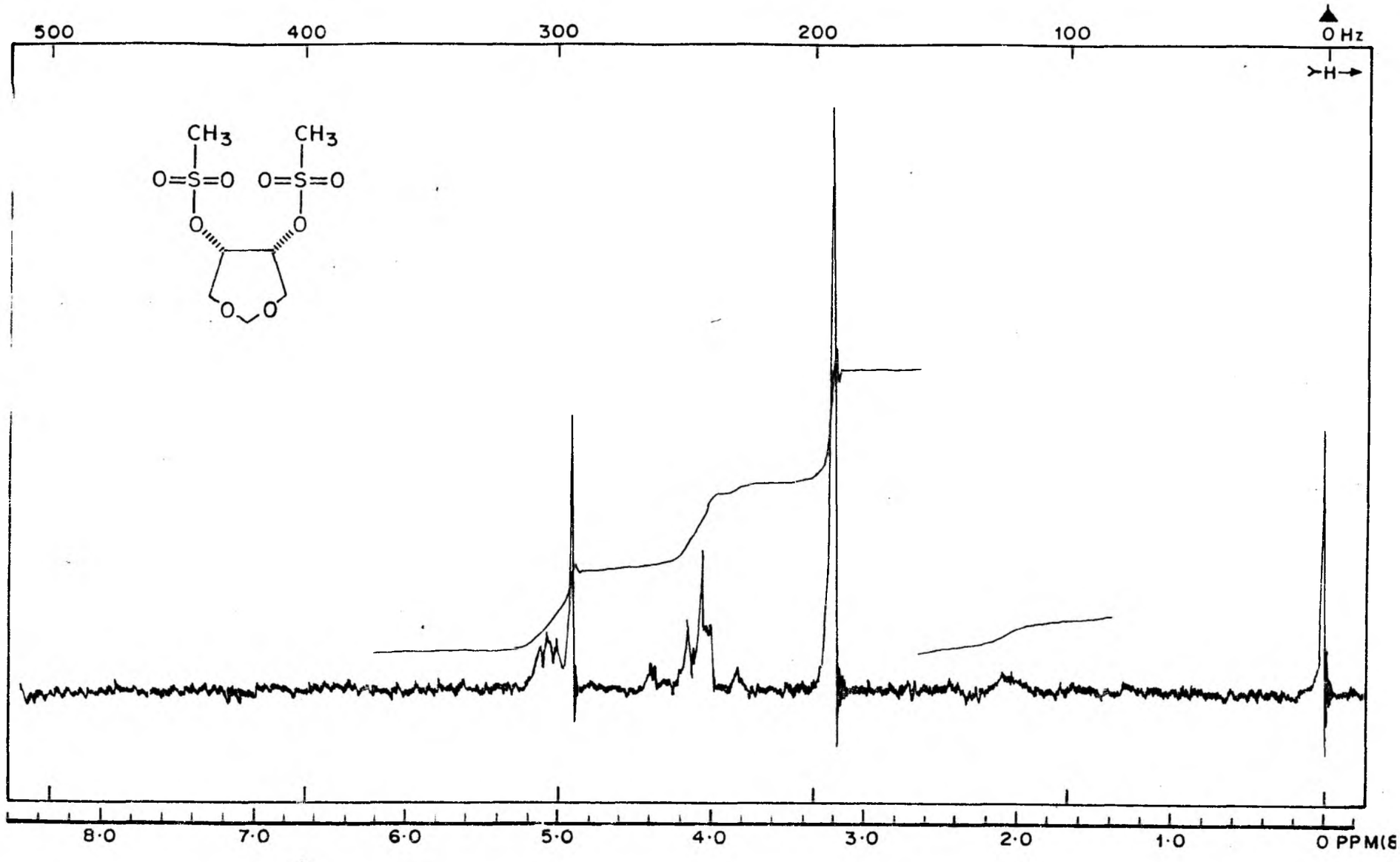

500
400
300
200
100
0 Hz
H
CH3
CH3
O=S=O
O=S=O
O
O
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

FIG. 2·3·2

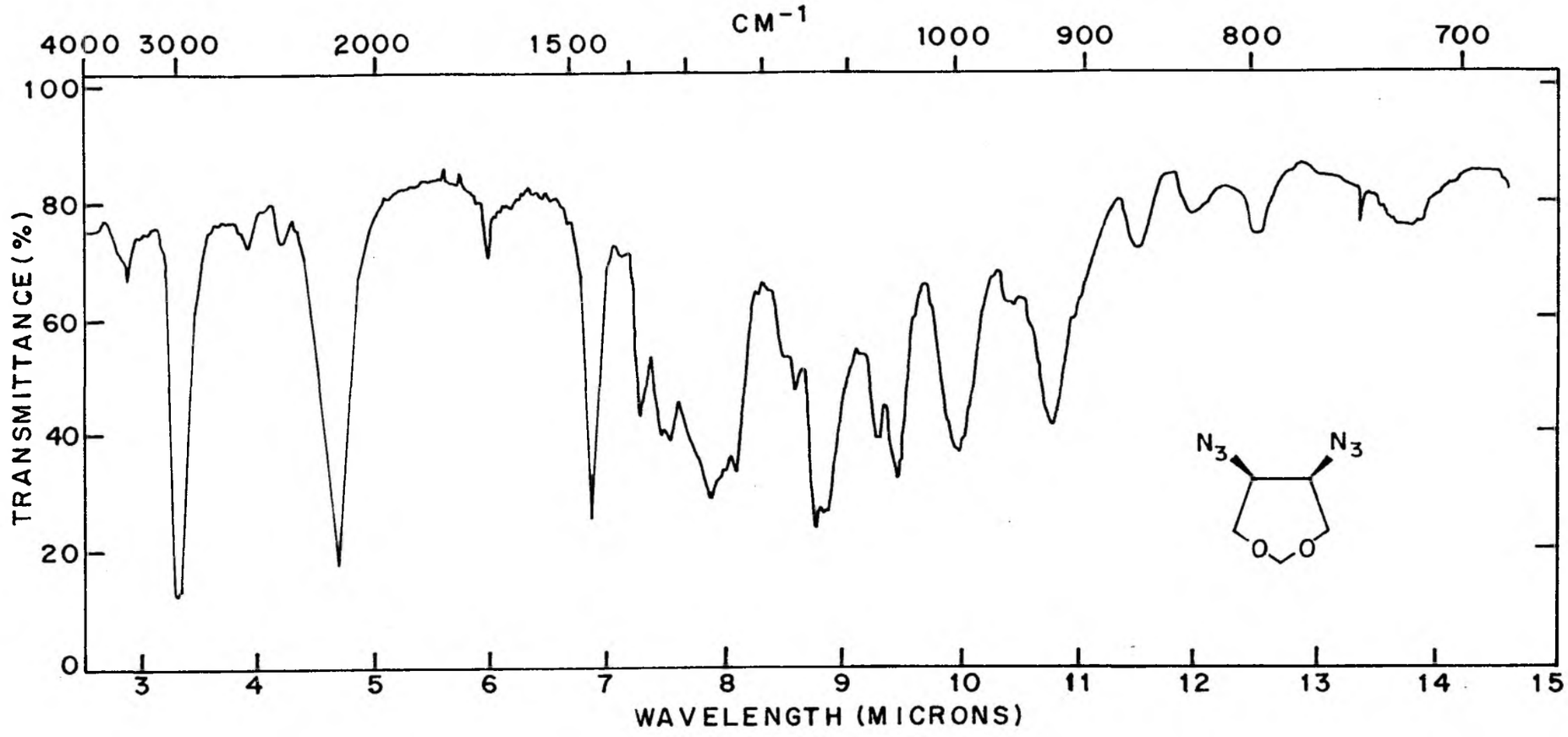

CM⁻¹
4000 3000 2000 1500 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
N3
N3
O
O

FIG. 2·3·3

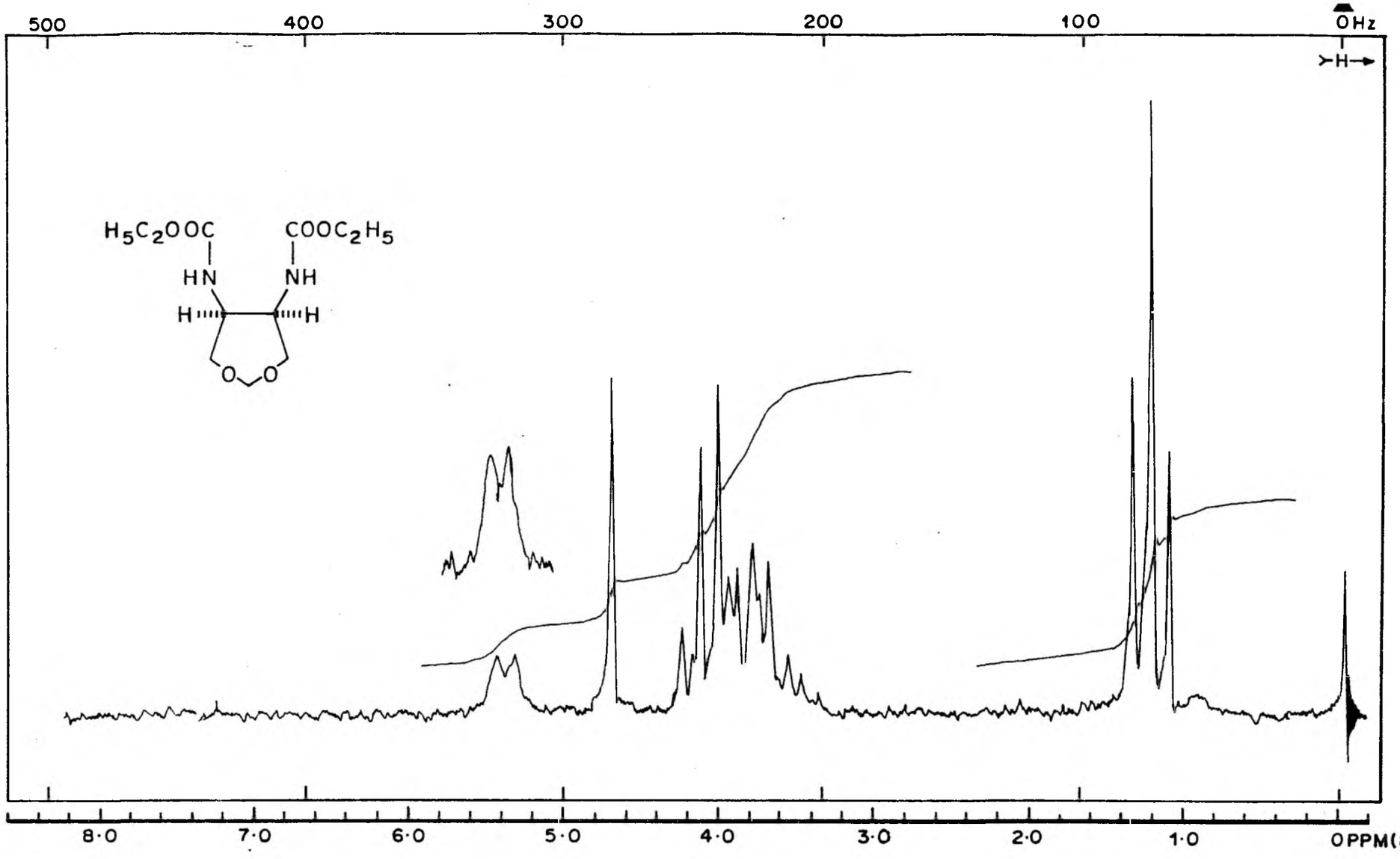

500
400
300
200
100
0Hz
>H<
H5C2OOC
COOC2H5
HN
NH
H
H
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0PPM(δ

FIG. 2·3·4

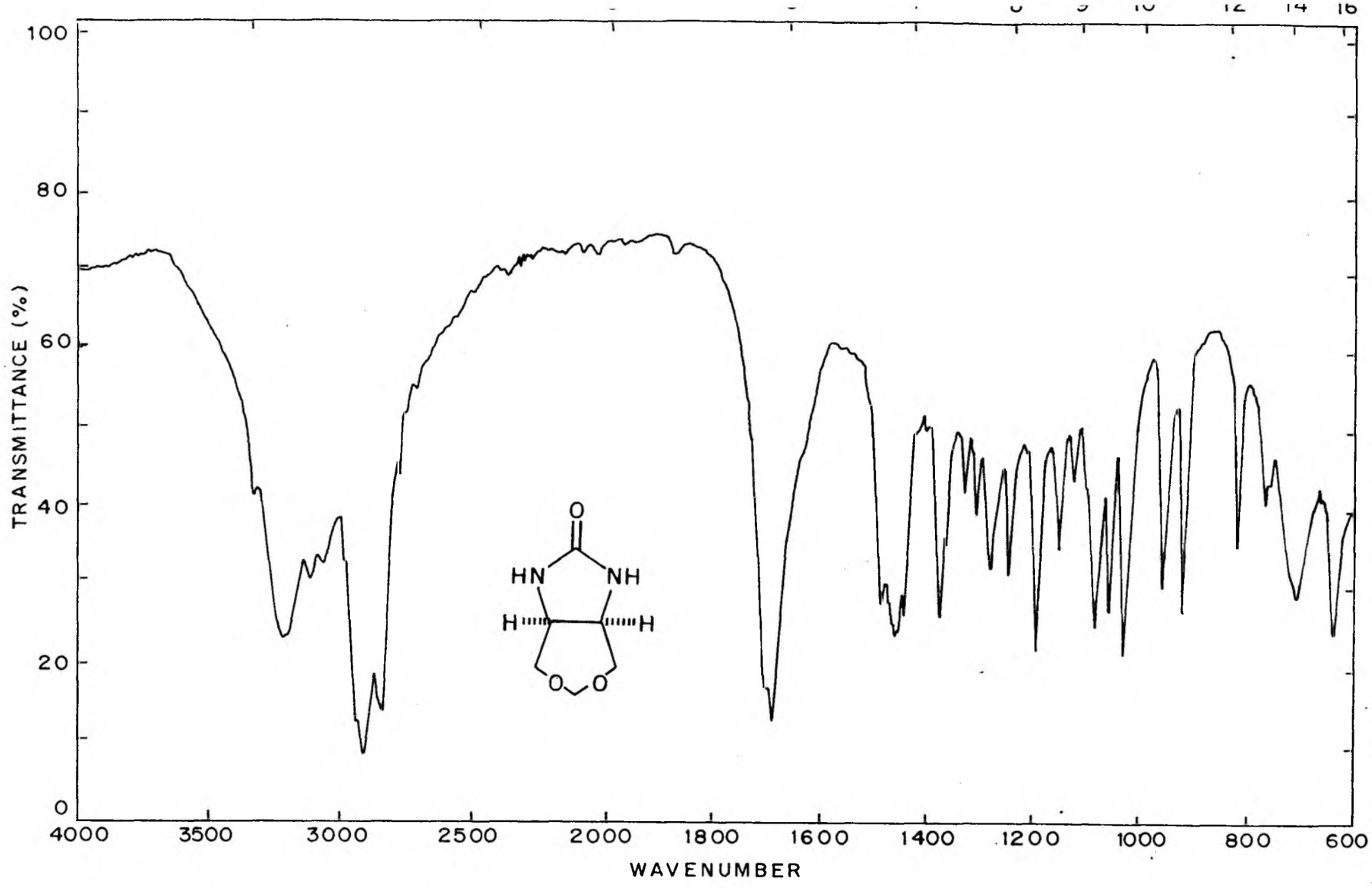

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
O
HN
NH
H
H
O
O

FIG. 2·3·5

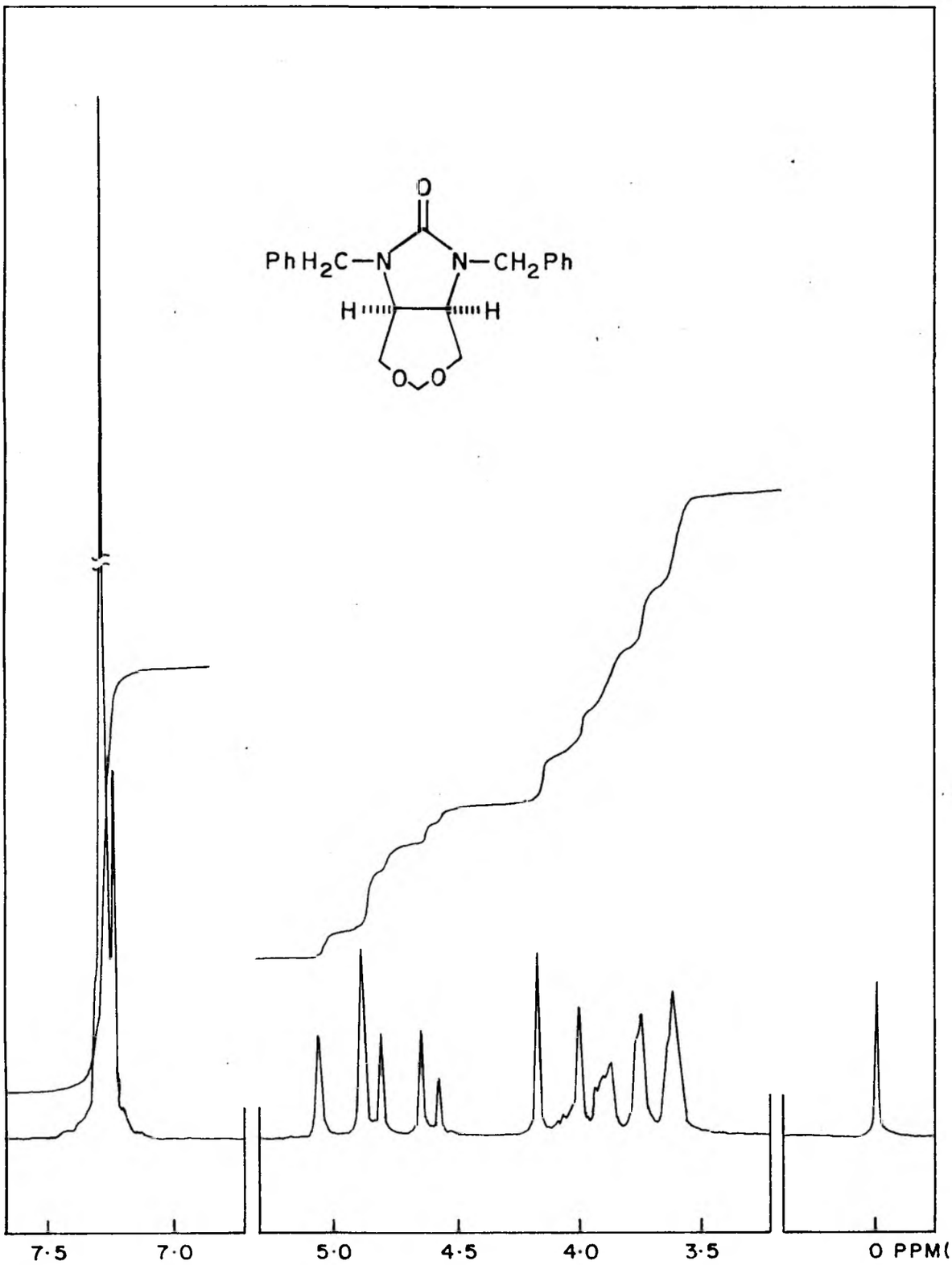


FIG. 2·3·6

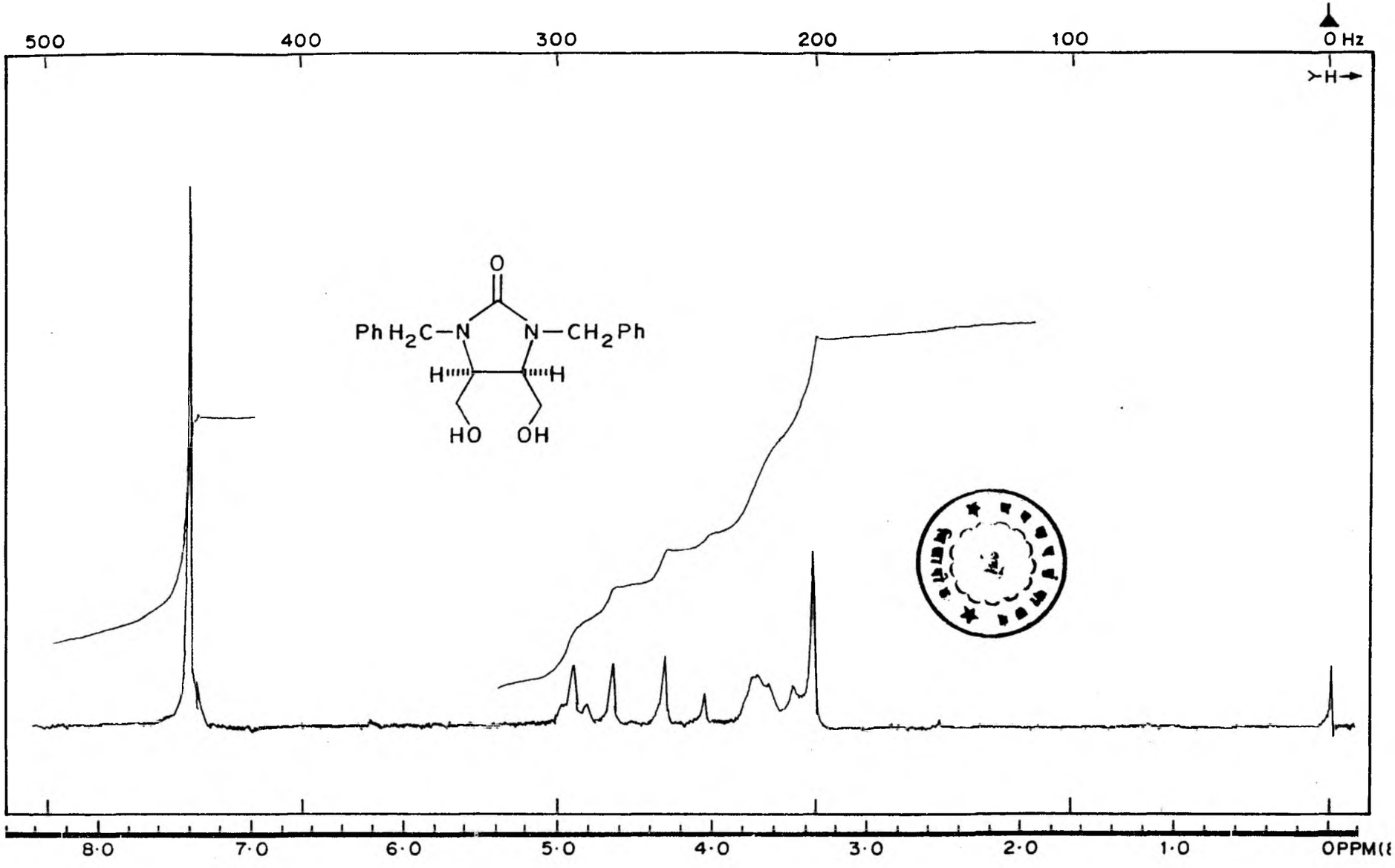

500
400
300
200
100
0 Hz
>H→
O
Ph H2C—N
N—CH2Ph
H
H
HO
OH
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0PPM

FIG. 2·3·7

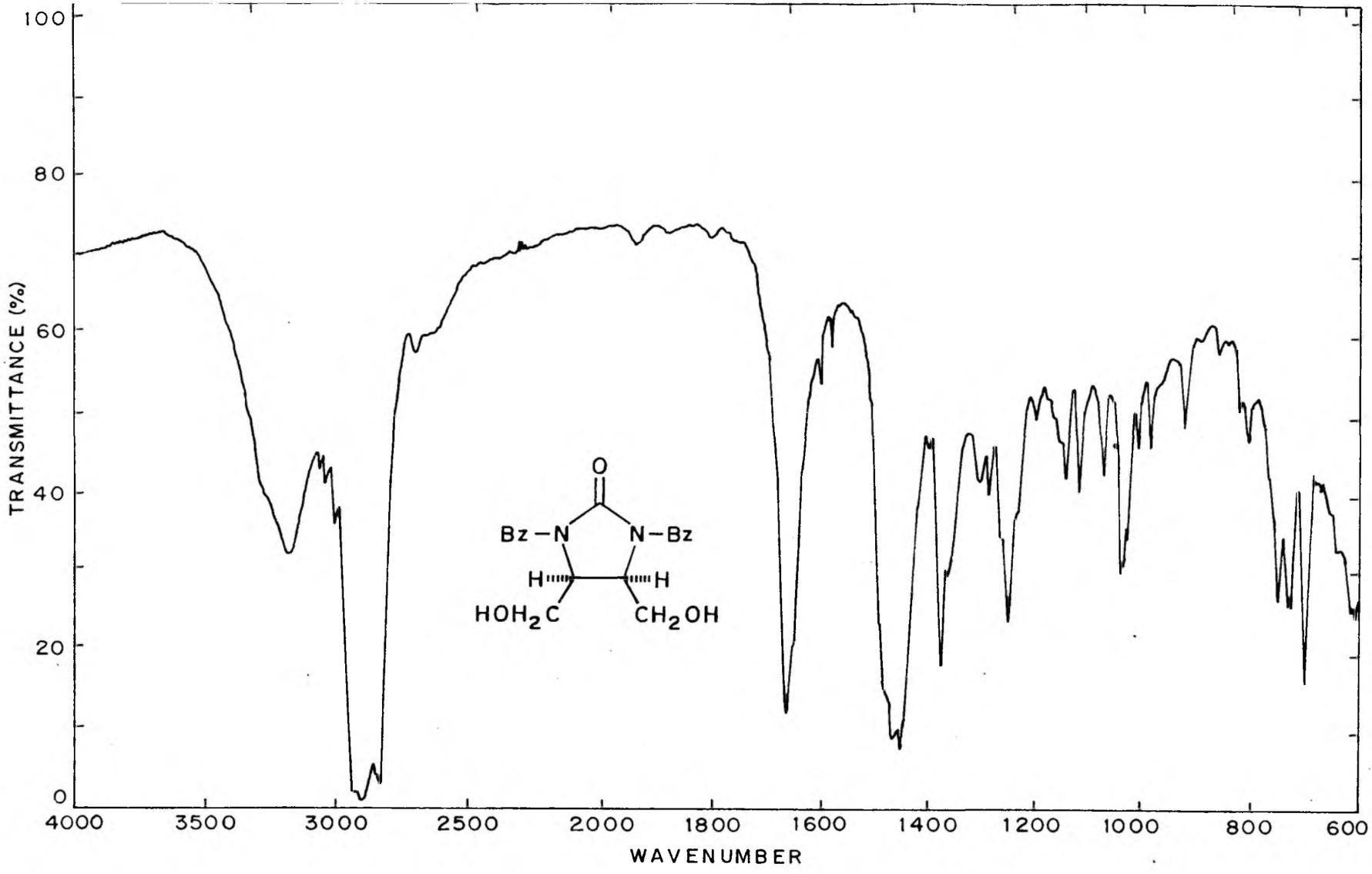

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
O
Bz–N
N–Bz
H
H
HOH2C
CH2OH

FIG. 2·3·8

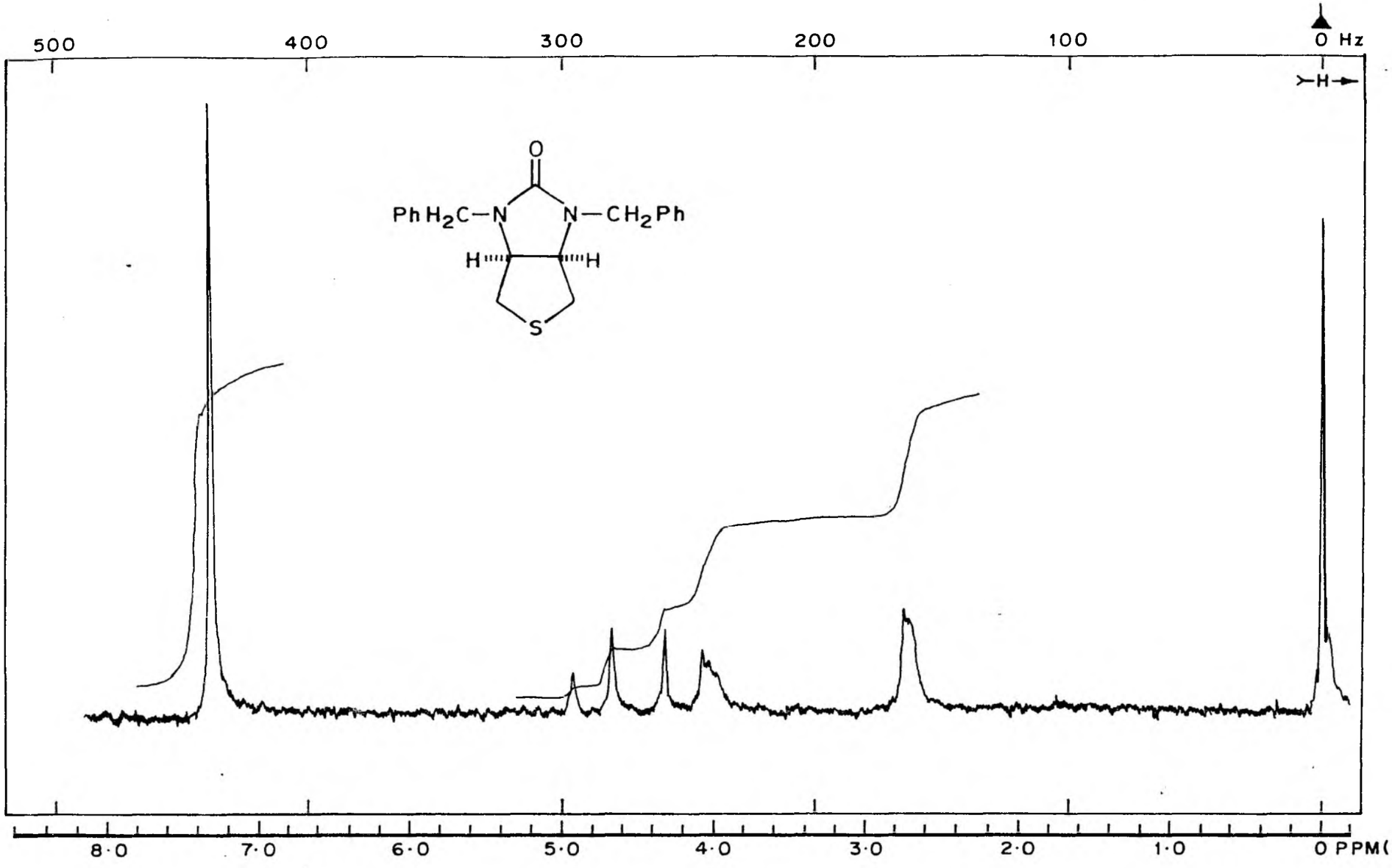

500
400
300
200
100
0 Hz
O
PhH2C—N
N—CH2Ph
H
H
S
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 2·3·9

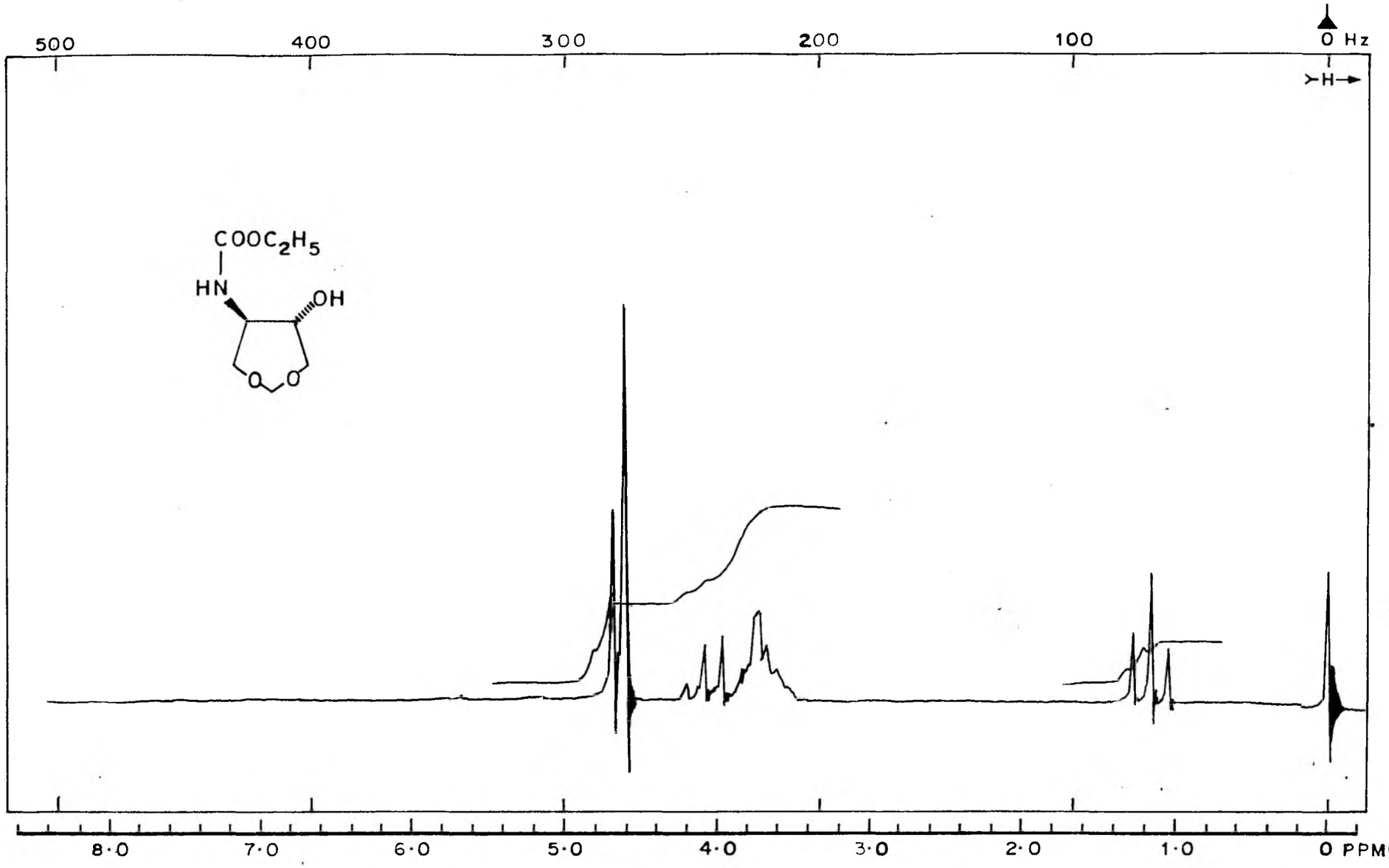

500
400
300
200
100
0 Hz
COOC2H5
HN
OH
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 2·3·10

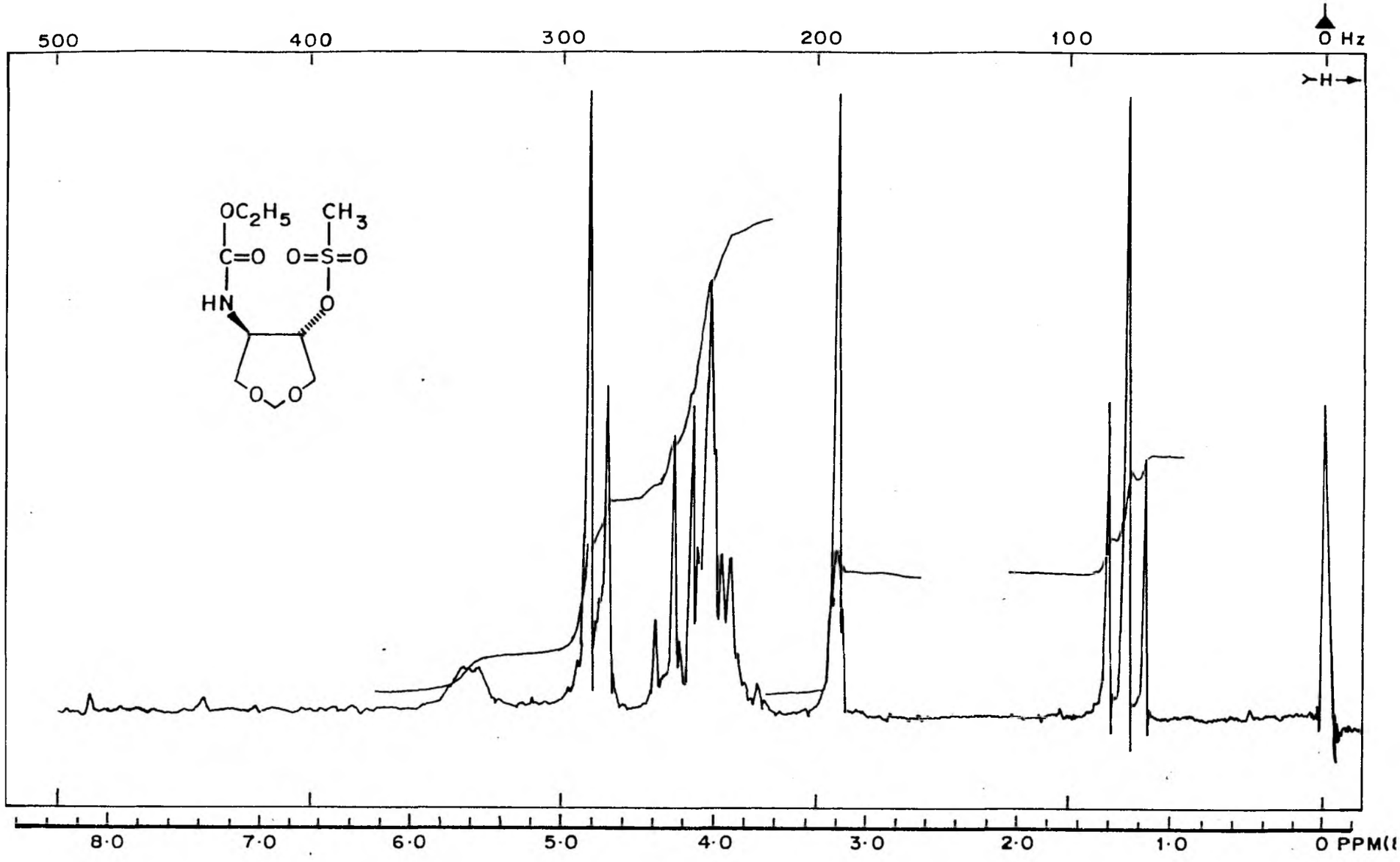
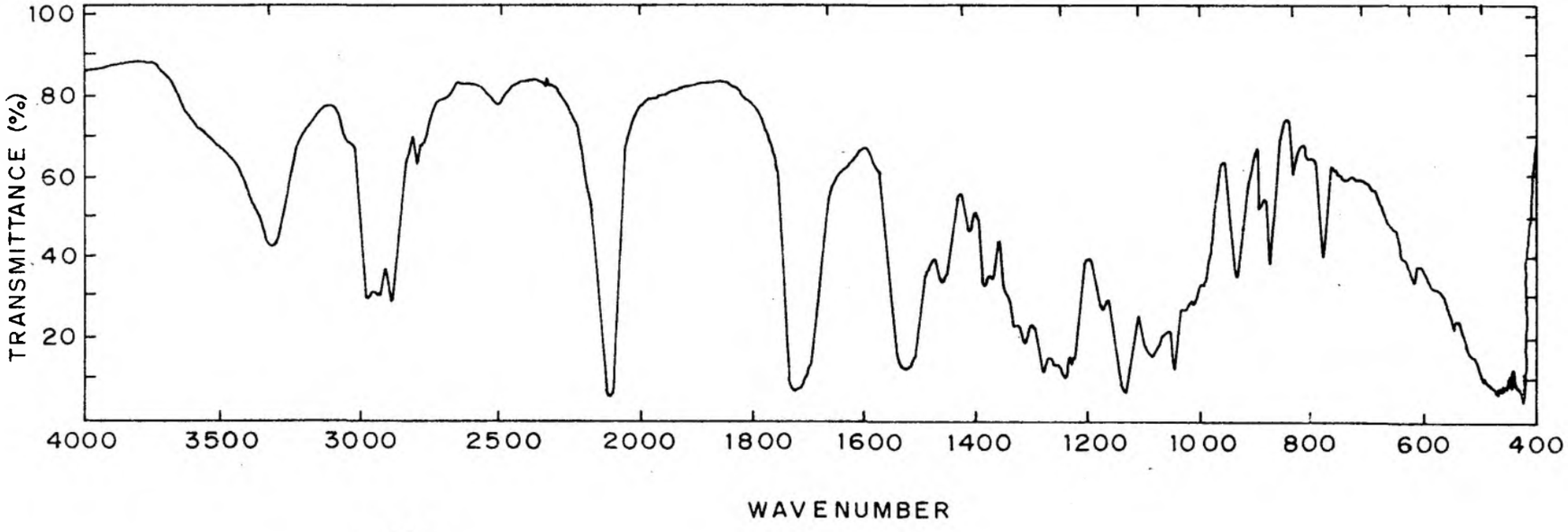

500
400
300
200
100
0 Hz
TMS
OC2H5
CH3
C=O
O=S=O
HN
O
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 2·3·11


100
80
60
40
20
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBER

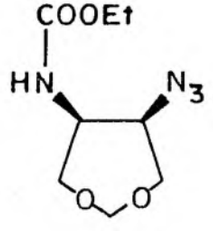

COOEt
HN
N3
O
O

FIG. 2·3·12

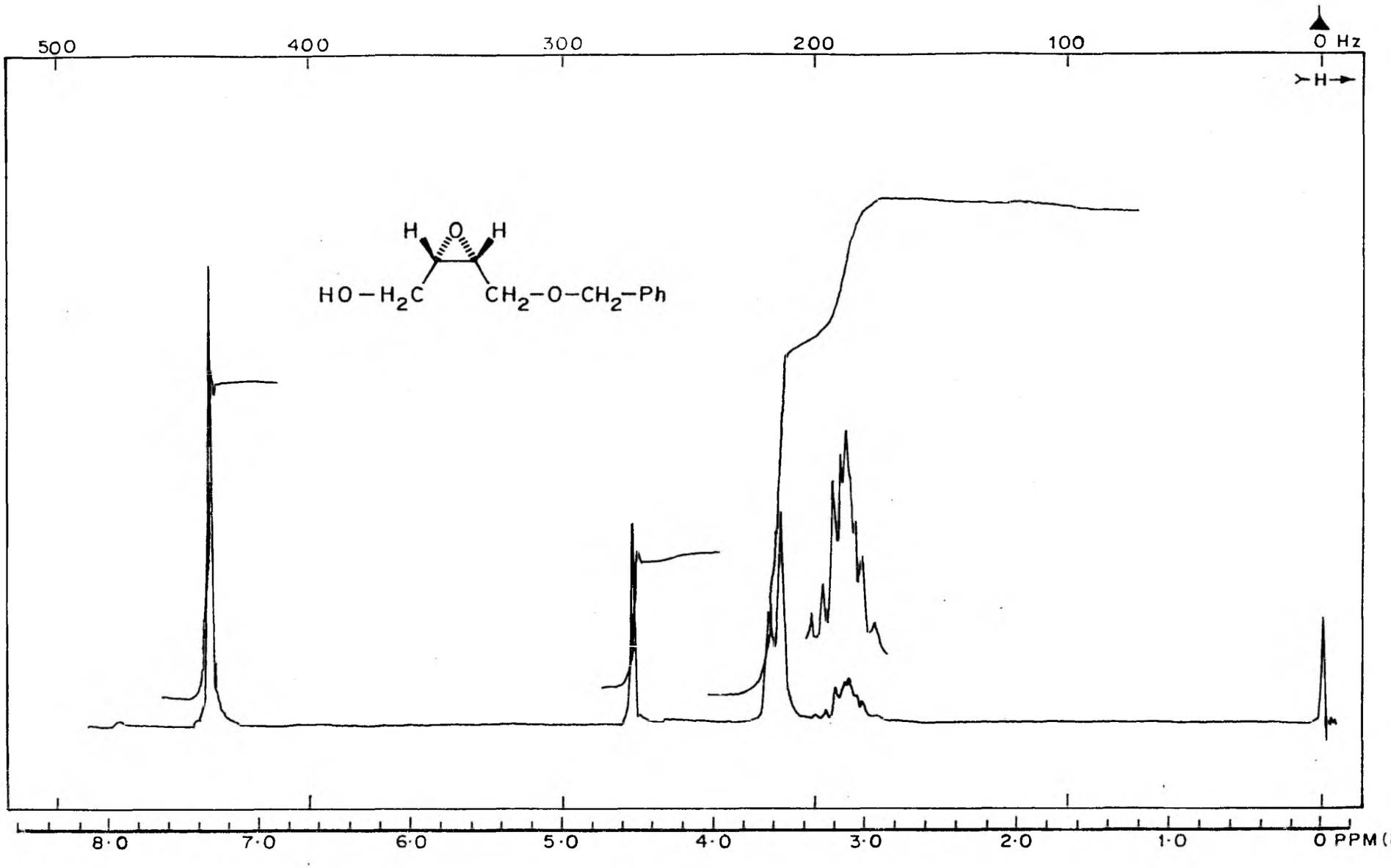

500
400
300
200
100
0 Hz
H
H
O
H
HO−H2C
CH2−O−CH2−Ph
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 2·3·13

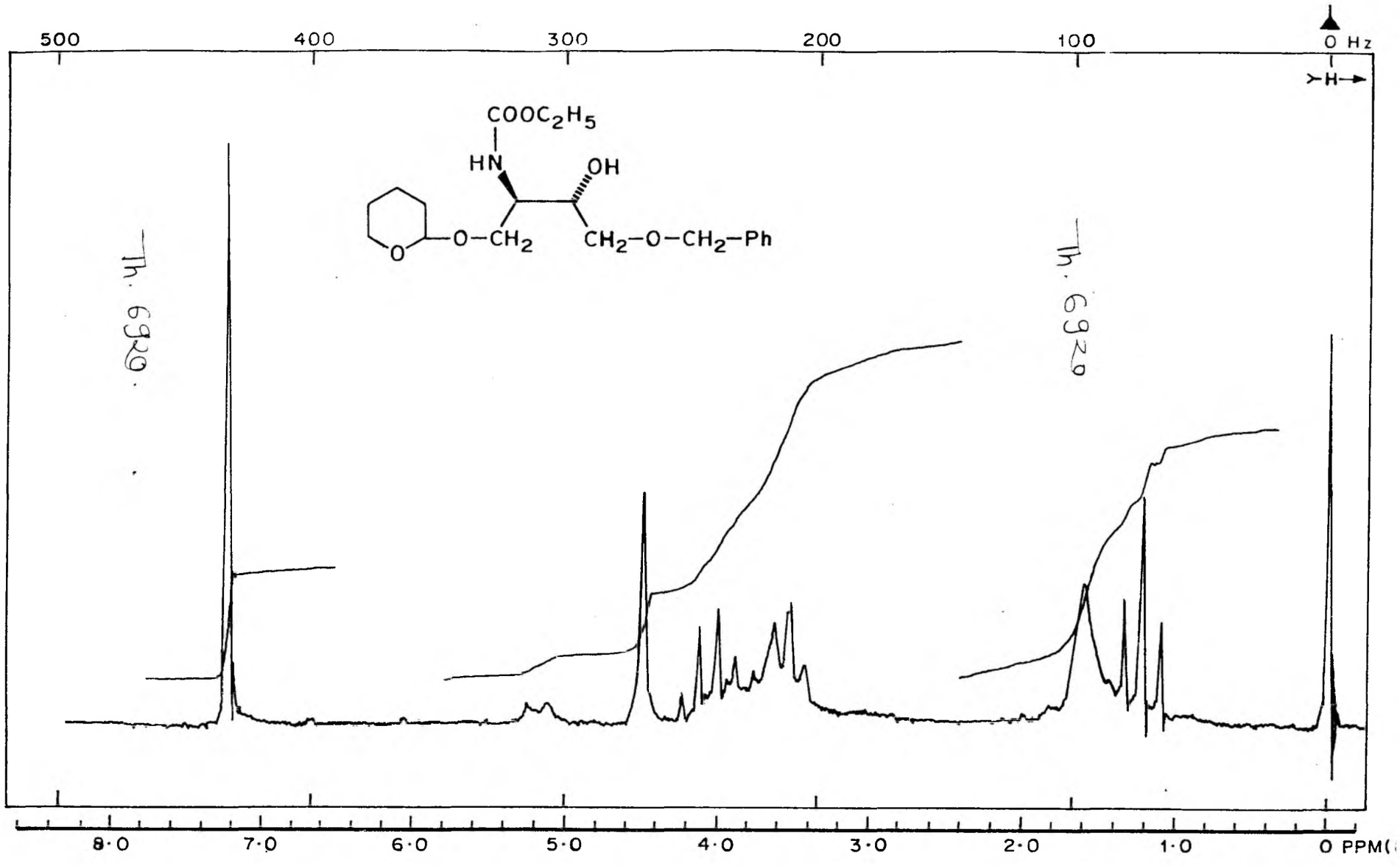

500
400
300
200
100
0 Hz
H
COOC2H5
HN
OH
O
O–CH2
CH2–O–CH2–Ph
Th. 6920
Th. 6920
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 2·3·14

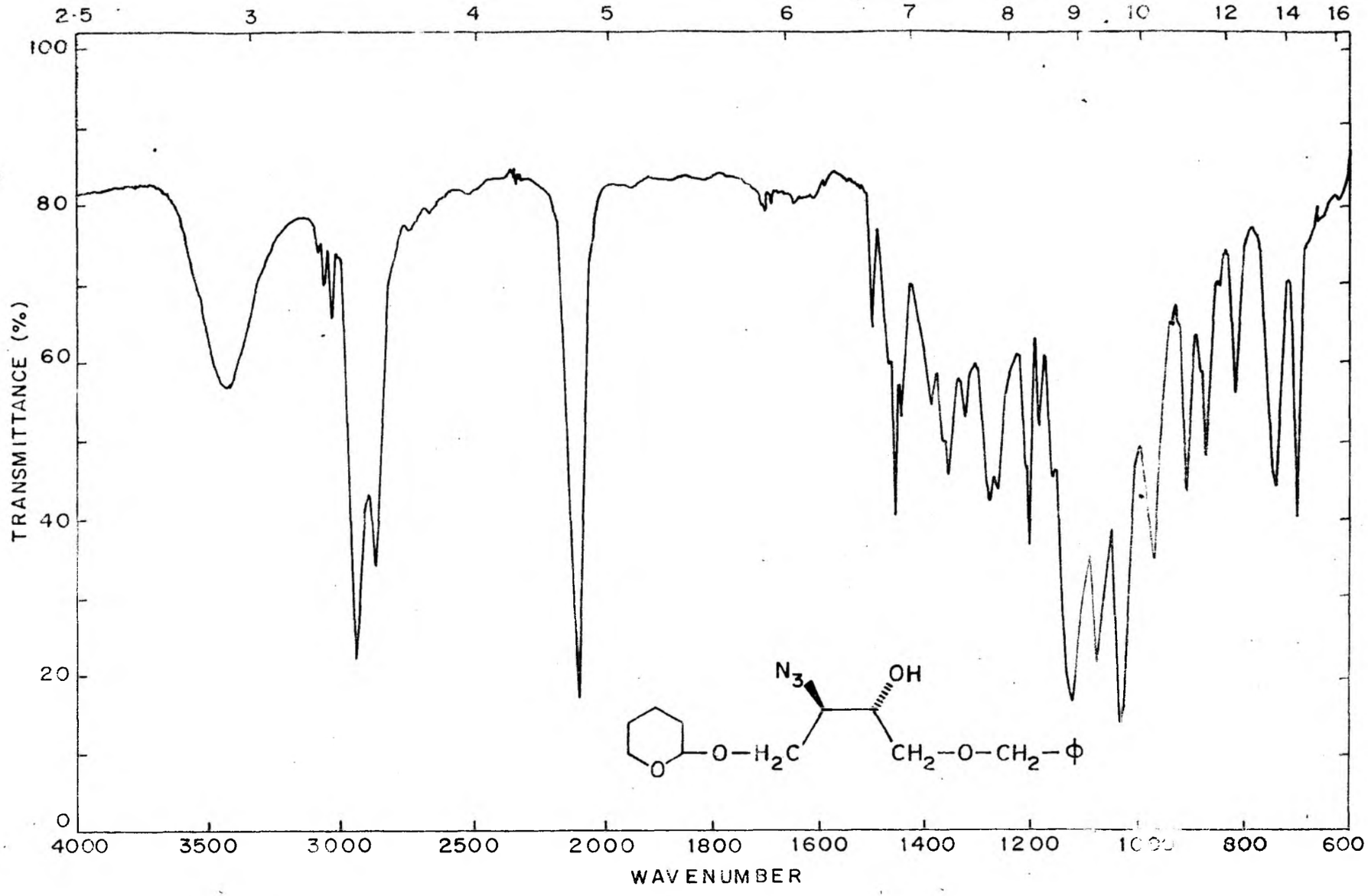

2·5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
N3
OH
O
O—H2C
CH2—O—CH2—ϕ

FIG. 2·3·15

2.4.0 REFERENCES

1 S. Lavielle, S. Bory, B. Moreau, M.J. Luche and A. Marquet
J.Am. Chem.Soc., 100,1558 (1978).

2 (a) J. Knappe in Annu. Rev. Biochemistry, 39, 757-776 (1970).
(b) J. Moss and D. Lane in Adv. in Enzymology, 35, 321-441 (1971).
(c) A.W. Alberts and P.R. Vagelos in The Enzymes (3rd Ed.) P.D. Boyer Academic Press, N.Y., 37-82 (1972).

3 H.Kotake, K. Inomata, Y.Murata
Chemistry Lett., pp.1073 (1976).

4 H. Kinoshita, M.F. Futagami, K. Inomata and H. Kotake
Chemistry Lett., 1275-1276 (1983).

5 Brannock K.C. & G.R. Lappin
J. Org. Chem., 21, 1366 (1956).

6 M.W. Miller
Tetrahedron Lett., 2545 (1969).

7 K.B. Sharpless
J. Am.Chem. Soc., 102, 5976 (1980).

8 M.W. Goldberg and L.H. Strenbach
U.S. Patent 2,489,236; Chem.Abstr., 45, 187 (1951).
M.W. Goldberg and L.H. Strenbach
U.S. Patent 2,489,234 (1949); Chem. Abstr., 45, 186 (1951).

9 Y. Aoki, H. Suzuka and Akiyama
Heterocycles, 3, 67 (1975).

10 S. Danischefsky and J. Regan
Tetrahedron Lett., 3919 (1981).

11 E. Hungerbuhler and D. Seebach
Helv. Chim. Acta, 65, No.70, Phase 3 (1981).

12 Gulbins and Hamann
Chem. Ber., 94, 3287 (1961).

13 M.B. Groen and E.H. Jacobs
Tetrahedron Lett., 39, 4029 (1972).

14 R. Huisgen
Angew. Chem., 75, 604 (1963); Angew Chem., Int. Ed. Engl. 2, 565 (1963); Angew Chem., 75, 742 (1963).

15 Elinor Wave
Chem. Rev., 46, 403-416 (1950).

16 F.G. Mann and W.J. Pope
J. Chem. Soc., 123, 1172 (1923).

17 (a) H. Gilman, W.Langham and F.W. Moore
J. Am. Chem. Soc., 62, 2327 (1940).
(b) H. Gilman, J.A. Beel, C.G. Brannen, M.W. Bullock,
G.E. Dunn and L.S. Miller
J. Am. Chem. Soc., 71, 1499 (1949).
(c) H. Gilman and F.K. Cartledge
J. Organometallic Chem., 21, 447 (1964).

CHAPTER - 3.0.0

SYNTHESIS OF (+) BIOTIN

FOREWORD

The diol (3), a proven key intermediate required in the synthesis of (+)biotin (4) has been prepared from D-glucose (1) via L-gulonolactone (6), where carbons 2^*, 3^*, 4^*, 5^* and 6 of D-glucose end up as the carbons 6, 2^*,3^*,4^* and 5 respectively of (+)biotin *via* the intermediate diol (3).

This chapter also describes our efforts in the conversion of Vitamin C (L-ascorbic acid) to (+)biotin derivative.

3.1.0 INTRODUCTION

The concept of asymmetric syntheses has been known to us for a long time and has been widely and ingeniously utilised in the formation of C-C bonds. In spite of these developments in this area, the control of absolute stereochemistry and regiospecific introduction of functional groups at the predetermined sites remained the crucial problem in the construction of moderately functionalised molecules. In recent years, carbohydrates have found enormous use in the synthesis of chiral molecules. As a result of these developments, four chiral syntheses of (+)biotin from sugars have been reported. These have been already described in Chapter 1.4.0 of this thesis.

In 1977 Ogawa et al.synthesised (+)biotin from D-glucose[1] (1) in which C-1/5 of the D-glucose became C-5,4*,3*,2*,6 of (+) biotin (biotin numbering) via the intermediate diol 2 (Chart 3.1.1). This is a very long synthesis involving about 23 steps. Also the yields in the conversion of the diol (2) to (+)biotin are poor. It was therefore thought of preparing biotin via the intermediate (3) (Chart 3.2.1) which has been converted to (+)biotin in reasonably good yields[2]. Earlier this intermediate was prepared from D-mannose[2] and D-arabinose[3] both of which are expensive sugars. This part of the thesis deals with the

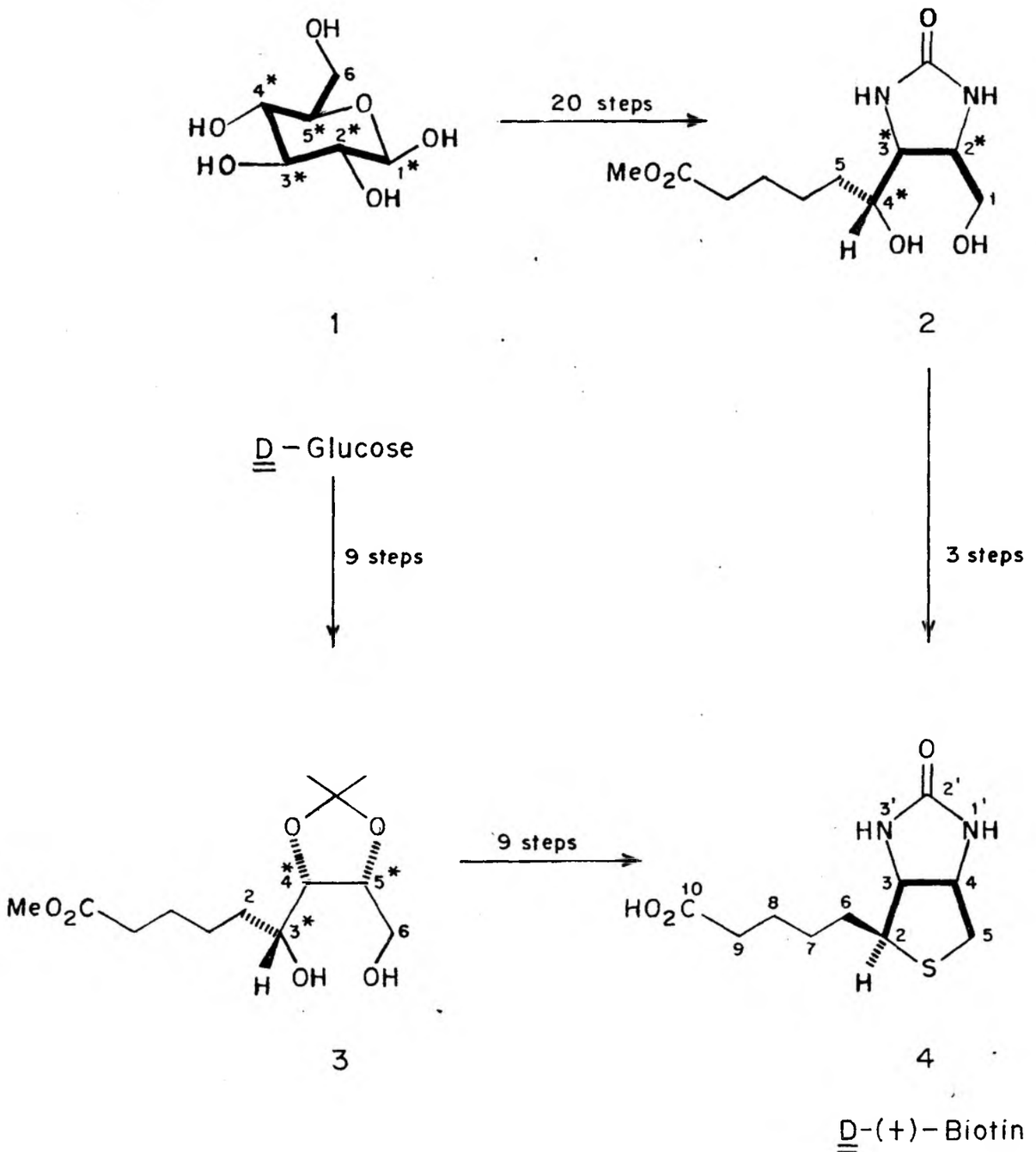


CHART – 3·1·1

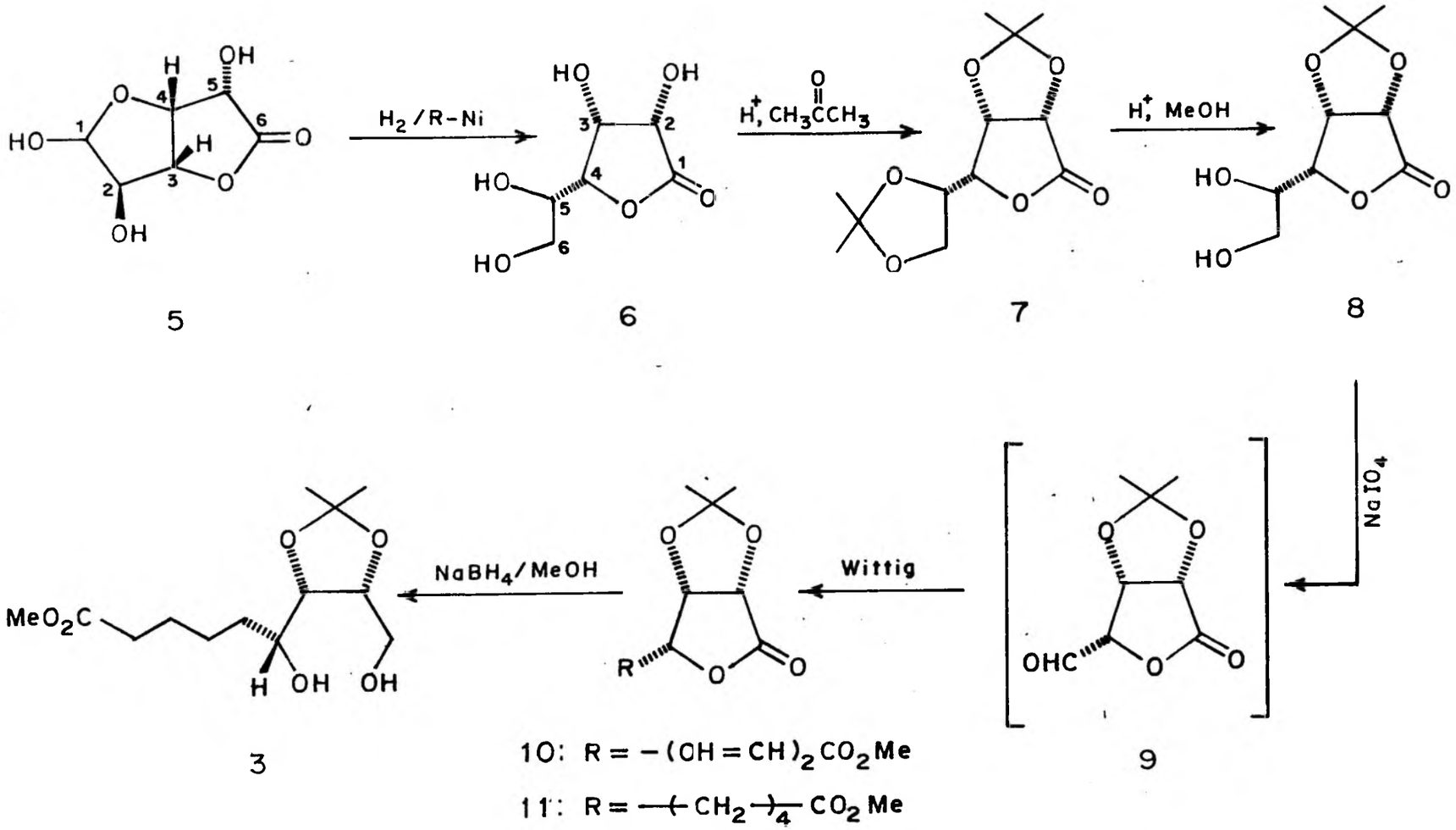
conversion of D-glucose, an inexpensive and abundantly available sugar to diol 3.

3.2.0 PRESENT WORK

D-Glucose to (+) Biotin: D-Glucuronolactone, obtained commercially from D-glucose in high yields on reduction over Raney-nickel furnished L-gulono-1,4-lactone[4], m.p. 180-181°, $[\alpha]_D^{26}$ +36.5°(C 4, H_2O).

Treatment of L-gulonolactone (6) with dry acetone in presence of catalytic amount of sulphuric acid gave the 2,3;5,6 di-O-isopropylidene derivative[5] (7) m.p. 149-150°, $[\alpha]_D^{26}$ +37° (C 4.6, $CDCl_3$). Selective hydrolysis of the 5,6-isopropylidene group was achieved with methanolic hydrogen chloride at room temperature to give the 2,3-O-isopropylidene derivative (8) in 48% yield, m.p. 143-146°, $[\alpha]_D^{26}$ +30° (C 2, C_2H_5OH). The ^1H NMR (D_2O) data of (8) was in agreement with the structure.

The diol (8) was subjected to oxidation with sodium metaperiodate in aqueous acetone at 0°. TLC of the reaction product after 30 minutes showed quantitative conversion of the diol to the desired aldehyde (9). However efficient isolation of (9) from the aq. reaction mixture by non-aqueous solvents (viz. $CHCl_3$, ether, etc.) was a problem. It was also found that the aldehyde was unstable. The problem was partly overcome by concentration of the aq. reaction mixture



5 6 7 8 9 3

CHART−3·2·1

under reduced pressure (below 40°C) and extracting the residue with methylene chloride several times. The extracts were dried and concentrated and were immediately added to a solution of excess [3-carbomethoxypropen-2-ylidene-1]-triphenyl phosphorane[6] in dry methylene chloride. Work up of this reaction and purification of the reaction product by column chromatography furnished only 10% [on the basis of diol (8)] of the desired unsaturated lactone (10), m.p. 137-138°; $[\alpha]_D^{25}$ +2° (C 1.4, chloroform); ^{1}H NMR spectrum of (10) revealed two C-methyl signals at δ 1.38 and 1.48 for isopropylidene group, a singlet due to methoxy carbonyl at 1.34 due to ester function. Resonance due to olefinic protons appeared in the range of 4.8 - 7.4. The remaining protons were located at the expected chemical shifts.

Hydrogenation of the unsaturated lactone (10) over 10% Pd/C at atmospheric pressure and room temperature resulted mainly in hydrogenolysis, and the desired lactone (11) could be isolated in very poor yields (ca. 2%) after extensive chromatography of the hydrogenated product. In order to avoid hydrogenolysis, the hydrogenation of (10) was carried out using sodium borohydride-reduced palladium catalyst[7] which is known to bring about hydrogenation without any hydrogenolysis. The result is almost quantitative conversion of 10 to 11 as a syrup, $[\alpha]_D^{25}$ +74° (C 1, chloroform).

^{1}H NMR of (11) showed multiplets at δ 2.0 corresponding to -$(CH_2)_4$-, indicating the saturation of olefinic bonds. Moreover resonance due to isopropylidene group, methoxycarbonyl and ring protons appeared at the expected chemical shifts.

The saturated lactone (11) was subjected to controlled sodium borohydride reduction at 0°C and the key intermediate (3) was isolated in 81% yield. m.p. 68°, $[\alpha]_D^{26}$ +14° (C 1 chloroform). This corresponded well with the reported data[2]. The ^{1}H NMR spectrum showed two C-methyl signals at δ 1.3 and 1.43 for isopropylidene group, a singlet due to methoxycarbonyl at 3.6. Resonance due to -$COCH_2$- and -$(CH_2)_3$ appeared in the range of 1.0 - 2.2. The remaining protons were located at the expected chemical shifts.

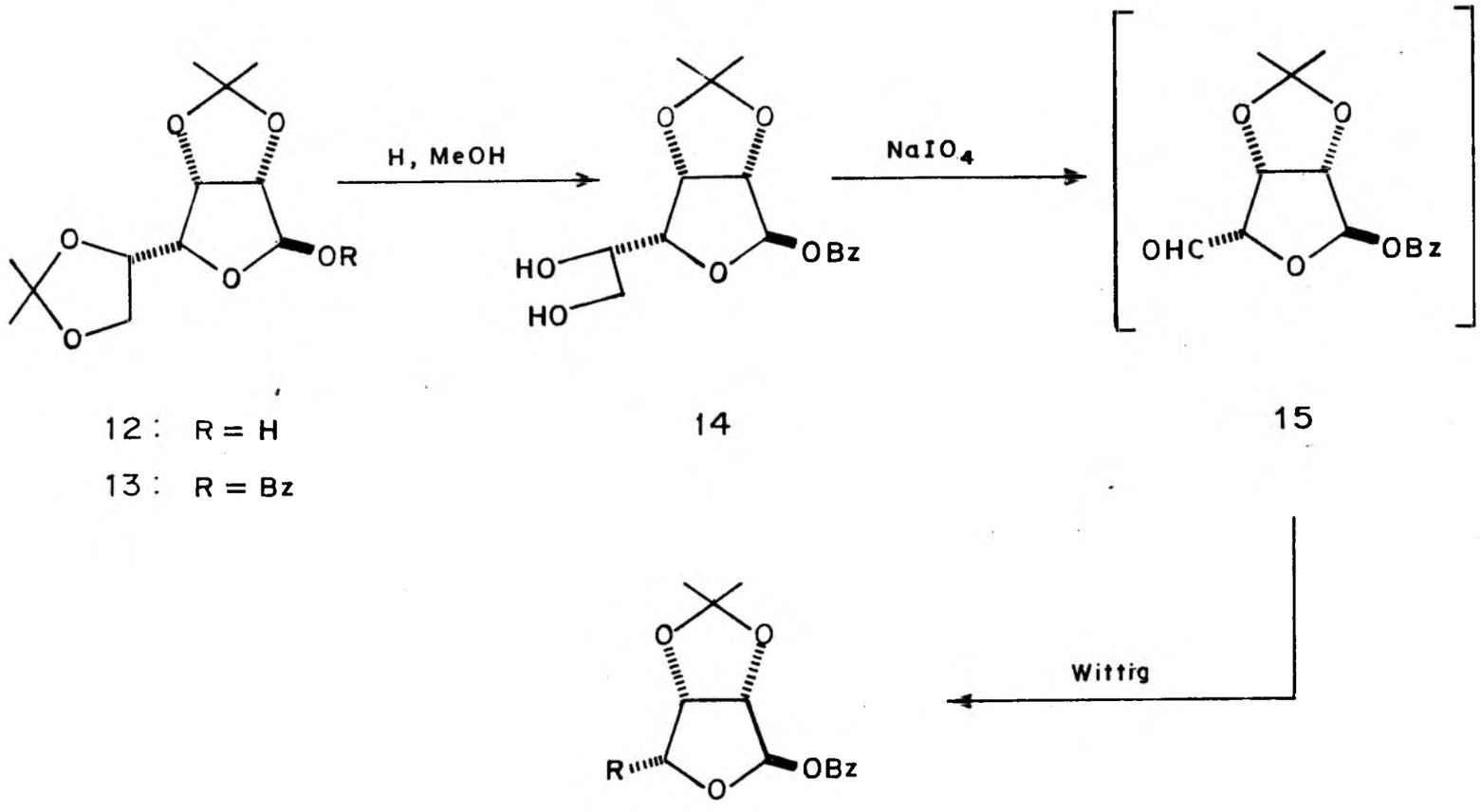
Gulonolactone (6) and its di- and mono-O-isopropylidene derivatives (7) and (8) showed less rotation than reported. This may be due to partial epimerization of the chiral centre C-2 in D-glucuronolactone (5) occurring during its formation by Ra-Ni reduction. When the C-2 of D-glucuronolactone gets epimerized the configuration of the product becomes identical to the mannonic acid lactone configuration, having opposite sign of rotation. Hence the net rotation becomes lower than expected. However this partial epimerisation at C-2

is immaterial as this asymmetric centre is being destroyed at the oxidation step (periodate) later in the sequence.

In order to solve the problem associated with isolation of the aldehyde (9) and thereby further improving the yield of the lactone (10) in the Wittig reaction, it was thought of reducing the lactone (6) to the corresponding hemiacetal (12) and protecting it as a benzoate (13). This would improve the solubility of the aldehyde (15) in organic solvents, such as dichloromethane, ether, etc. (Chart3.2.2).

Thus treatment of 2,3; 5,6-di-O-isopropylidene-1,4-lactone (7) with sodium borohydride[8] in methanol at 0°C, followed by O-benzoylation with benzoyl chloride-pyridine gave the crystalline benzoate (13) in 96% yield, m.p. 127-128°. The ^{1}H NMR spectrum showed the expected chemical shifts.

Selective hydrolysis of benzoate with methanolic hydrogen chloride afforded diol (14) in 95% yield, whose periodate oxidation in aqueous acetone at 0°C gave the aldehyde (15) in quantitative yields as judged by TLC. The aldehyde (15) was then treated with excess of [3-carbomethoxypropen-2-ylidene-1]-triphenylphosphorane in methylene chloride and then unsaturated compound (16) was isolated in 79% yield by simple extraction with methylene chloride without difficulty. The ^{1}H NMR spectrum showed



12 : R = H

13 : R = Bz

14

15

16 : R = $-(CH=CH)_2CO_2Me$

17 : R = $-(CH_2)_4CO_2Me$

CHART – 3·2·2

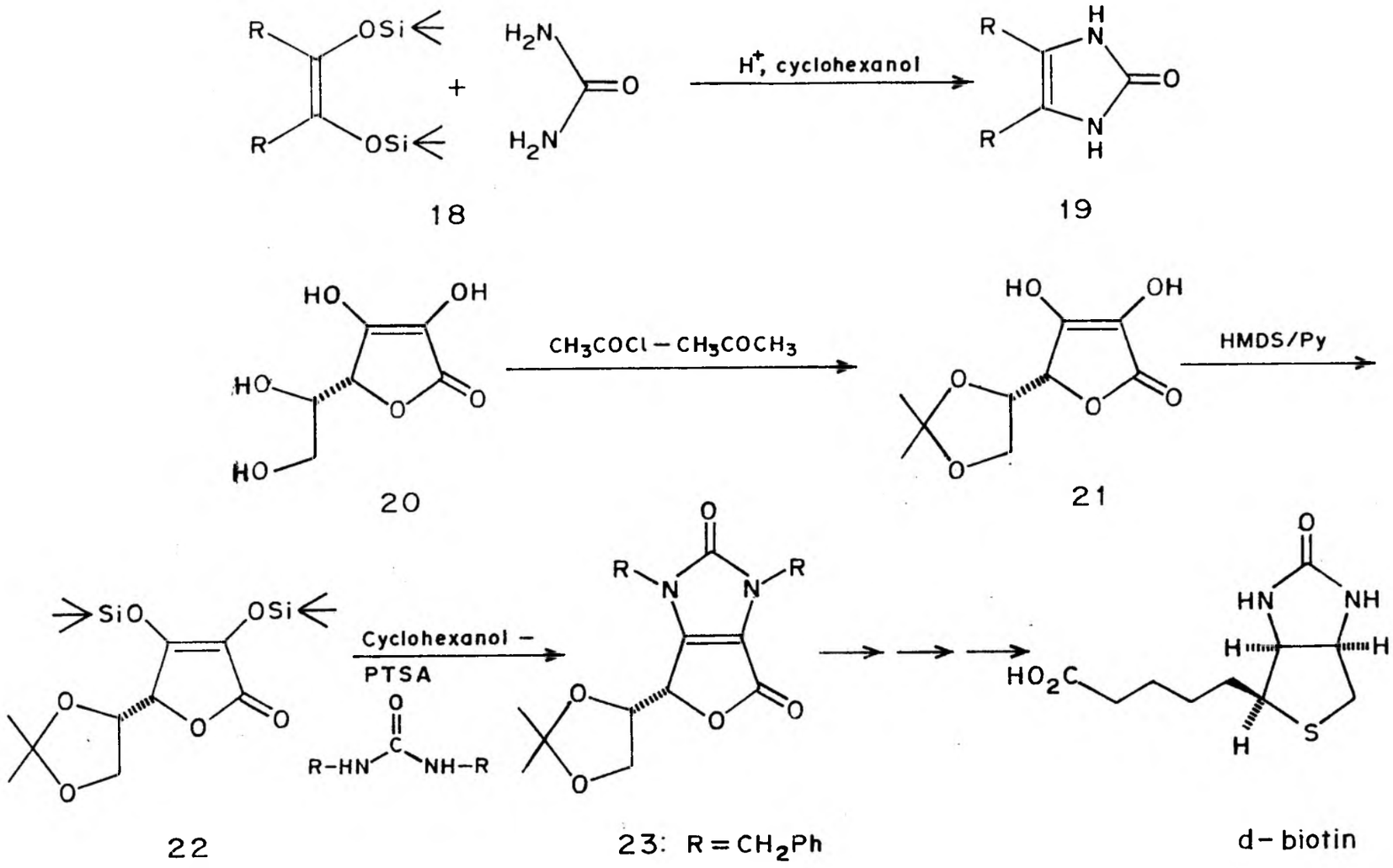
two C-methyl signals at δ 1.34 and 1.50 for isopropylidene group, a singlet due to carbomethoxy at δ 3.78. Resonance due to olefinic protons appeared in the expected range, with suitable chemical shifts. The aromatic protons appeared at δ 7.3 - 7.7 and 8.08.

Hydrogenation of (16) with borohydride-reduced palladium chloride at room temperature gave the saturated benzoate (17) in quantitative yields. The compound (17) was converted to diol (3) in high yields by reported procedure[2], viz. by base-catalysed ester exchange in methanol, followed by sodium borohydride reduction. The properties of (3) were in agreement with those reported[2].

Conversion of the diol into (+)biotin has been achieved by Ohrui et al.[2] and therefore the above mentioned synthesis of the key intermediate (3) constituted a total synthesis of (+)biotin.

Attempted synthesis of (+)biotin from L-ascorbic acid:
This part deals with our attempts at converting L-ascorbic acid to (+)biotin intermediates. Bredereck and Kochergin reported[9-12] the conversion of bis-siloxyalkene (18) into imidazolidone (19) by reacting with urea, in the presence of acid as shown in (Chart 3.2.3).

On the basis of this reaction, it was planned to prepare the compound (22) from L-ascorbic acid and its further elaboration to give (+)biotin (Chart 3.2.3).

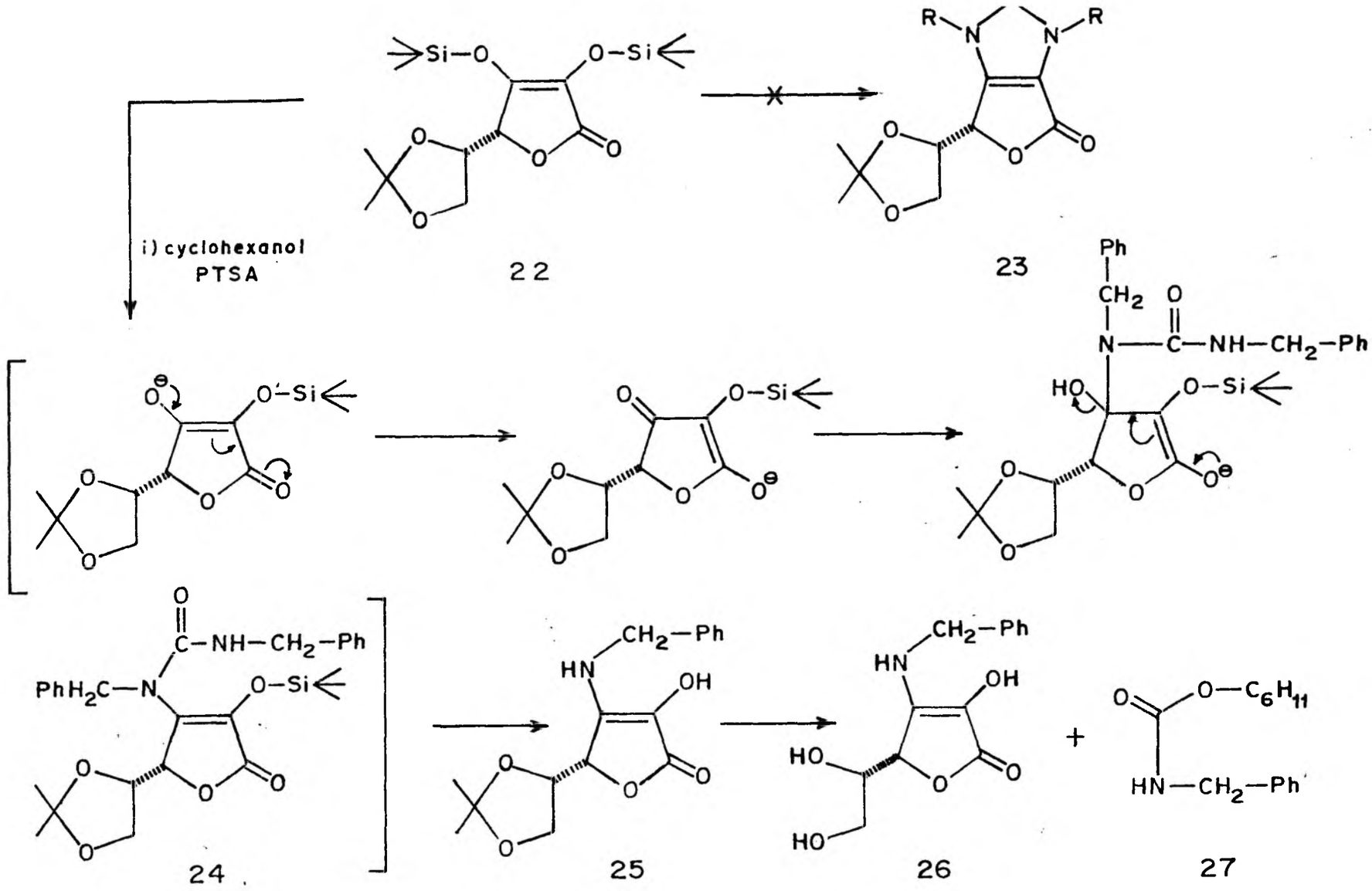

R
OSi
R
OSi
+
H_2N
H_2N
O
H^+, cyclohexanol
R
H
N
O
N
H
R
18
19
HO
OH
HO
HO
O
O
20
$CH_3COCl - CH_3COCH_3$
HO
OH
O
O
O
O
21
HMDS/Py
SiO
OSi
O
O
O
O
22
Cyclohexanol –
PTSA
R-HN
C
NH-R
O
R
N
N
R
O
O
O
O
23: R = CH_2Ph
HO_2C
O
HN
NH
H
H
H
S
d-biotin

CHART– 3·2·3

L-ascorbic acid (20) was converted into 5,6-O-isopropylidene derivative[13] (21), m.p. 210-218°. Treatment of (21) with hexamethyldisilazane in pyridine gave rise to bis-O-trimethylsilyl product (22). The IR showed absence of absorption due to -OH group.

Compound (22) on refluxing with dibenzylurea in cyclohexanol containing a trace of PTS acid[10] gave two products as judged by TLC separation of which by column chromatography gave first cyclohexyl benzyl carbamate (27), formed obviously from the reaction of dibenzylurea (or substituted dibenzyl urea) with cyclohexanol. The second fraction to be eluted from the column was given the structure (26) on the basis of its spectra data. The formation of (26) probably occurred by an initial desilylation followed by condensation with dibenzylurea as shown in (Chart 3.2.4) to form 24. The substituted urea 24 instead of cyclisation to the imidazolidone (23) preferred to undergo cleavage by nucleophilic attack of cyclohexanol to form 25 and the carbamate 27. During the reaction and isolation, the isopropylidene group gets hydrolysed and 26 is isolated. Compound 26 is characterised by its IR and ^{1}H NMR, Mass. and also by its reconversion to 25.

Since the above sequence did not yield the imidazolidone derivative 23, work was discontinued.



CHART—3·2·4

3.3.0 EXPERIMENTAL

Experiments requiring anhydrous ethanol, methanol, dichloromethane, were prepared by procedure given in the Text book of Practical Organic Chemistry by Vogel. D-Glucurono-3,6-lactone was procured from EGA-CHEMIE. It showed m.p. 172-174°, $[\alpha]_D^{25}$ +18.5 (C 8, H_2O). It was converted into 2,3; 5,6-di-O-isopropylidene-L-gulono-1,3-lactone (7) by literature procedures[5]. It showed m.p. 149-150°C, $[\alpha]_D^{26}$ +37 (C 4.6, $CHCl_3$).

Preparation of 2,3-O-isopropylidene-L-gulono-1,4-lactone (8)

A solution of 2,3; 5,6-di-O-isopropylidene-L-gulono-1,4-lactone (7) 5.2 g in methanol (100 ml) containing conc. hydrochloric acid (1 ml) was stirred at room temperature for 0.5 hr, then neutralised with conc. ammonia, and concentrated under reduced pressure. The residue was extracted with dry acetone, the extract was concentrated and the residue was recrystallised from ethyl acetate-light petroleum to give 8 (2.4 g, 48%) m.p. 143-146°, $[\alpha]_D^{26}$ +30 (C 2, ethanol).

Analysis: Calculated for $C_9H_{14}O_6$: C, 49.54; H, 6.42; Found: C, 49.23; H, 6.58%.

Preparation of (2S, 3S, 4R)-2,3-Isopropylidene dioxy-4-(1E,3E)-4-methoxy carbonyl-1,3-butadienyl-4-butanolide (10)

To a solution of (8) (1.744 g, 8 m.mol) in acetone a solution of sodium metaperiodate (27 ml, 0.7 M) was added

dropwise during 5 min. and the mixture stirred at 0° for 0.5 hr. Ethylidene glycol (2.5 ml) was then added and stirring continued for 0.5 hr at 0°C. Ethanol (150 ml) was added and the resulting solid was collected. The filtrate was concentrated to 5 ml under reduced pressure 25-30° and extracted with dichloromethane (5 x 20 ml). The combined extracts were dried (Na_2SO_4) and added dropwise to a solution of (3-methoxy carbonyl-2-prophenylidene) triphenylphosphorane (5.77 g, 16 m.mol) in dichloromethane (30 ml). The mixture was stirred for 4 hr, and then concentrated under reduced pressure at room temperature. The residue was eluted from a column (75 g) of silica acid with light petroleum-ethyl acetate (1:1) to give 10 (0.195 g, 9.28%), m.p. 137-138°, $[\alpha]_D^{25}$ +2° (c 1.4, chloroform);

$Nujol_{max}$ 1790 and 1720 cm^{-1} (lactone and ester)C=O respectively, Fig.3.3.1. ^1H NMR ($CDCl_3$) δ 1.38 and 1.48 (2S, 6H, CMe_2), 3.74 (S, 3H, CO_2Me), 4.82 (d, 1H, $J_{6,7}$ 3.15 $J_{7,8}$ Hz H-7), 4.84 (S, $J_{8,7}$ Hz, H-8), 5.43 (dd, 1H, $J_{6,7}$ 3.15, $J_{6,5}$ 8.66 (Hz, H-6), 5.94 (dd, 1H, $J_{5,6}$ 8.66, $J_{5,4}$ 11.02 Hz (H-5), 6.02 (d, 1H, $J_{2,3}$ 15.7 Hz, H-2), 6.42 (dd, 1H, $J_{4,3}$ 11 Hz, H-4) and 7.48 (dd, 1H, $J_{3,4}$ 11 Hz, $J_{3,2}$ 15.7 Hz, H-3). Fig.3.3.2.

Analysis: Calculated for $C_{13}H_{16}O_6$: C, 58.20; H, 5.96; Found: C, 58.55; H, 5.82%.

Preparation of (2S,3S,4R)-2,3-isopropylidene dioxy-4-(4-methoxy carbonylbutyl)-4-butanolide (11)

A solution of 10 (0.2 g) in methanol (10 ml) was hydrogenated at 1 atmosphere and 0° for 0.5 hr using borohydride-reduced Pd catalyst (5 mg). The mixture was then filtered and concentrated to furnish 11 as a syrup (0.195 g), $[\alpha]_D^{25}$ +74° (C 1 chloroform); liquid $_{max}$ 1790 and 1740 cm^{-1} (lactone and ester>C=O, respectively). Fig.3.3.3. ^1H NMR ($CDCl_3$) δ 1.41 and 1.48 (2s, 6H, CMe_2), 1.5 - 1.9 (m, 6H, 3 CH_2 - 3,4,5), 2.36 (t, 2H, $COCH_2$), 3.7 (s, 3H, CO_2Me), 4.3 - 4.5 (m, 1H, H-6) and 4.68 - 4.86 (m, 2H, H-7,8). Fig. 3.3.4.

Preparation of (6R, 7S, 8R)-6,9-dihydroxy-7,8-(isopropylidene dioxy) nonanoate (3)

To a solution of 11 (0.2 g) in methanol at 0° was added sodium borohydride (0.2 g) in portion. The mixture was stirred for 4 hr at 0°, poured into cold water, and extracted with dichloromethane (5 x 20 ml). The combined extracts were washed with saturated aqueous ammonium chloride, dried, and concentrated and the residual liquid (0.19 g) was eluted from a column of silica acid with light petroleum-ethyl acetate (1:1) to furnish 3 (0.165 g, 81.3%), $[\alpha]_D^{26}$ +14 (C 1,chloroform); lit. $[\alpha]_D^{20}$ +12.3° (C 2, chloroform). Film $_{max}$ 3430 (OH) and 1745 cm^{-1} (CO_2Me) Fig.3.3.5. ^1H NMR ($CDCl_3$) δ 1.3 and 1.43 (2s, 6H, CMe_2), 2.28 (m, 2H,

$COCH_2$), 1 - 1.9 (m, 6H, 3 CH_2-3,4,5) and 3.6 (s, 3H, CO_2Me). Fig.3.3.6.

Analysis: Calculated for $C_{13}H_{24}O_6$: C,56.52; H, 8.69; Found: C, 56.28; H, 8.90%.

Preparation of 2,3:5,6-Di-O-isopropylidene-L-gulose (12)

To an ice-cold solution of 7 (2.58 g) in methanol (25 ml) was added sodium borohydride (0.39 g) slowly with stirring. After 0.5 hr, the solvent was removed under vacuum and the residue was crystallised from ethyl acetate-light petroleum to give 12 (2.4 g, 92%), m.p. 113-115°C (lit.114-115°), $[\alpha]_D^{24}$ +51° (C 1, chloroform).

Analysis: Calculated for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69; Found: C, 55.63; H, 8.06%.

Preparation of 1-O-Benzoyl-2,3;5,6-di-O-isopropylidene L-gulose (13)

To an ice cold mixture of pyridine (1.6 ml, 0.02 mol) and dry dichloromethane (5 ml) was added with stirring a solution of benzoyl chloride (1.8 ml, 0.015 mol) in dichloromethane (10 ml). After 5 min. a solution of 12 (2.64 g, 0.01 mol) in dichloromethane (15 ml) was added dropwise. The mixture was stirred at 0° for 4 hr and then poured into ice-water, the aqueous layer was extracted with dichloromethane layer were washed with water, aqueous sodium hydrogen carbonate and water, dried and concentrated. Recrystallisation of the residue from ethyl acetate gave 13

(3.6 g, 96%), m.p. 127-128°, $[\alpha]_D^{25}$ +13° (C 1.6, chloroform).

Analysis: Calculated for $C_{19}H_{24}O_7$: C, 62.63; H, 6.59; Found: C, 62.34; H, 6.60%.

Preparation of 1-O-Benzoyl-2,3-O-isopropylidene-L-gulose (14)

A solution of 13 (3.6 g) in methanol (50 ml) containing conc. hydrochloric acid (0.5 ml) was stirred at room temperature for 1.5 hr, neutralised with conc. ammonia, and concentrated under vacuum at room temperature. The residue was extracted with dry ethyl acetate, the extract was concentrated to 20 ml,and light petroleum (b.p. 60-80°) was added to slight turbidity. On cooling, 14 (3.1 g, 95%) separated, m.p.174-175°, $[\alpha]_D^{25}$ +91° (C 1.2, ethanol); $Nujol_{max}$ (OH) and 1730 cm^{-1} (benzoate>C=O).

Analysis: Calculated for $C_{16}H_{20}O_7$: C, 59.25; H, 6.17; Found: C, 59.55; H, 6.23%.

Preparation of 1-O-benzoyl-5,6;7,8-tetradeoxy-2,3-O-isopropylidene-D-lyxo-non-5,7-dienofuranuronate (16)

The procedure was essentially similar to that described above for 10 and gave 16 (79.6%), m.p. 89-90°. IR: Fig.3.3.7. ^1H NMR ($CDCl_3$) δ 1.34 and 1.5 (2s, 6H, CMe_2), 3.78 (s, 3H, CO_2Me), 4.89 (m, 2H, H-2,3), 5.13 (d, 1H, H-4), 5.85 - 6.5 (m, 4H, H 1,5,6,8), 7.3 - 7.7 (m, 4H, 3 ArH, H-7) and 8.08 (m, 2H, 2 ArH). Fig. 3.3.8.

Analysis: Calculated for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88;

Found: C, 64.50; H, 5.88%.

Preparation of 1-O-benzoyl-5,6;7,8-tetradeoxy-2,3-O-isopropylidene-D-lyxo-nonofuranuronate (17)

A solution of 16 (200 mg) in methanol (2 ml) was hydrogenated at room temperature and atmospheric pressure over borohydride reduced Pd catalyst (5 mg). After hydrogen absorption ceased (0.5 hr), the solution was decanted and concentrated to furnish 17 (0.195 g) as a liquid which crystallised on storage; m.p. 66-67°; $[\alpha]_D^{25}$ +30° (c 3.2, chloroform). ^{1}H NMR ($CDCl_3$) δ 1.0 - 1.8 (m, 6H, CH_2-5,6,7), 1.28 and 1.43 (2s, 6H, CMe_2), 2.3 (t, 2H, $-CH_2CO_2Me$), 3.6 (s, 3H, CO_2Me), 4.1 (m, 1H, H-4), 4.75 (m, 2H, H-2,3), 6.3 (s, 1H, H-1) and 7.25 - 8.05 (2 m, 5H, ph). Fig.3.3.9.

Preparation of 5,6-O-isopropylidene L-ascorbic acid (21)

This was prepared by the procedure reported in literature[13].

Preparation of bis-disylyl enol ether of L-ascorbic acid 5,6,O-isopropylidene derivative (22)

1.08 g (50 m.mole) of 5,6-O-isopropylidene L-ascorbic acid (21) was dissolved in 2 ml of pyridine to this 800 mg (50 m.mole) of hexamethyl disilazane was added, the reaction mixture was stirred for 1 hr at room temperature, then it was warmed to 80°C for 1 hr. Pyridine was removed under vacuum, bis-disylyl enol ether was crystallised from dry chloroform-

pet.ether to give 22 (300 mg) in 83% yield. m.p. 184-186°. $Nujol_{max}$ 1780, 1700 cm^{-1} (lactone and enol silyl ether). The ^1H NMR ($CDCl_3$) δ 0.1 to 0.35 (m, 9H, 2 x $SiMe_3$), 1.40 (s, 6H, CMe_2), 4.13 (m, 3H, 1H, H-5, 2H, H-6), 4.51 (d, 1H, H-4).

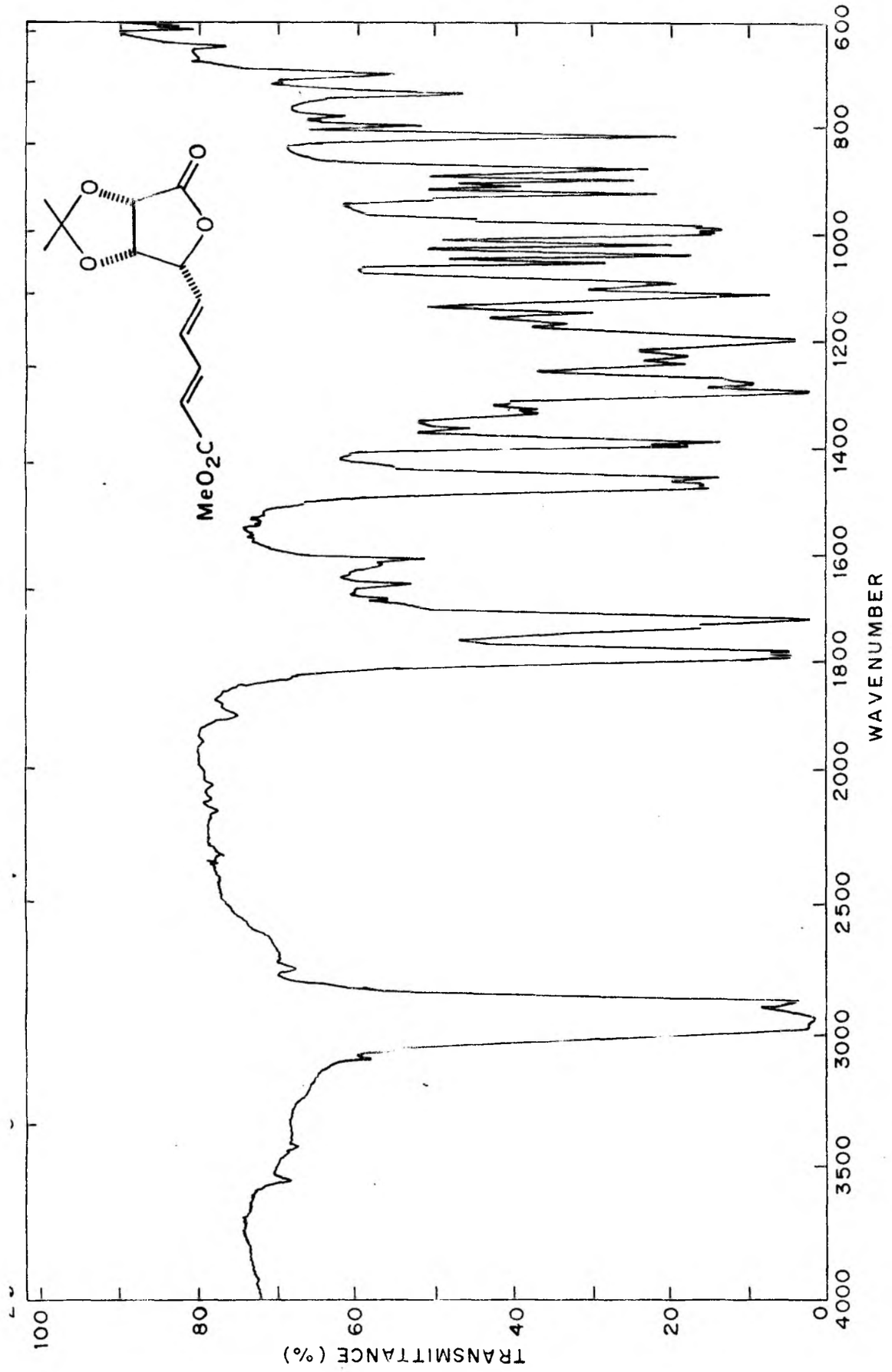
Reaction of bis disylyl enol-ether of L-ascorbic acid (22) with dibenzyl urea

To a solution of bis-disylyl enol-ether of L-ascorbic acid 22 (360 mg, 1 m.mole) and dibenzyl urea (240 mg, 1 m.mole) in cyclohexanol was added catalytic amount of para-toluene sulfonic acid. The reaction mixture was refluxed for 6 hr. The TLC in 25% ethylacetate-hexane) showed the disappearance of dibenzyl urea. Cyclohexanol was distilled off. The crude product was resolved on silica gel column elution with benzene-hexane (1:1) mixture yielded the pure product (24), m.p. 98-100°, $Nujol_{max}$ 3330, 1730 cm^{-1} (-NH and HN-C(=O)-O-R). ^1H-NMR (CCl_4) δ 1.2 - 2 (m, 10H), 4.40 (2H, CH_2-Ø), 4.80 (m, 1H -O-C(H)-), 7.4 (s, 5H-ArH). Elution with ethyl acetate yielded pure compound 25 (50 mg), m.p. 135-137°. ^1H NMR (d_6 DMSO) δ 3.68 (d, 2H, H-6), 4.08 (m, 1H, H-5), 4.80 (m, 3H, H-4 and CH_2-Ø), 7.48 (m, 5H-Ar). Fig.3.3.10.

Analysis: Calculated for $C_{13}H_{14}O_5N$: C, 59.0; N, 5.3; Found: C, 58.5; H, 4.95; N, 5.4%.

Preparation of 5,6-isopropylidene of (26)

To a solution of 26 (500 mg) in 10 ml of acetone was added one drop of acetyl chloride. The reaction mixture was stirred for overnight. Acetone was removed under reduced pressure. Residue was dissolved in methylene chloride and washed with water. The organic layer was dried, concentrated to give 25 (500 mg), as a viscous oil. ν_{max}^{film} 3320, 1810 cm^{-1} (-OH, lactone). ^1H NMR δ 1.40 and 1.32 (s, 6H, CMe_2), 3.72 - 4.20 (m, 3H, 2H, H-6, 1H, H-5), 4.52 - 5.0 (m, 3H, H-4, CH_2-Ø), 7.6 (s, 5H, Ar-H). (d_6 DMSO)


TRANSMITTANCE (%)
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80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
MeO2C
O
O
O
O

FIG. 3·3·1

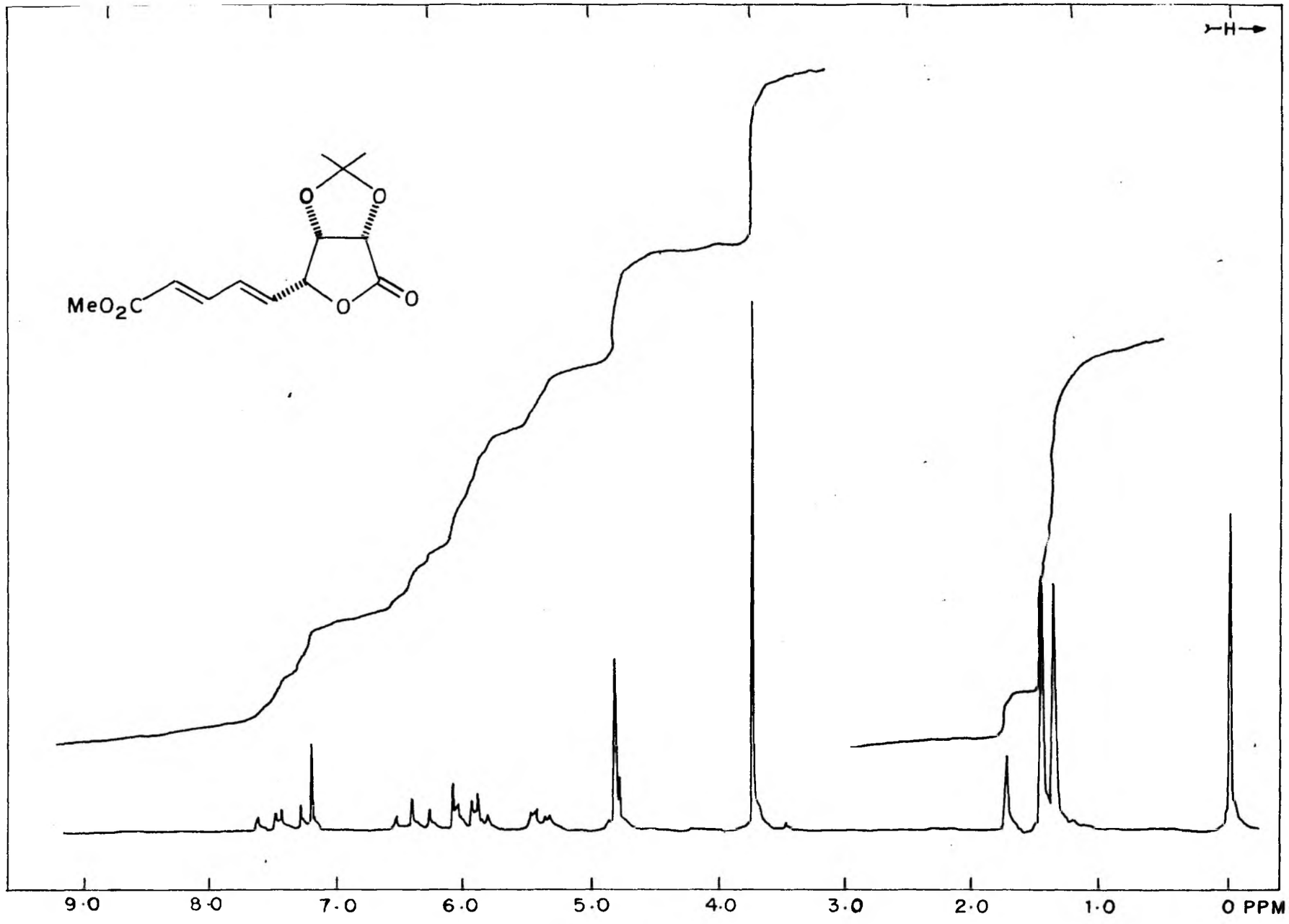
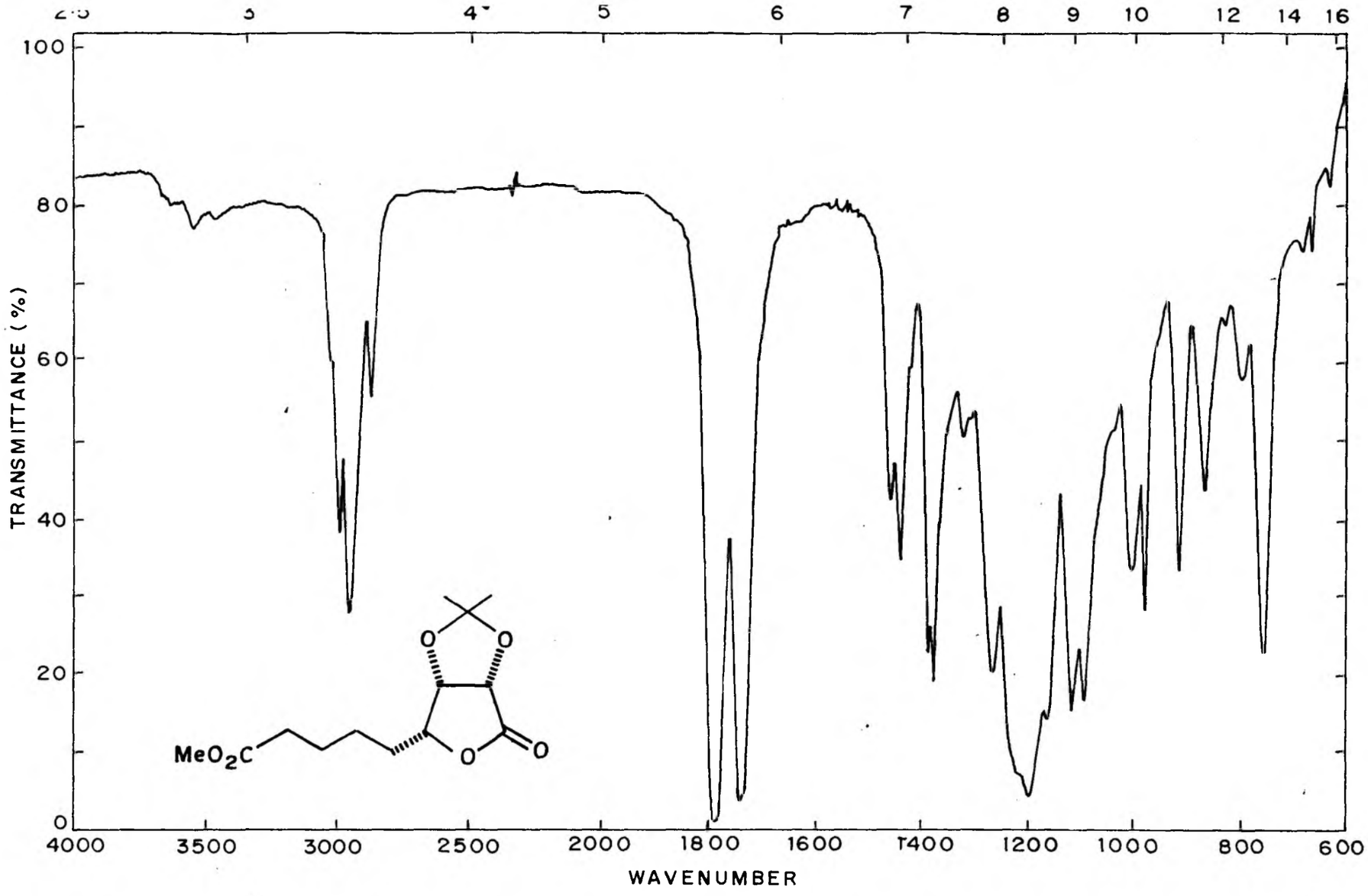


FIG. 3·3·2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80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
MeO2C
O
O
O
O

FIG. 3·3·3

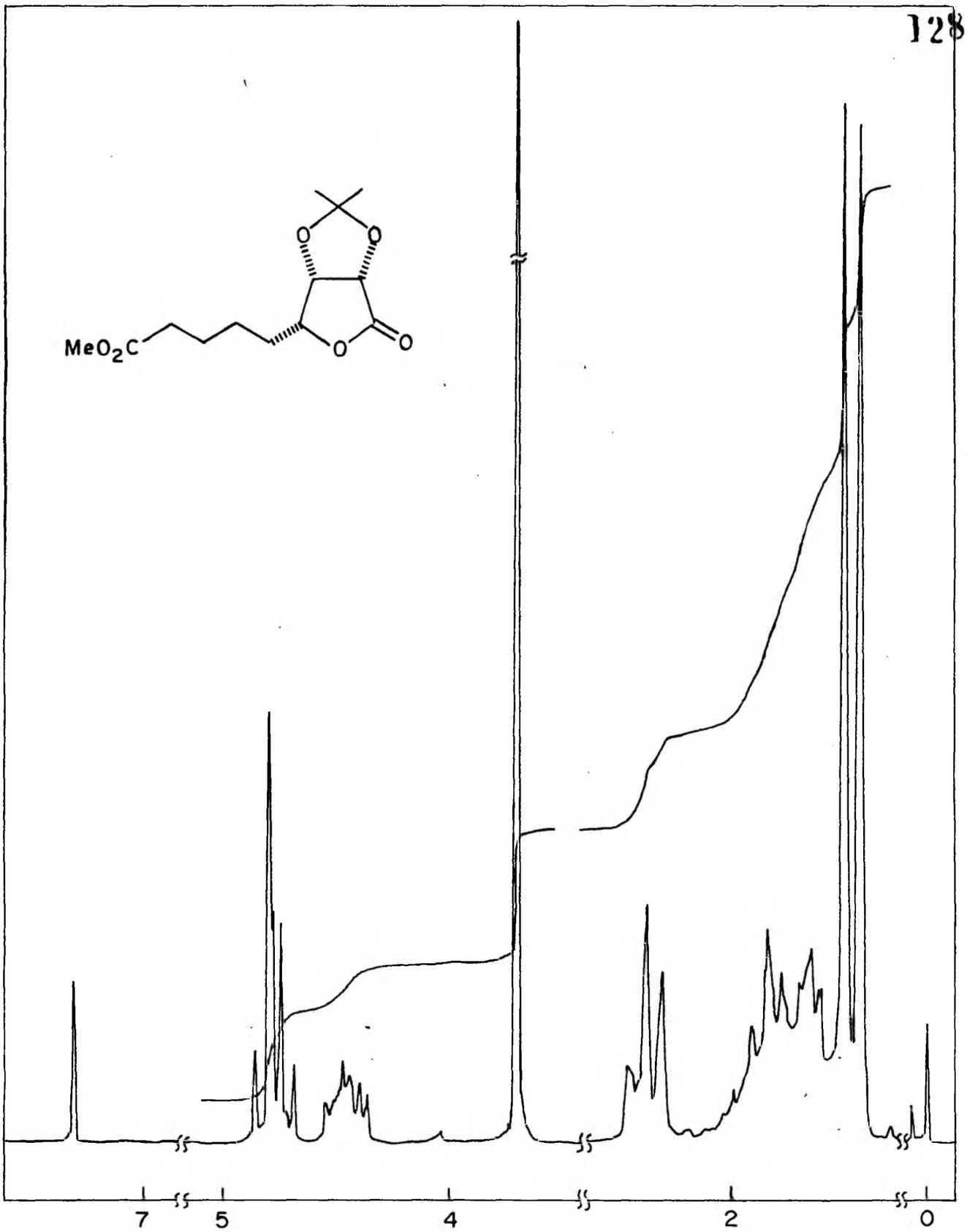


FIG. 3·3·4

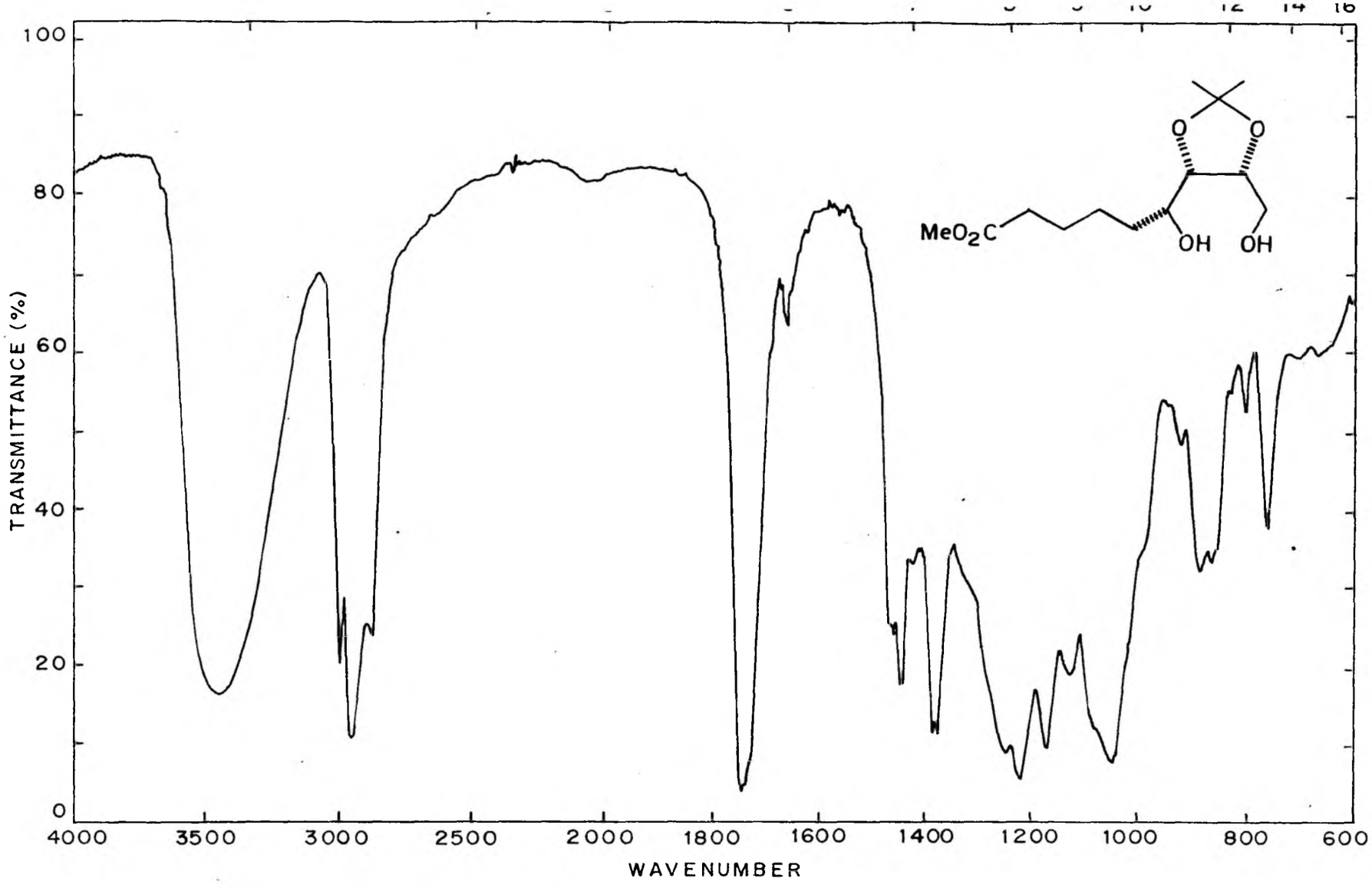

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
MeO2C
O
O
OH
OH

FIG. 3·3·5

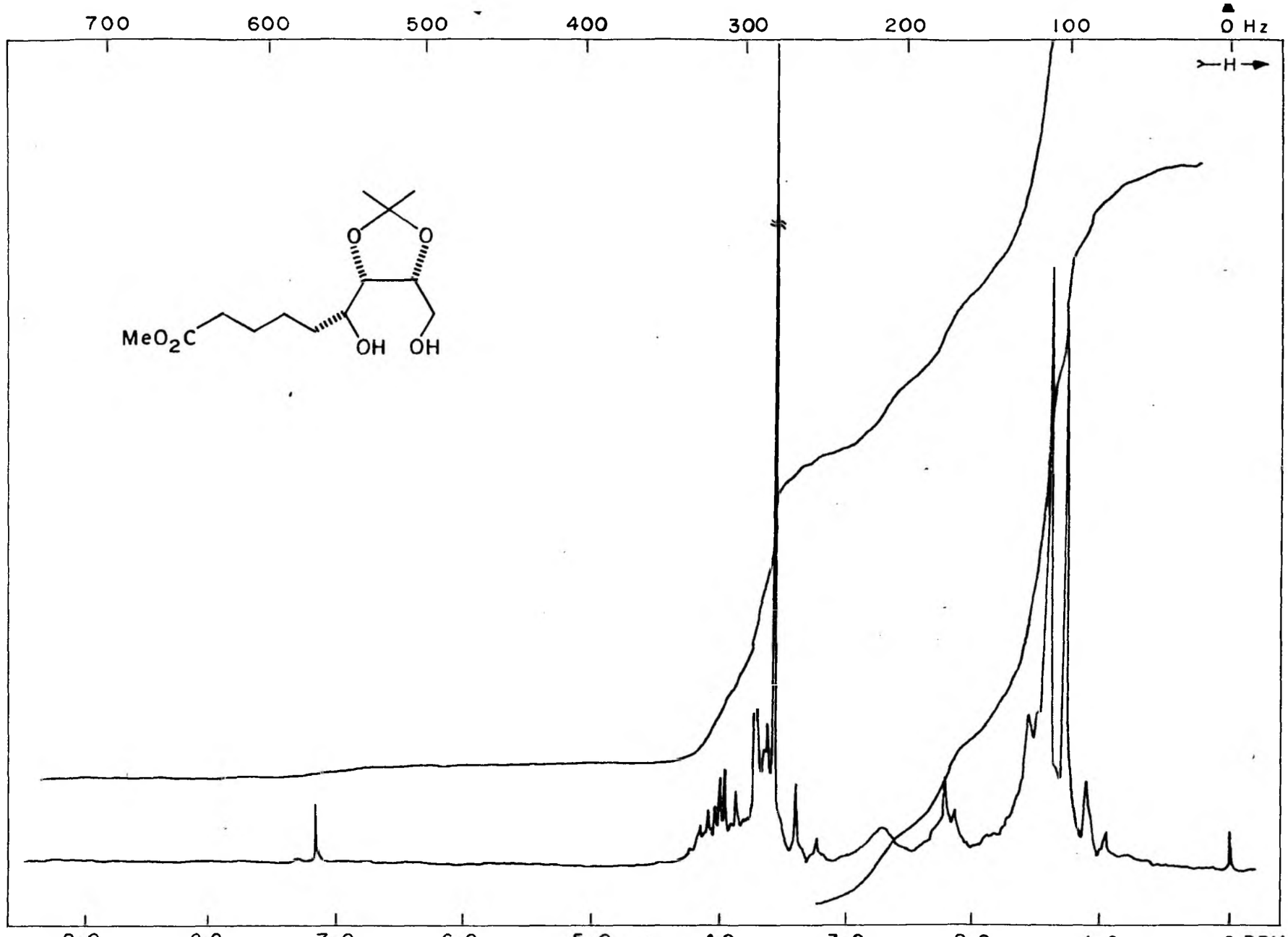

700
600
500
400
300
200
100
0 Hz
H
MeO2C
OH
OH
O
O
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIG. 3·3·6

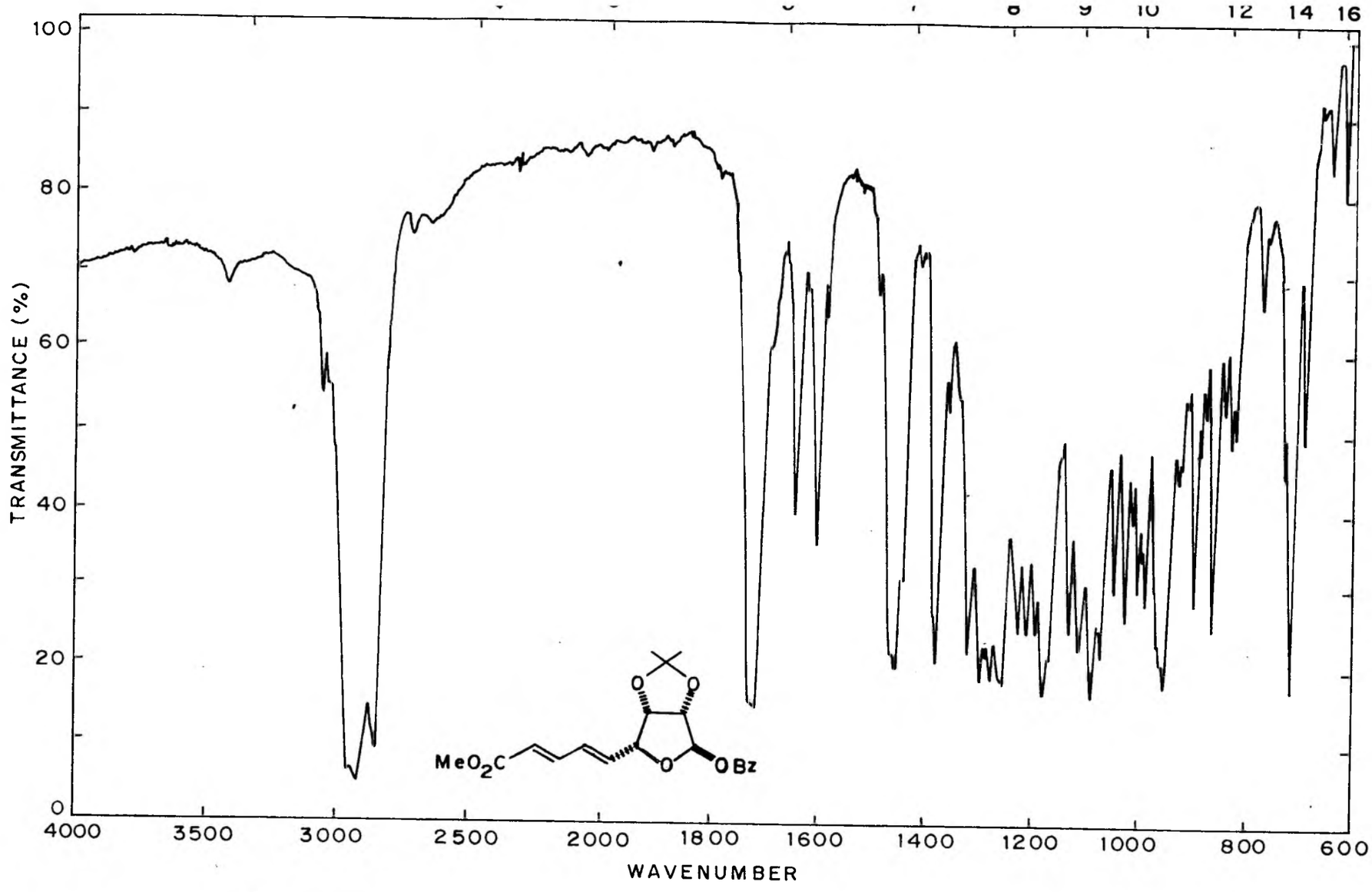

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
12
14
16
MeO2C
OBz

FIG. 3·3·7

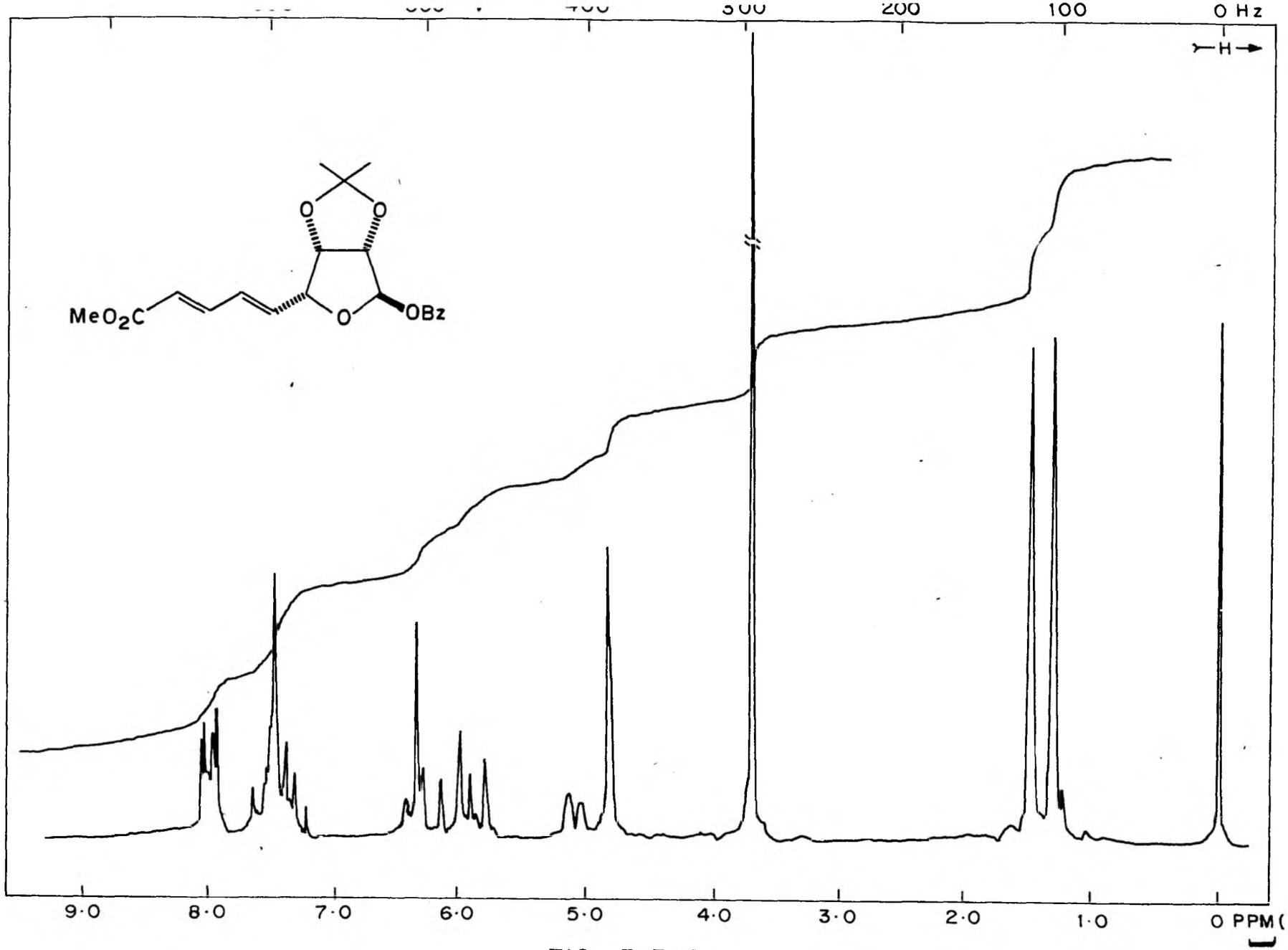


FIG. 3·3·8

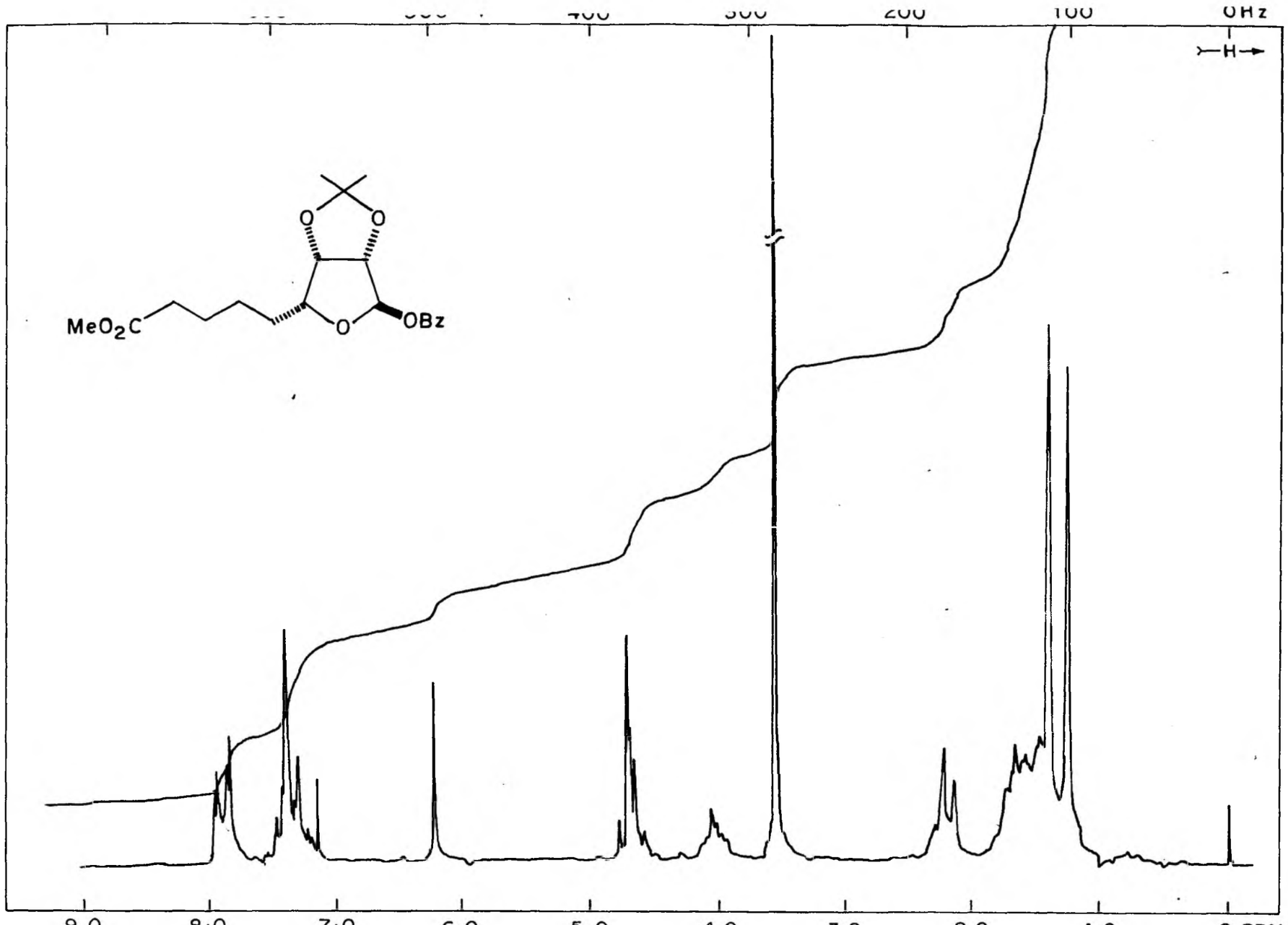


FIG. 3·3·9

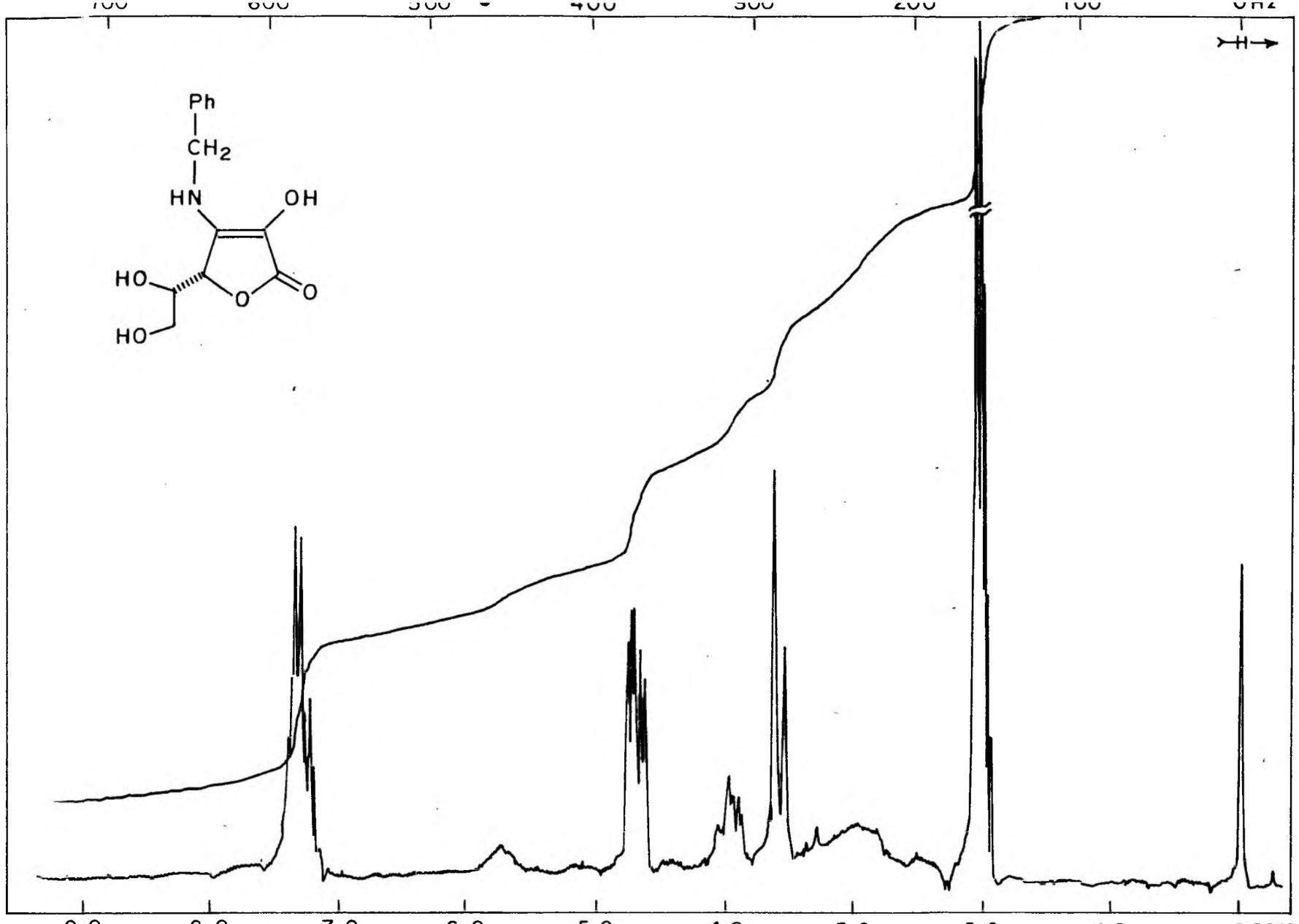


FIG. 3·3·10

3.4.0 REFERENCES

1 T. Ogawa, T.Kawano and M.Matsui
Carbohydr. Res., 57 C31-C35 (1977).

2 H. Ohrui and S. Emoto
Tetrahedron Lett., 2765-2766 (1975).

3 R.R. Schmidt and M. Maier
Synthesis 9, 747-748 (1982).

4 M. Ishidata, Y. Imai, Y. Hirasaka and K.Umemoto
Chem. Pharm. Bull., 11, 173-176 (1965).

5 H. Ogura, H.Takakashi and T. Itoh
J. Org. Chem., 37, 72-73 (1972).

6 E. Buchta and F. Amdree
Chem. Ber., 92, 311-316 (1959).

7 T.W. Russell and D.M. Duncan
J. Org. Chem., 39, 3050-3052 (1974).

8 R.K. Hulyalkar
Can. J. Chem., 44, 1594-1596 (1966).

9 H. Bredereck, G. Theilig
Chem. Ber. 86, 88 (1953).

10 H. Bredereck, R. Gompper, H.G. Von Schuh, G. Theilig
Angew. Chem., 71, 753 (1959).

11 P.M. Kochergin, Zh. Obshch. Khim. 31,1093, 1010 (1961).

12 P.M. Kochergin, V.E. Bogachev, M.G. Fomenko
USSR Patent 137517 (1960); Chem. Abstr. 56, 475 (1962).

13 K.G.A. Jackson et al.
Can. J. Chem., 47, 2498 (1963).

CHAPTER - 4.0.0

PREPARATION OF CHIRAL INTERMEDIATES FOR (+) BIOTIN SYNTHESIS

FOREWORD

The potential chiral intermediate (14) for the synthesis of (+)biotin, and a similar achiral intermediate (27) for (±)biotin have been prepared from L-cystine (2), and urea, pyruvic acid (29), ethylmercaptoester (31b) respectively.

This chapter also describes our studies at the cyclisation of (14) to give (16).

4.1.0 The present chapter deals with the synthesis of chiral intermediates for d-biotin (1) from L-cystine 2 (Chart 4.1.1) and mainly describes the preparation of compound (5) which is a potential chiral biotin intermediate and its attempted cyclisation to (6). The bicyclic compound (6) would show the properties of a reactive enamine and could be directly alkylated to (7) which would undergo decarboxylation to (8), stereocontrolled reduction of the double bond in compound (8) would then lead to the formation of d-biotin (1).

In accordance with this planned strategy (Chart 4.1.1) L-cystine (2) was converted into dicarboxylic acid (3) in 95% yield, by reduction with sodium in liquid ammonia, followed by condensation with chloroacetic acid[1]. Treatment of compound (3) with aqueous potassium cyanate at 70°C for 4 hr led to the formation of the 5-(carboxymethylthiomethyl)hydantoin ~~mercapto)propionic acid~~ (4) as a viscous oil which was found to be contaminated with inorganic impurities.

The acid (4) was subjected to esterification with diazomethane, and a semisolid was isolated, which failed to crystallise to furnish the ester (5) in pure form. Since the compound (5) is highly soluble in water and insoluble in non-aqueous solvents, purification became difficult.

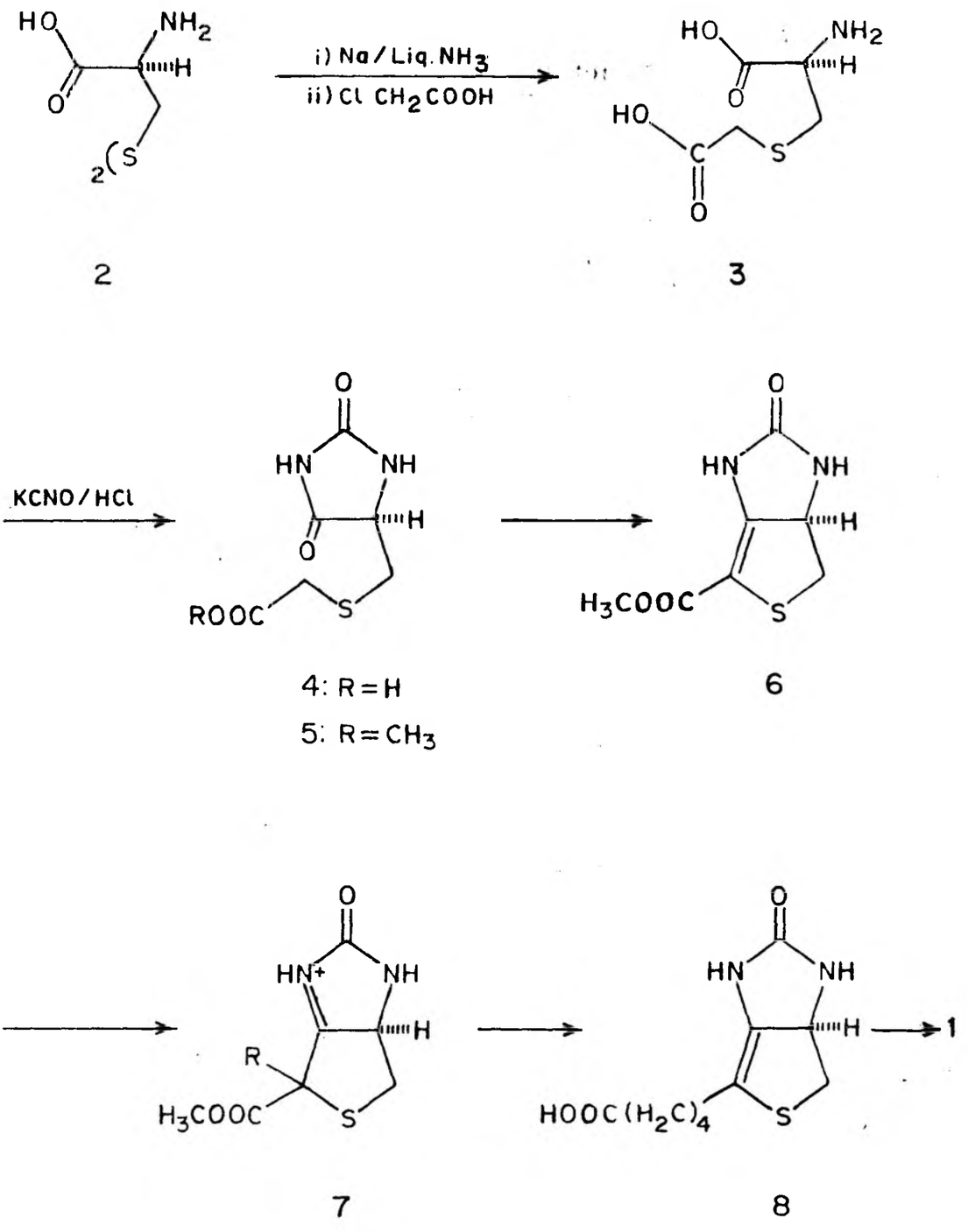

HO
NH2
H
O
S
2
i) Na / Liq. NH3
ii) Cl CH2COOH
HO
NH2
H
O
HO
C
S
O
2
3
KCNO / HCl
O
HN
NH
H
O
ROOC
S
4: R = H
5: R = CH3
H3COOC
6
HN+
R
H3COOC
7
HOOC(H2C)4
8
1

CHART — 4·1·1

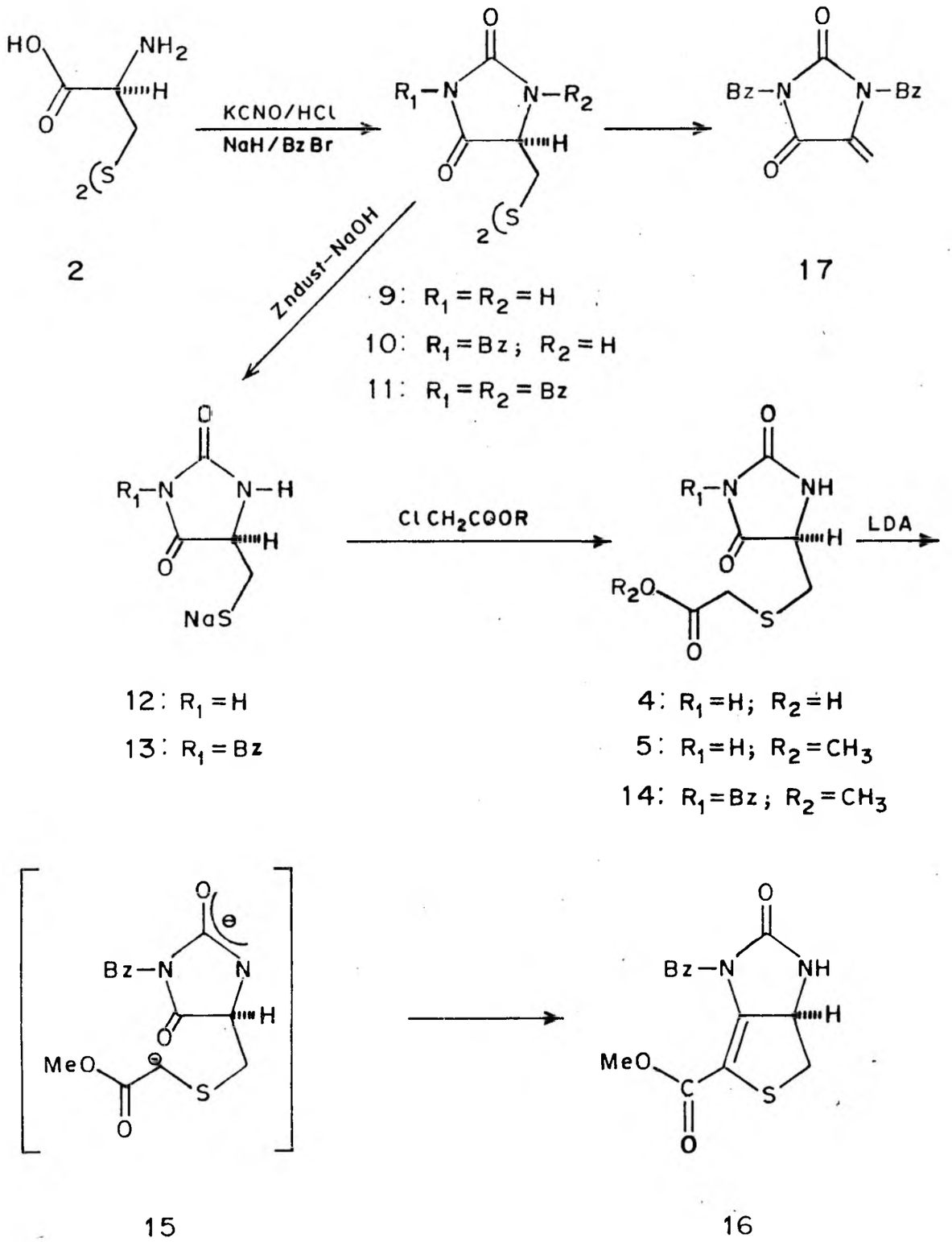
In an alternate approach, it was planned to prepare the required ester (5) as shown in (Chart 4.1.2).

The cystine (2) was converted to dimer hydantoin (9) by treating with aqueous potassium cyanate[2]. The crystalline dimer hydantoin was reduced with sodium in liquid ammonia to give the sodium salt[3] (12) which on treatment with aqueous chloroacetic acid or its methyl ester failed to furnish the required acid (4) or ester (5) respectively.

Due to the problems associated in the preparation of hydantoin acid (4) and ester (5) it was felt that N-benzyl protected derivatives would be more suitable compounds because of its expected solubility as well as handling ease. Also it was felt that N^3-benzyl derivative like 14 is ideally suited for base-catalysed cyclisation to N^3-benzyl protected ester (16) via the dianion (15).

Accordingly the dimer hydantoin (9) was subjected to monobenzylation using benzyl bromide under basic conditions. But all attempts to obtain (10) resulted in the formation of dibenzyl methylene hydantoin (17), m.p. 68°.

Finally an altogether new approach has been developed for the preparation of N^3benzyl 5-(methoxycarbonyl-methyl-thiomethyl) hydantoin (14) as shown in (Chart 4.1.3).


KCNO/HCl
NaH/BzBr
Zndust-NaOH
ClCH2COOR
LDA
2
9: R1=R2=H
10: R1=Bz; R2=H
11: R1=R2=Bz
17
12: R1=H
13: R1=Bz
4: R1=H; R2=H
5: R1=H; R2=CH3
14: R1=Bz; R2=CH3
15
16

CHART—4·1·2

The diester hydrochloride (18) was prepared in 90% yields, from diacid (3) by its esterification with dry MeOH-HCl at 0°C for 12 hr. The amine hydrochloride (18) was treated with anhydrous sodiumacetate in methanol at R.T. to give free amine (19). The amine (19) was then heated in dichloroethane to reflux for 2 hr to give the thiolactam as viscous oil in 80% overall yield on diacid (3). ν_{max}^{Nujol} 1710 and 1670 cm^{-1} (ester and lactam>C=O respectively). The ^1H NMR spectrum showed a multiplet centered at δ 3.10 for C-2 methylene, a singlet at δ 3.37 for C-6 methylene. Singlet due to carbomethoxy methyl appeared at δ 3.83. The methine proton at C-3 was located at δ 4.50.

A mixture of thiolactam (20) and benzyl isocyanate in toluene was heated under reflux for 3 hr to afford the required adduct (21) in 94% yield, m.p. 170-172°, $[\alpha]_D$-7° (C2, $CHCl_3$) ν_{max}^{Nujol} 1750, 1720, 1680 cm^{-1} (ester, amine, lactam C=O respectively). It was envisaged that the adduct (21) on treatment with base would rearrange as depicted in (Chart 4.1.3), via (22), to give the required N^3-benzyl substituted hydantoin methyl ester (14). The adduct on treatment with sodium hydride gave a mixture of products (TLC). Treatment with sodium alkoxides also afforded a mixture of products. Finally it was found that catalytic amount of triethylamine in methanol at R.T.

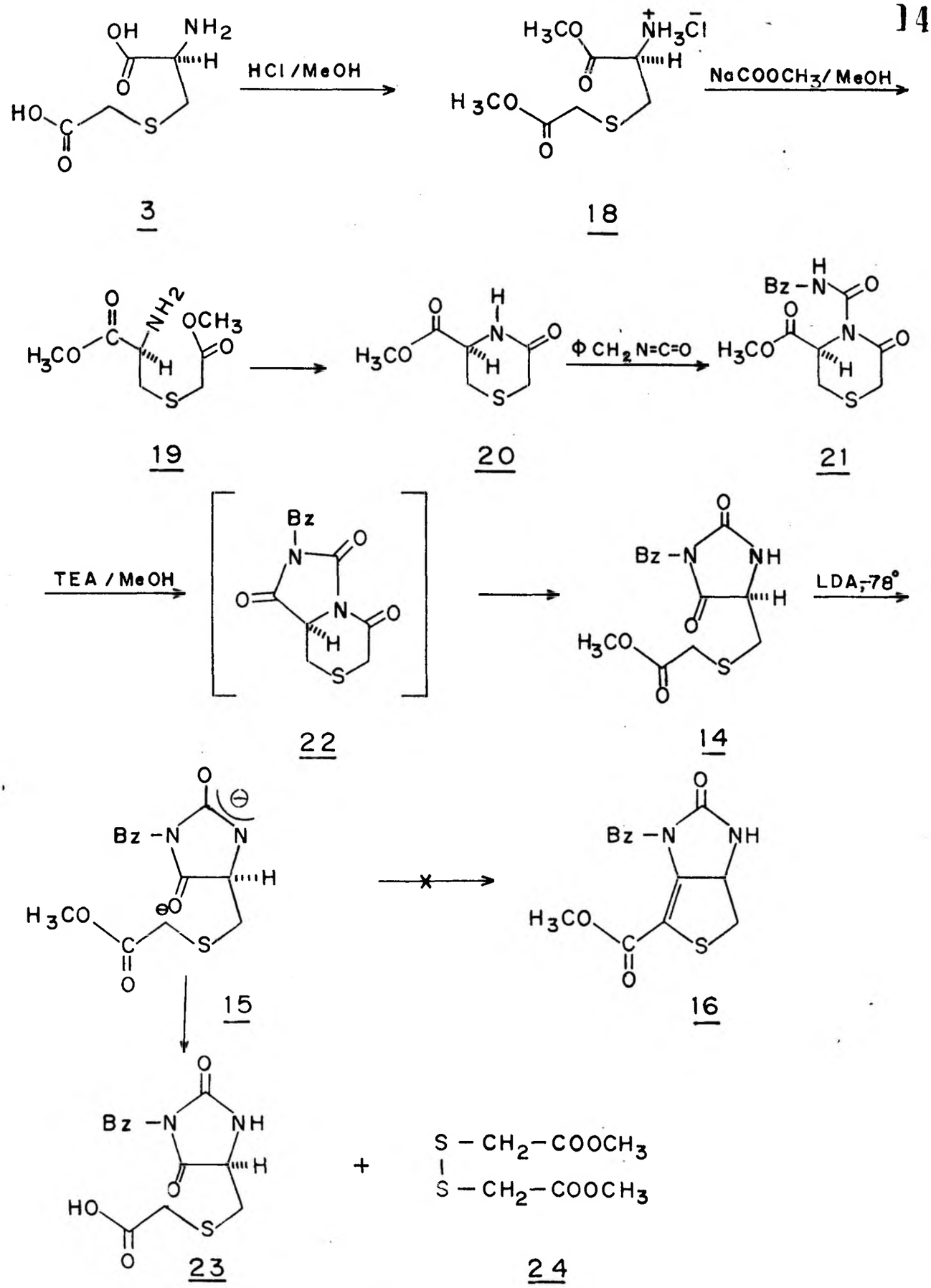

HCl / MeOH
NaCOOCH3 / MeOH
TEA / MeOH
LDA, -78°
Φ CH2 N=C=O
3
18
19
20
21
22
14
15
16
23
24

CHART - 4·1·3

led to the formation of the required compound (14), in almost quantitative yield, without any racemisation, m.p. 98-100°C, $[\alpha]_D^{21}$ -18.5 (C1, $CHCl_3$), ν_{max}^{Nujol} 1790, 1720 cm^{-1} (amide and ester>C=O respectively). The structure of 14 was also confirmed by X-ray crystallographic studies, Fig.4.2.13.

The cyclisation of (14) was then tried using LDA. In the presence of LDA the monobenzyl derivative (14) would give rise to the formation of dianion (15). In (14) the amide anion may be formed earlier than and in preference to the other anion α - to 4-keto function which would hopefully prevent the isomerisation of the chiral centre, during the cyclisation of the dianion (15) to (16), when the monobenzyl derivative is treated with 2 eq. of LDA at -78°C for 30 minutes no reaction was observed (TLC). The temperature was raised to -60° to -50° and after 30 min. TLC indicated the mixture of products from which the trace amount of acid (23) was isolated after the conventional work up of the reaction mixture along with some disulfide (24). Since the reaction was carried out in highly dry conditions the formation of acid could be through a cyclisation of dianion to give (22) and subsequent hydrolysis on work up.

In order to circumvent the cyclisation of (15) to the lactam (22), it was felt essential to block the NH-function

with trimethyl silyl group which can be easily introduced at low temperature and can conveniently be removed while working up of the reaction mixture.

Accordingly the monobenzyl derivative (14) in dry THF was treated with one equivalent of LDA at -78°C for 30 minutes and one equivalent of trimethyl sylyl chloride was added at the same temperature. It was further stirred for 30 min. then one more equivalent of LDA was added. No change in reaction mixture was observed (TLC) after stirring for prolonged time at -78° when the reaction mixture was warmed to -60° a mixture of products was formed, from which two major products were isolated. One product was confirmed as dimer (24). The ^{1}H NMR showed two signals at δ 3.66 and 3.86 for ester methyl and methylene adjacent to sulphur respectively. The structure of the second product could not be assigned on the basis of spectral studies.

From the preceding experiments it was concluded that the base catalysed cyclisation to form compound (16) could not be realised because of the side reactions dominating over the required reaction. However, it was thought worthwhile exploring the acid catalysed cyclisations. The monobenzyl derivative (14) on treatment with sulfuric acid in methylene chloride at R.T. resulted in a mixture of products (TLC). Lowering the temperature below -5° resulted in no reaction,

with $POCl_3$ and P_2O_5 at 50-60°C. The compound (14) formed a complicated mixture of products as judged by TLC. Alternately when the above experiment was carried out with BF_3-etherate, titanium tetrachloride etc. no reaction was observed at ambient temperature while at high temperature, simple hydrolysis of the carbomethoxy function was observed. However, with polyphosphoric ester (PPE) at 140°C the monobenzyl derivative (14) gave a new product with some dimer (24) when 10% PTS acid in tetrachloroethane was used to effect the cyclisation, the same product was obtained quantitatively. On the basis of the physical properties it was not possible to assign the structure of the above new product. But the X-ray studies (Fig.4.2.14) clearly indicated that the product was not the required compound (16). It was the bicyclic lactam (22) which was postulated as the intermediate in the formation of 14 (Chart 4.1.3). The structure (22) obtained above was further proved by treating with catalytic amount of triethyl amine in methanol at 0°C to give ester (14).

From the aforementioned studies the problem associated with the cyclisation step on (14) were found to be: (i) elimination of sulfur functionality under base catalysed conditions and (ii) cyclisation under acid-catalyses at high temperature. The formation of bicyclic product was due to the free -NH- group which was taking part in the reaction. Though efforts to block the free -NH- group with

acetic anhydride-sodium acetate resulted in the formation of N-acetyl derivative, which on heating with acid catalyst at 100°C deacetylation took place to give 14. Previous studies showed that benzyl groups instead of acetyl cannot be introduced in (14) by base catalysed reactions as this would result only in elimination products.

However, the efforts were directed to prepare the 1,3-dibenzyl-5-(ethoxycarbonylmethylthiomethyl) hydantoin (27) by altogether different route as shown in (Chart 4.1.4). Although compound 27 formed by this route was a chiral, the studies on its cyclisation reactions could be made before a chiral synthesis is achieved.

The dibenzyl hydantoin (25) prepared by the procedure reported in literature[4] was alkylated with chloromethyl-mercapto ethylacetate (26) using LDA. The required N,N'-dibenzyl derivative (27) was formed in 10% yield. $\nu_{max}^{liquid\ film}$ 1720, 1780 cm^{-1} (ester and amide >C=O respectively). The other products formed were as shown in (Chart 4.1.4). The low yield in the formation of (27) prompted us to explore other reaction based on studies made by S. Murahashi *et al*.[6] during the reaction of pyruvic acid with urea as shown in (Chart 4.1.5).

The methylene hydantoin was prepared by condensing urea with pyruvic acid (29) followed by dehydration.

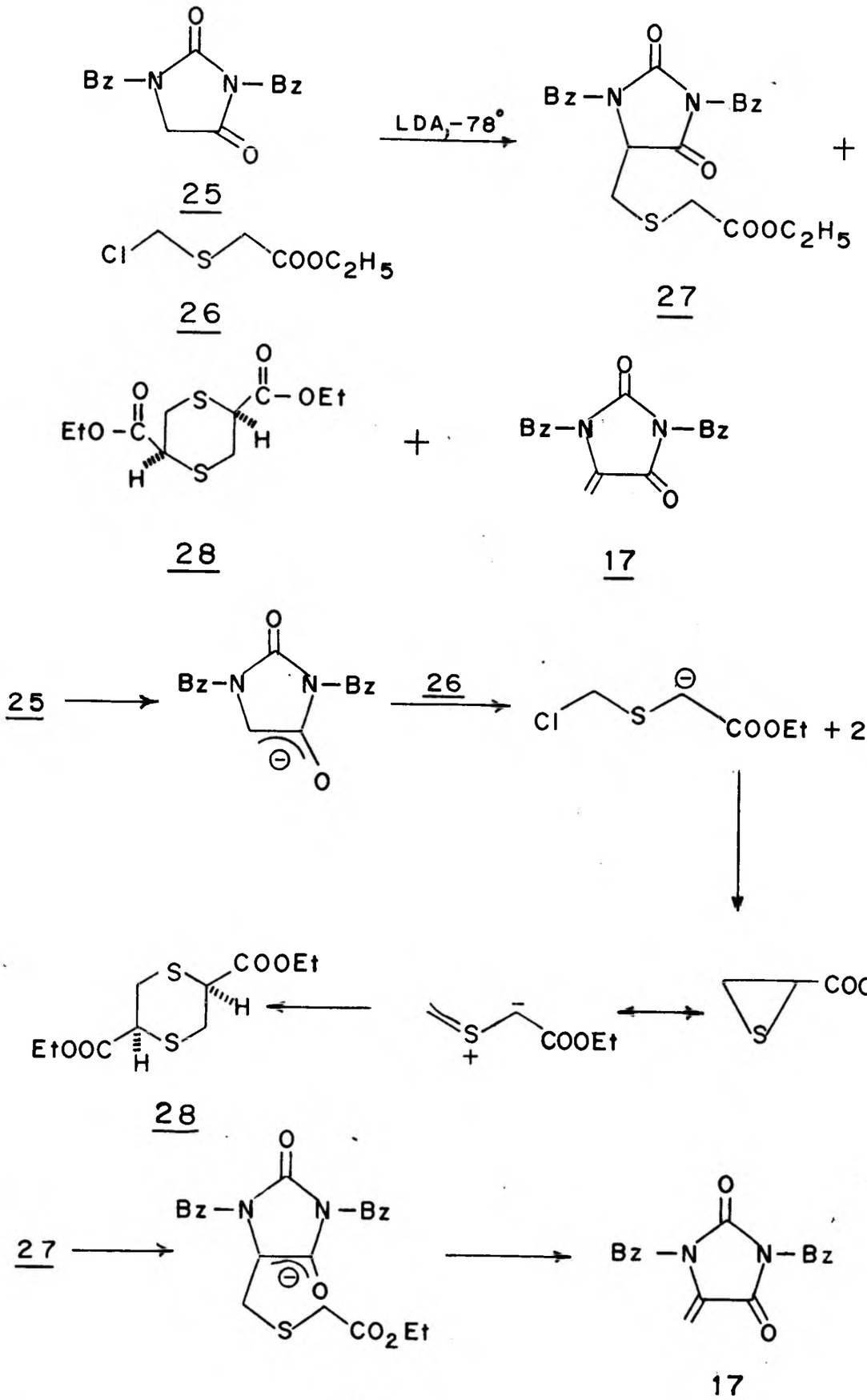

Bz
N
Bz
O
LDA, -78°
25
Cl
S
COOC2H5
26
27
EtO
OEt
H
28
17
25
26
COOEt + 25
COOEt
EtOOC
CO2Et

CHART - 4·1·4

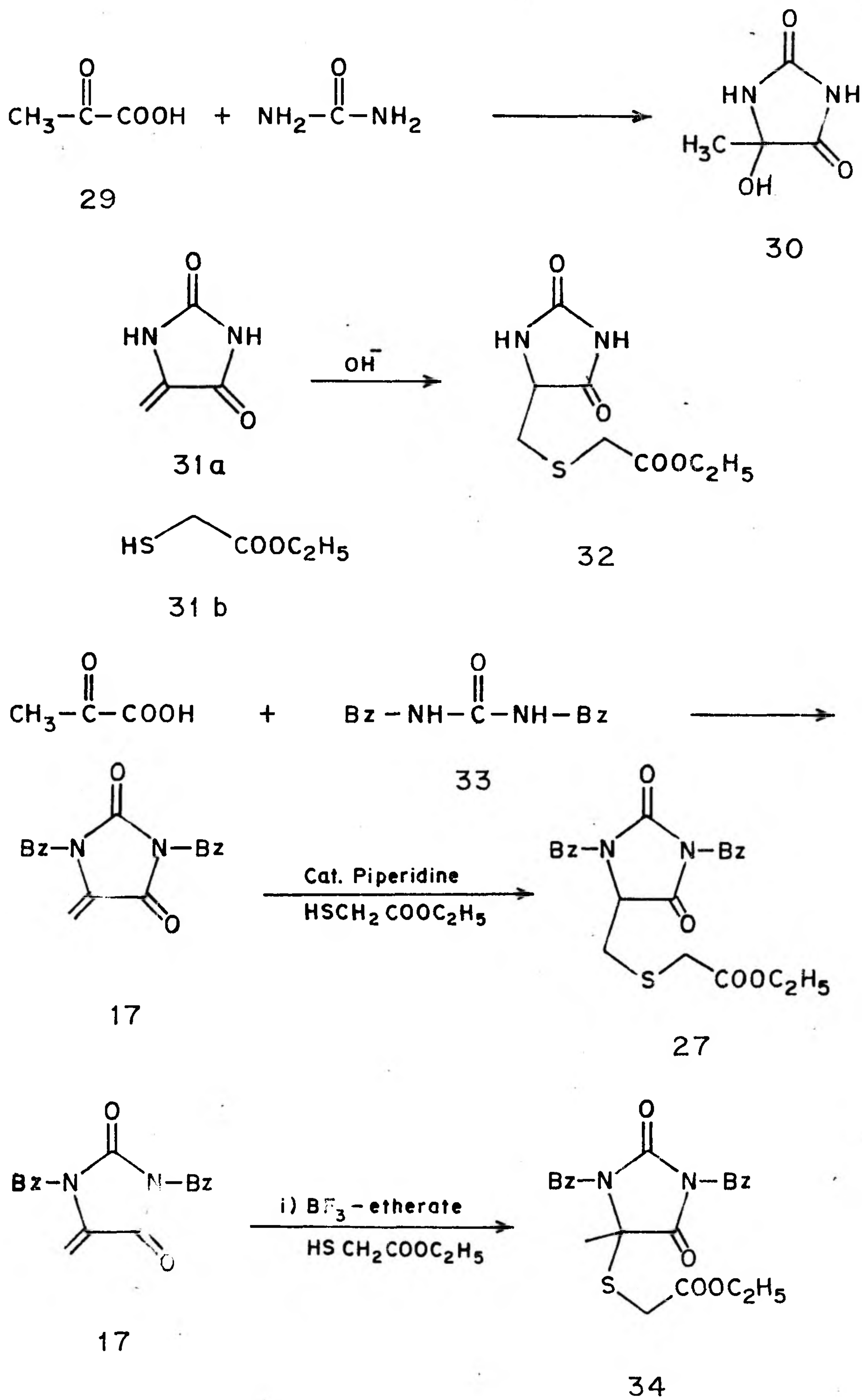

29
30
31a
OH⁻
32
31 b
33
17
Cat. Piperidine
HSCH2 COOC2H5
27
17
i) BF3-etherate
HS CH2COOC2H5
34

CHART – 4·1·5

Michael addition on methylene hydantoin (31) with ethylmercaptoacetate furnished 5-(ethoxy carbonylmethyl-thiomethyl) hydantoin (32) in 80% yields, m.p. 101°C.

On the basis of the above reaction, 50% pyruvic acid in water was treated with dibenzyl urea (33) for 3 hr on steam bath, to give dibenzyl methylene hydantoin (17) in quantitative yields. The spectral data was in agreement with the previously reported data. Ethyl mercaptoacetate was added to the methylene dibenzyl hydantoin (17) in the presence of piperidine to give (27) in almost quantitative yields. The spectral properties confirms the structure assigned as (27). Under acid catalysis viz. using BF_3-etherate instead of Michael adduct (27), the compound (34) was isolated in 90% yields. Cyclisation studies on (27) as well as other methods of ring formation from 14, to elaborate them further to biotin structure are worthwhile taking up.

4.2.1 EXPERIMENTAL

Anhydrous solvents required were prepared by procedure given in the Text Book of Practical Organic Chemistry by Vogel (Fourth Edn.).

D-isopropyl amine was distilled over calcium hydride; $TiCl_4$, BF_3 etherate and trimethyl chlorosilane were distilled prior to use.

n-Butyl lithium was prepared according to the reported procedure from lithium (15.4 g, 2.2 moles) and butyl chloride (92.5 g, 1 mole) in pet. ether at a reflux or lithium (7.7 g, 1.1 mole) and butyl bromide (68.5 g, 0.5 mole) in ether at -10 to 30° and estimated by the double titration method of Gilman[7].

Preparation of diacid (3) from cystine

3 was prepared according to the procedure reported in literature[1], m.p. 190-2° (lit. m.p. 194°).

Preparation of 5-(carboxymethylthiomethyl)hydantoin(4) ~~propionic acid (4)~~

To a solution of diacid (3) 8.95 g (5 m.moles) in water (100 ml) was added potassium cyanate 4.86 g (6 m.mole) in water (50 ml) and were allowed to react for 30 minutes at 70° with stirring. The reaction mixture was refluxed with 50 ml of 6N HCl for 1 hr. The solution was allowed to

to stand overnight in a refrigerator, no separation of the product was observed. Complete removal of the water furnished thick mass which failed to crystallise.

Preparation of ester (5)

The above mentioned thick mass was esterified with diazomethane, which resulted in a mixture of products, from which it was not possible to isolate the ester (5).

Preparation of dimer hydantoin (9)

(9) was prepared according to the procedure reported in literature[2], m.p. 300°C (decomp.).

Reaction of dimer hydantoin (9) with benzyl bromide

A mixture of dimer hydantoin 4.68 g (20 m.mole) and anhydrous potassium carbonate (8 g) in acetone (100 ml) was refluxed with slow addition of benzyl bromide 3.4 g (20 m.moles). After 4 hr, the formation of new product was observed (TLC). The reaction mixture was filtered, acetone was removed, the residue was dissolved in water, extracted with ether (3 x 20 ml). Removal of the solvent furnished crystalline solid (17) in 40% yield, m.p. 68°, M^+ 292, $Nujol_{max}$ 1790, 1720, 920 cm^{-1} (C_2, C_4, >C=O and exocyclic methylene respectively). ^1H NMR (CCl_4) δ 4.66 and 5.33 (dd, 2H), 7.20 (d, 10H, Ar-H), Fig.4.2.1.

Reaction of dimer hydantoin (9) with benzyl bromide in the presence of sodium hydride

A mixture of dimer hydantoin 1.1 g (5 m.moles) and

sodium hydride 240 mg (10 m.moles) was stirred in DMF for 1 hr R.T. Benzyl bromide was added 1.7 g (10 m.moles) to the green coloured reaction mixture. The reaction mixture was allowed to stir for 4 hr at R.T. After the conventional work up of the reaction mixture, the dibenzyl-hydantoin (17) was isolated in 30% yield.

Esterification of the diacid (3) to the diesterhydro-chloride (18)

The diacid (3) 10 g in dry methanol was cooled to 0°C, the solvent was saturated with hydrogen chloride gas. The reaction mixture was kept at 0° for 12 hr. Removal of the methanol furnished the dimethyl ester hydrochloride whose spectral and physical properties were in agreement with the reported sample, m.p. 97° (lit.[1] m.p. 98-100°), $[\alpha]_D^{20}$ -12.4. (C 2, chloroform)

Preparation of 3-carbomethoxy-5-keto 1,4-thiazine (20)

To a solution of dimethyl ester hydrochloride 18 (2.43 g, 10 m.mole) in dry methanol was added anhydrous sodium acetate 0.84 g (10 m.mole). The reaction mixture was allowed to stir for 2 hr. The precipitated sodium chloride was filtered. Removal of the methanol gave (19) as a thick mass which on refluxing in dichloroethane for 2 hr gave the viscous liquid which was purified by column chromatography to give 20 (1.5 g, 85%), ν $Nujol_{max}$ 1710,

1670 cm^{-1} (ester and lactam >C=O, Fig.4.2.2). ^1H NMR ($CDCl_3$)δ 3.10 (m, 2H, H-2), 3.37 (s, 2H, H-6), 3.83 (s, 3H, $CO_2\underline{CH_3}$), 4.50 (m, 1H H-3), 7.60 (s, 1H, -N<u>H</u>-), Fig.4.2.3.

Reaction of thiolactam (20) with benzyl-isocyanate

To a solution of thiolactam (20) 1.75 g (10 m.mole) in dry toluene was added benzylisocyanate 1.31 g (10 m.mole). The reaction mixture was refluxed for 3 hr. The trace amount of solid separated was filtered, and then concentrated under reduced pressure at 40°C. The residue was eluted from column of silica acid with light petroleum-ethylacetate (1:1) to give 21 (2.9 g, 94.1% yield, m.p. 170-172°, $[\alpha]_D^{25}$ -7° (C 2, $CHCl_3$). $Nujol_{max}$ 1750, 1720, 1680 cm^{-1} (ester, amide, lactam>C=O) respectively, Fig.4.2.4. ^1H NMR ($CDCl_3$) δ 3.20 (m, 2H, H-2), 3.33 (s, 2H H-6), 3.83 (s, 3H, $CO_2\underline{CH_3}$), 4.50 (d, 2H, CH_2-Ø), 6.0 (m, 1H, H-3), 7.33 (s, 5H, Ar-H), Fig.4.2.5.

Analysis: Calculated for $C_{14}H_{15}O_4N_2$: C, 54.5; H, 5.1; N, 9.09; Found: C, 54.5; H, 5.4; N, 9.15%.

Preparation of N^3-benzyl 5-(methoxycarbonyl-methyl-thiomethyl) ~~mesoar~~ hydantoin (14)

The compound 21 308 mg (1 m.mole) was dissolved in methanol and was cooled to 0°. To this catalytic amount of triethylamine was added, the reaction mixture was stirred for 30 minutes at 0°, then at R.T. for 3 hr. It

was neutralised with hydrochloric acid. Methanol was distilled off, the residue was dissolved in chloroform and then washed with water, dried. Removal of the solvent furnished crystalline solid 14 300 mg (97.4%), m.p. 98-100°C, $[\alpha]_D^{25}$ -18.5° (C 1, $CHCl_3$), $\nu Nujol_{max}$ 1790, 1720 cm^{-1} (amide and ester >C=O respectively), Fig.4.2.6. ^1H NMR ($CDCl_3$) δ 3.0 (m, 2H, H-6), 3.20 (s, 2H, -S-$\underline{CH_2}$-C(=O)-) 3.66 (s, 3H, COO$\underline{Me}$), 4.26 (m, 1H H-5), 4.60 (s, $\underline{CH_2}$-Ø), 6.53 (s, 1H, -N$\underline{H}$-), 7.16 (s, 5H, Ar-H), Fig.4.2.7. M^+ 308. X-ray Fig.4.2.13.

Cyclisation of (14) with LDA

A two-necked round bottom flask of 25 ml capacity was fitted with a three way stop cock. A magnetic spinning bar was introduced in the flask and the other neck closed with a rubber septum. The flask was flame dried under diminished pressure, flushed with dry nitrogen and finally maintained under a slight positive pressure of nitrogen. A solution of diisopropylamine (120 mg, 1.2 m.moles) on 2 ml of dry THF was introduced into the flask with a syringe. The flask was cooled to 0°C, in an ice-bath and a solution of n-butyllithium (0.6 ml of 2M solution in petroleum ether, 1.2 m.mole) was added dropwise with a syringe. After stirring at 0° for 15 min, a solution of LDA in THF was cooled to -79°C, to this the solution of 14 (308 mg, 1 m.mole) in 2 ml of THF was added slowly. The

solution was allowed to stir for 30 mins at -79°C, and then trimethyl silyl chloride (108 mg, 1 m.mole) was added. The reaction mixture was stirred for another 15 mins at -79°C. A solution of one more equivalent of LDA (prepared with same quantities (1.2 m.moles) was added to the reaction flask. The resulting reaction mixture was stirred for 30 mins at -79°C. No change in the starting material was observed (TLC). The reaction mixture was further warmed to -60°C.. A complicated mixture of products were formed (TLC). The reaction mixture was quenched with acetic acid at -78°C, then was diluted with water. The aqueous layer was extracted with ethyl acetate, washed with water, dried, and concentrated to give the crude product, from which the compound 24, 50 mg was isolated. ν liquid film 1750 cm^{-1} (ester >C=O). ^1H NMR:($CDCl_3$)δ 3.66 (s, 6H, $COOCH_3$), 3.86 (s, 4H, 2X $-S-CH_2-\overset{O}{\overset{\|}{C}}-$).

Cyclisation of (14) with conc. H_2SO_4

To a solution of compound 14 (308 mg, 1 m.mole) in dry methylene chloride was added catalytic amount of conc. H_2SO_4. The reaction mixture was stirred for 30 mins. at R.T. The mixture of the products are observed (TLC). After working up of the reaction, the dimer 24 (70 mg) was isolated in pure form. The IR, NMR are identical with the dimer isolated in LDA reaction above.

Cyclisation of (14) with PTS acid

The compound 14 (154 mg) was dissolved in 5 ml of

tetrachloroethane to which catalytic amount of PTS acid was added. The solution was refluxed for 4 hr, solvent was evaporated under reduced pressure at 50°C. The residue was dissolved in water, and then extracted with ethyl acetate. The ethyl acetate extract was washed with sat. $NaHCO_3$ solution then with water. Removal of the solvent gave the residue (125 mg) which was crystallised from chloroform-pet.ether, m.p. 198-200°C. The X-ray studies of the above compound confirms the structure as (22), Fig.4.2.14.

Preparation of N^1-acetyl derivative of compound 14

A mixture of 14 (308 mg, 1 m.mole) anhydrous sodium acetate (110 mg, 1.25 m.mole) and acetic anhydride (2 ml) was heated on water bath for 3 hr. Methanol was added to the reaction mixture to quench the excess of acetic anhydride. Methyl acetate formed was removed under reduced pressure. The residue was dissolved in chloroform, washed with water, dried, removal of the solvent furnished N^1acetyl derivative as viscous oil (300 mg, 85% yield). ν_{max} Nujol 1800, 1725 cm^{-1} (amide, and acetyl ester >C=O) respectively. ^1H NMR: δ 2.60 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 3.0 (s, 2H, $-S-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.33 (m, 2H, CH_2-S-), 3.66 (s, 3H, $-COOCH_3$), 4.66 (m, 3H, H-5 and CH_2-Ph), 7.20 (s, 5H, Ar-H). ($CDCl_3$)

Preparation of dibenzyl hydantoin (25)

Dibenzyl hydantoin was prepared according to the procedure reported in literature[4]. m.p. 64°, lit. m.p. 64-65°.

Preparation of chloromethyl mercaptoethylacetate[5] (26)

The mixture of ethylmercapto acetate (70 g, 0.5 mole) and p-formaldehyde (45 g, 0.5 mole) and $MgSO_4$ (7 g) in 500 ml of dichloromethane was stirred at -50°C in dry ice-acetone bath. Dry hydrogen chloride was passed to the solution for 90 minutes at -50°. The stirring was continued for 2 hr at room temperature. The reaction mixture was filtered, solvent was removed, the product was distilled at 0.2 mm, 50°C, to give compound 26 (60% yield). M^+ 168.

Reaction of dibenzyl hydantoin with chloro methyl mercapto ethyl acetate

A two-necked round bottom flask of 25 ml capacity was fitted with a three way stopcock. A magnetic spinning bar was introduced into the flask and the other neck closed with a rubber septum. The flask was flame dried under diminished pressure, flushed with nitrogen and finally maintained slight positive pressure of nitrogen. A solution of diisopropylamine (120 mg, 1.2 m.mole) in 2 ml of dry THF was introduced into the flask with a syringe. The flask was cooled to 0° in an ice-bath and a solution

of n-butyl-lithium (0.6 ml, 1.2 m.mole) of 2M solution in petroleum ether was added dropwise with a syringe. After stirring at 0° for 15 minutes the solution was cooled to -78° in a dry ice-acetone bath, and the dibenzyl hydantoin 24 (260 mg, 1 m.mole) in dry THF was added over a period of 10 minutes. After 30 minutes the chloromethyl mercapto-ethylacetate (168 mg, 1 m.mole) in 1 ml of THF was introduced slowly. The reaction was continued for 45 mins. at -78°. The formation of mixture of products were observed (TLC). The reaction mixture was quenched with acetic acid, diluted with aqueous ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium hydrogen carbonate, then with water. Removal of the solvent furnished the crude oil. The oil obtained was resolved on silica acid column. Elution with 5% ethyl acetate gave 60 mg of the dimer 28 as a black syrup. $\nu_{max}^{liquid\ film}$ 1750 cm^{-1} (ester>C=O). ^1H NMR ($CDCl_3$): 1.33 (t, 6H, $-COOCH_2CH_3$) 3.33 (s, 4H, 2X CH_2), 4 - 4.5 (q, s, 4H, 2H), Fig.4.2.8. Elution with 15% ethyl acetate-light petroleum gave 17 (45 mg). The spectral data was in agreement with the product 17 obtained earlier.

Third fraction to be eluted with 40% ethyl acetate-light petroleum was a syrup, 20 mg. By spectral evidence it was the required alkylated product 27. M^+ 412. ν_{max}^{liquid}

1780, 1720 cm^{-1} (amide, ester >C=O) respectively, Fig.4.2.9. ^1H NMR (CCl_4): δ 1.16 (t, 3H, $-COOCH_2\underline{CH_3}$), 2.80 (s, 2H, $-S-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-$), 2.93 (d, 2H, $-\underline{CH_2}-S-$), 3.63 - 4.10 (m, 4H, 2H-$COO\underline{CH_2}CH_3$, 1H, H-5, 1H $-\underset{|}{\overset{|}{C}}-\underline{H}$-Ph), 4.43 (s, 2H, $-N^3-\underline{CH_2}Ph$), 4.83 (d, 1H, $-\underset{|}{\overset{|}{C}}H$-Ph), 7.0 (s, 10H, Ar-H), Fig.4.2.10.

Preparation of 5-methylene hydantoin[6] (31a)

Prepared according to the reported procedure by a two step synthesis from urea and pyruvic acid[6]. m.p. 210°C (decomp.), lit. m.p. 214°C (decomp.).

Reaction of 5-methylene hydantoin (31a) with ethyl-2-mercapto acetate (31b)

A two-necked round bottom flask (250 ml) capacity was fitted with a three way stopcock. A magnetic spinning bar was introduced in the flask followed by 31a (11.2 g of 0.1 mole) and 100 ml of dry ethyl alcohol containing catalytic amount of KOH. The flask was closed with a rubber septum. Ethyl-2-mercapto-acetate (31b) (12 g, 0.1 mole) was added dropwise with the help of syringe under nitrogen. The reaction mixture was stirred at R.T. for 5 hrs. Solvent was removed and the residue was recrystallised from hot ethyl alcohol to give 32 12.5 g (54% yield), m.p. 101°C, M^+ 232. ^1H NMR: Fig.4.2.11.

Analysis: Calculated: C, 41.3; H, 5.16; N, 11.7; Found: C, 41.5; H, 5.44; N, 11.46%.

Preparation of 1,3-dibenzyl-5-methylene hydantoin (17)

The mixture of 50% pyruvic acid in water (29) (2.2 g, 0.025 mole) in 3 ml of water and 6 g, 0.025 mole of dibenzyl urea (33) was treated on steam bath for 3 hr. The reaction mixture was diluted with 10 ml of water and extracted with ethyl acetate. The organic layer was dried, removal of the solvent furnished 17 7.6 g, 91.4% yields. m.p. 68°C. Spectral properties were in agreement with the compound reported earlier.

Preparation of 1,3 dibenzyl 5-(ethoxycarbonylmethylthiomethyl)-~~1,3-dibenzyl~~ hydantoin 27

A two-necked round bottom flask 100 ml capacity containing 17 (2.9 g, 0.01 mole) and catalytic amount of pyperidine in ethanol was added ethyl mercapto acetate 31b (1.2 g, 0.01 mole) under nitrogen. The reaction mixture was stirred for 2 hr at room temperature, and was neutralised with hydrochloric acid. Removal of the solvent furnished the crude product, which was dissolved in chloroform, washed with water, dried, evaporation of the solvent gave 27 (4 g, 97.5% yield). IR:Fig.4.2.9; NMR: Fig.4.2.10.

Cyclisation of 14 with PTS acid

The compound 27 (300 mg) was dissolved in tetrachloroethane containing catalytic amount of PTS acid. The solution was heated to reflux for about 4 hr. No change in the starting

material was observed (TLC).

Reaction of 1,3-dibenzyl-5-methylene hydantoin with ethyl mercapto acetate catalysed by BF_3-etherate

A two-necked round bottom flask 50 ml capacity containing 17 (1.45 g, 0.005 mole) and catalytic amount of BF_3-etherate in dichloromethane was added ethylmercapto-acetate 31b (0.6 g, 0.005 mole) under nitrogen. The reaction mixture was stirred for 1 hr at R.T. and was neutralized with sodiumbicarbonate. Removal of the solvent furnished the crude product, which was dissolved in chloroform, washed with water, dried, evaporation of the solvent gave 32 (1.9 g, 96% yield). ^1H NMR (CCl_4): Fig.4.2.12. M^+ 412.

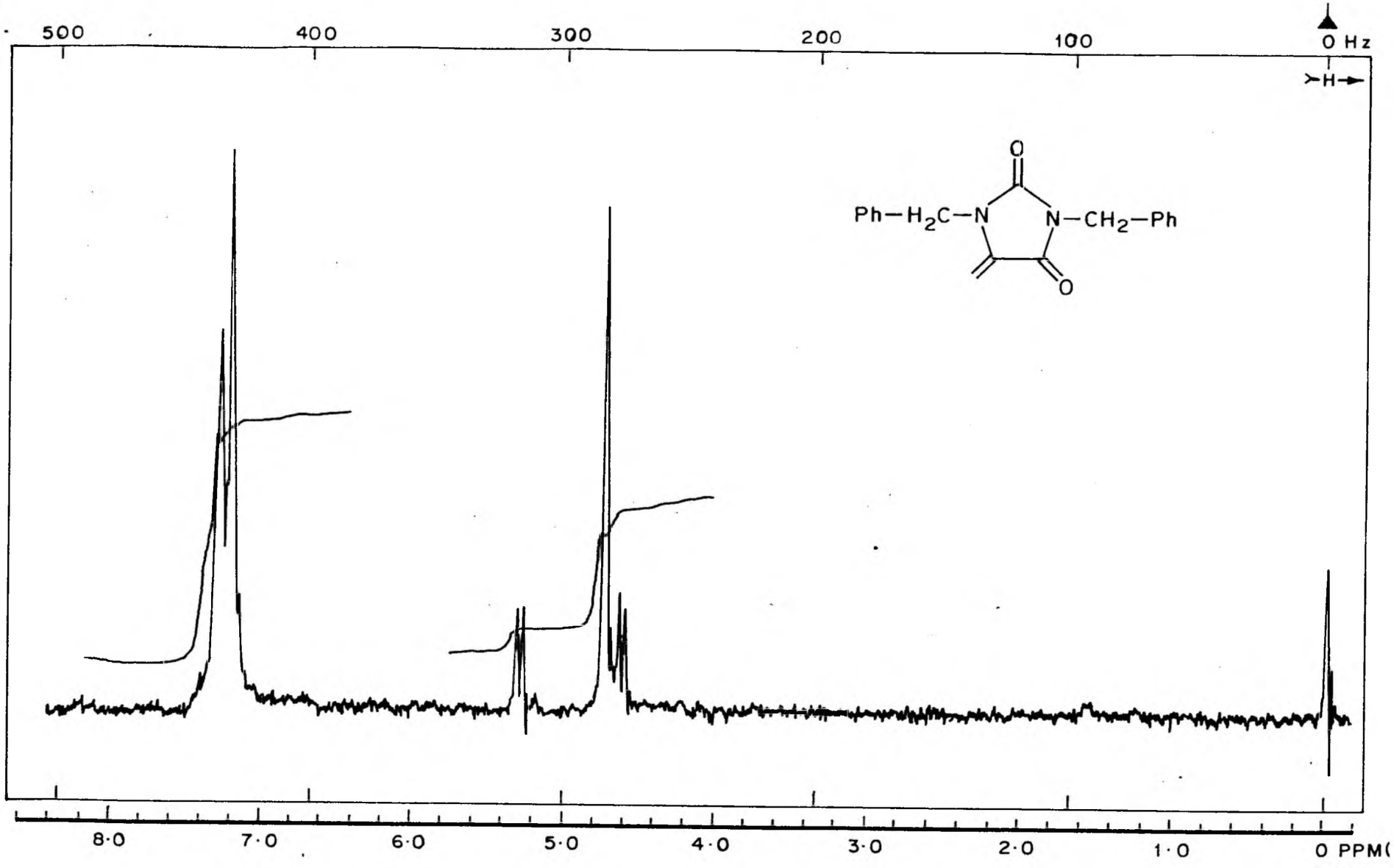

500
400
300
200
100
0 Hz
>H→
Ph—H2C—N
N—CH2—Ph
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(

FIG. 4·2·1

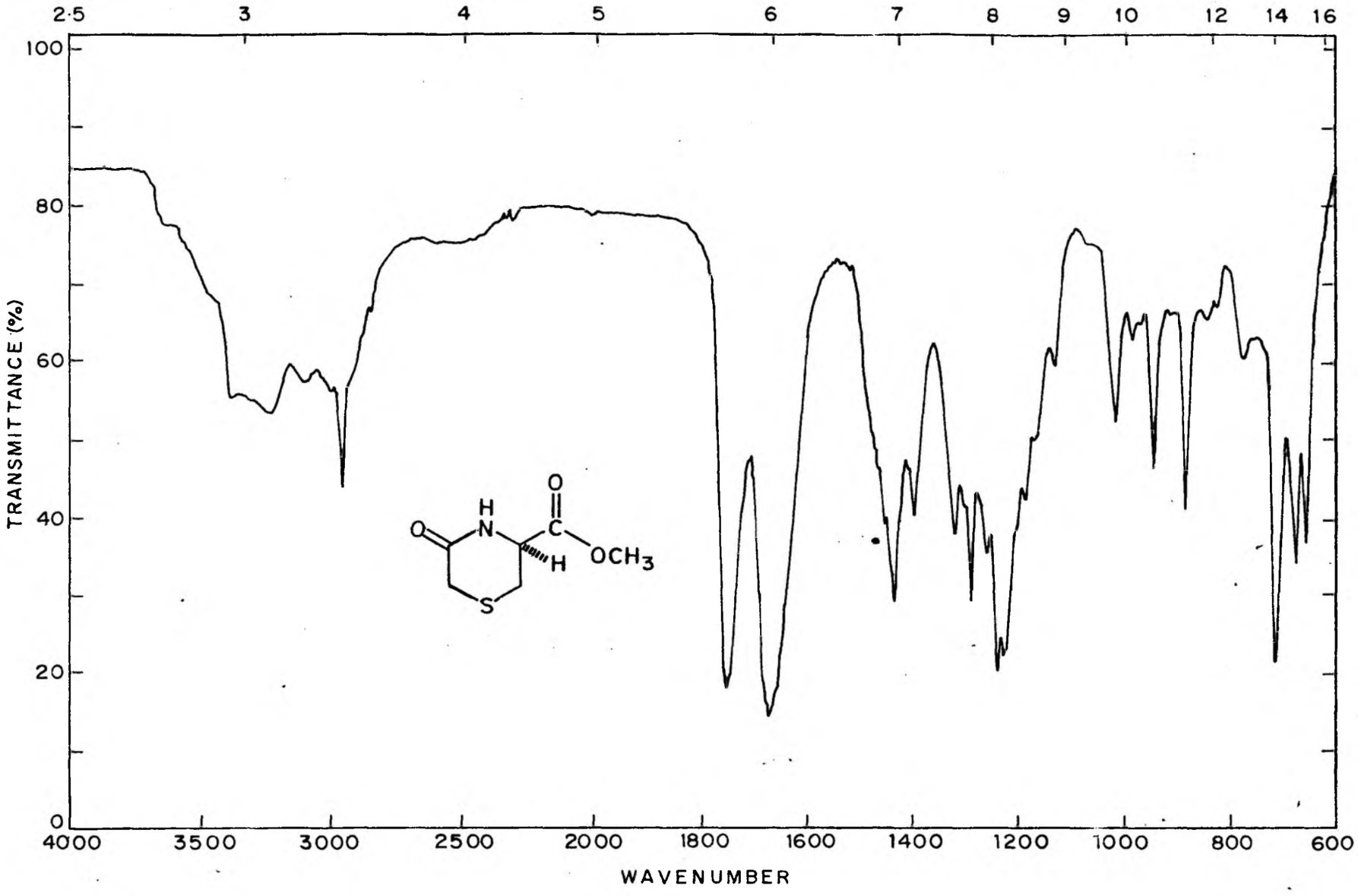

2·5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
O
H
N
O
C
OCH3
H
S

FIG. 4·2·2

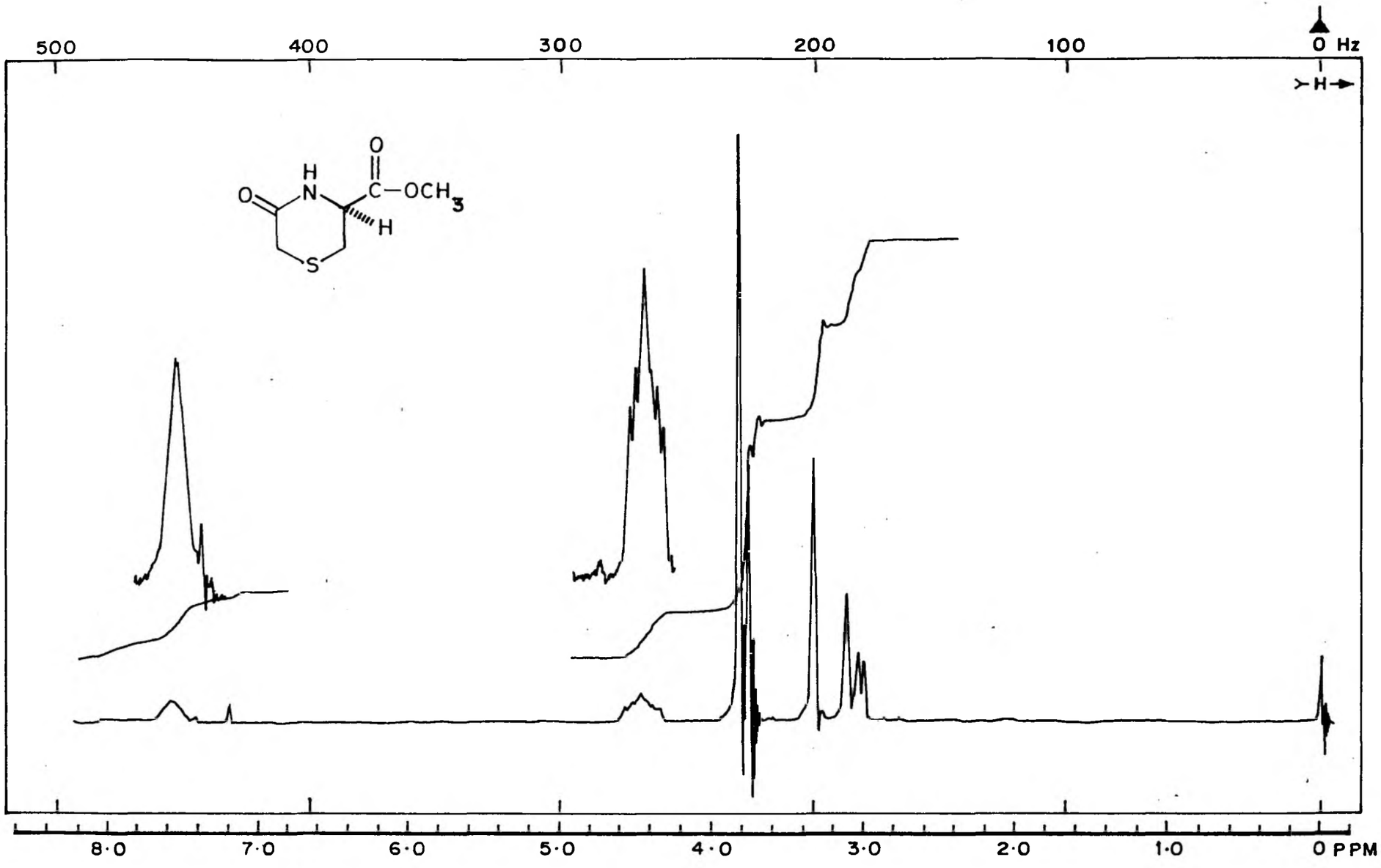

500
400
300
200
100
0 Hz
H
O
H
N
O
C—OCH3
H
S
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 4·2·3

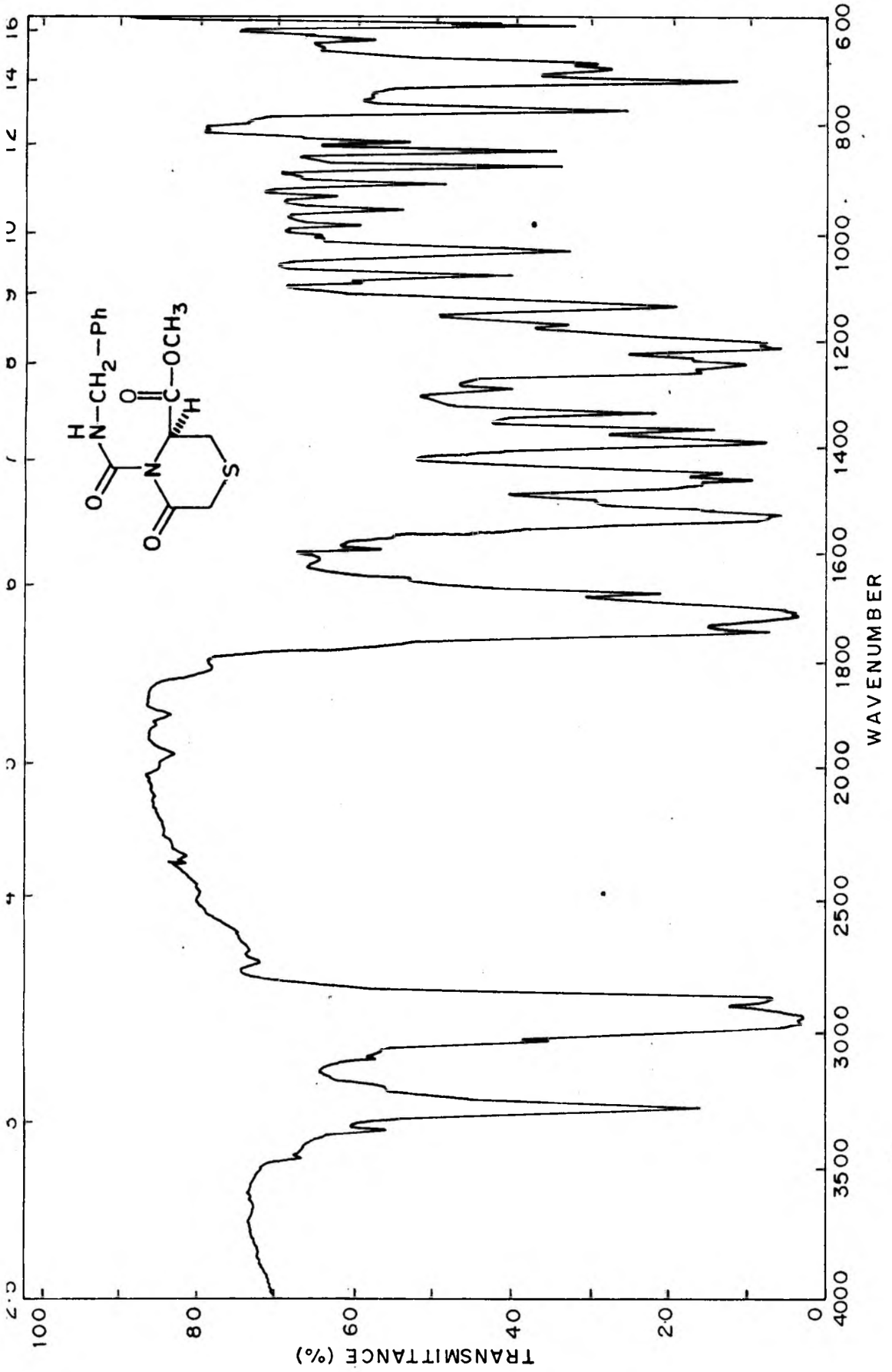

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
H
N—CH2—Ph
O
O
C—OCH3
H
N
S
O
O

FIG. 4·2·4

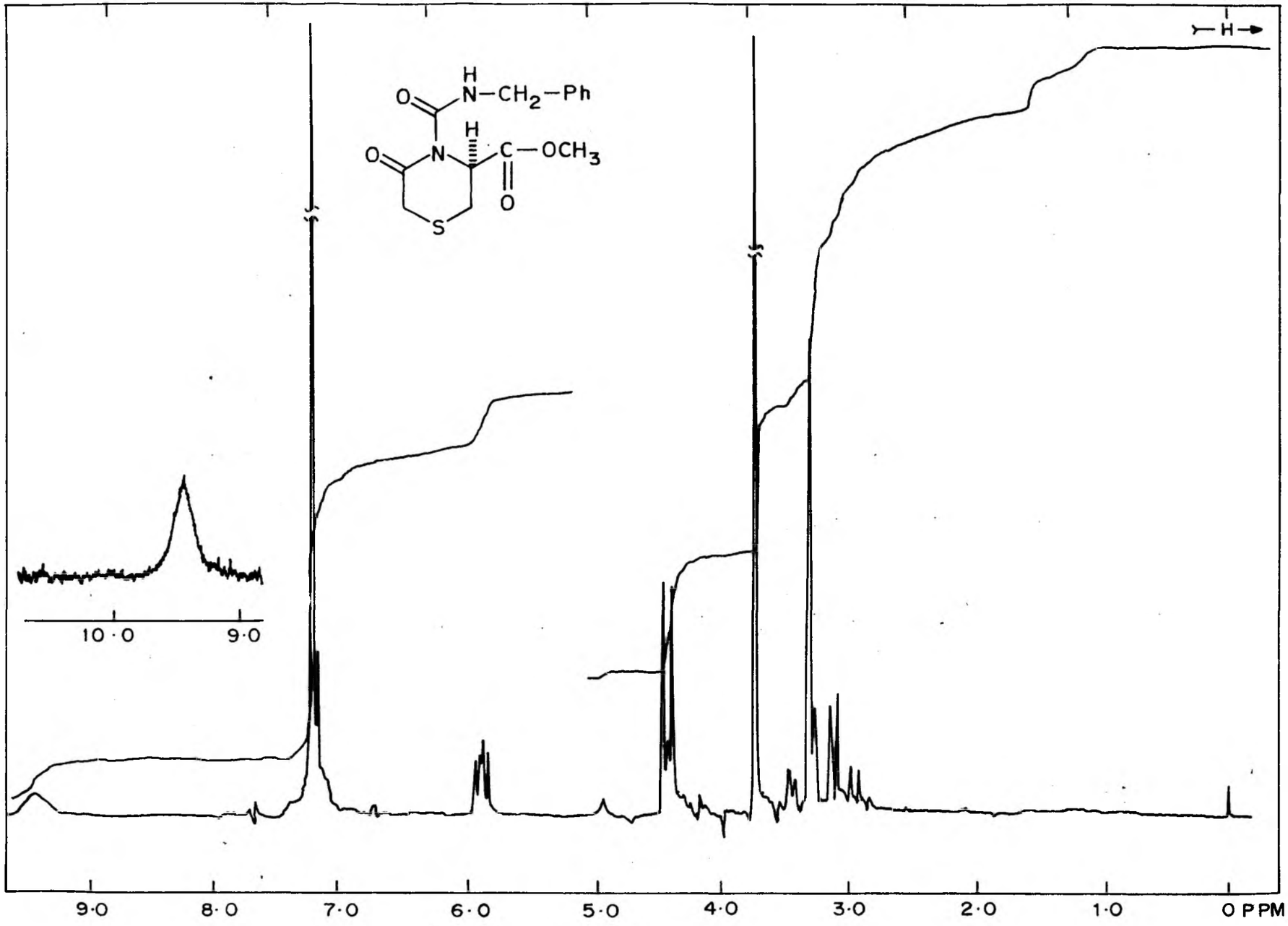


FIG. 4·2·5

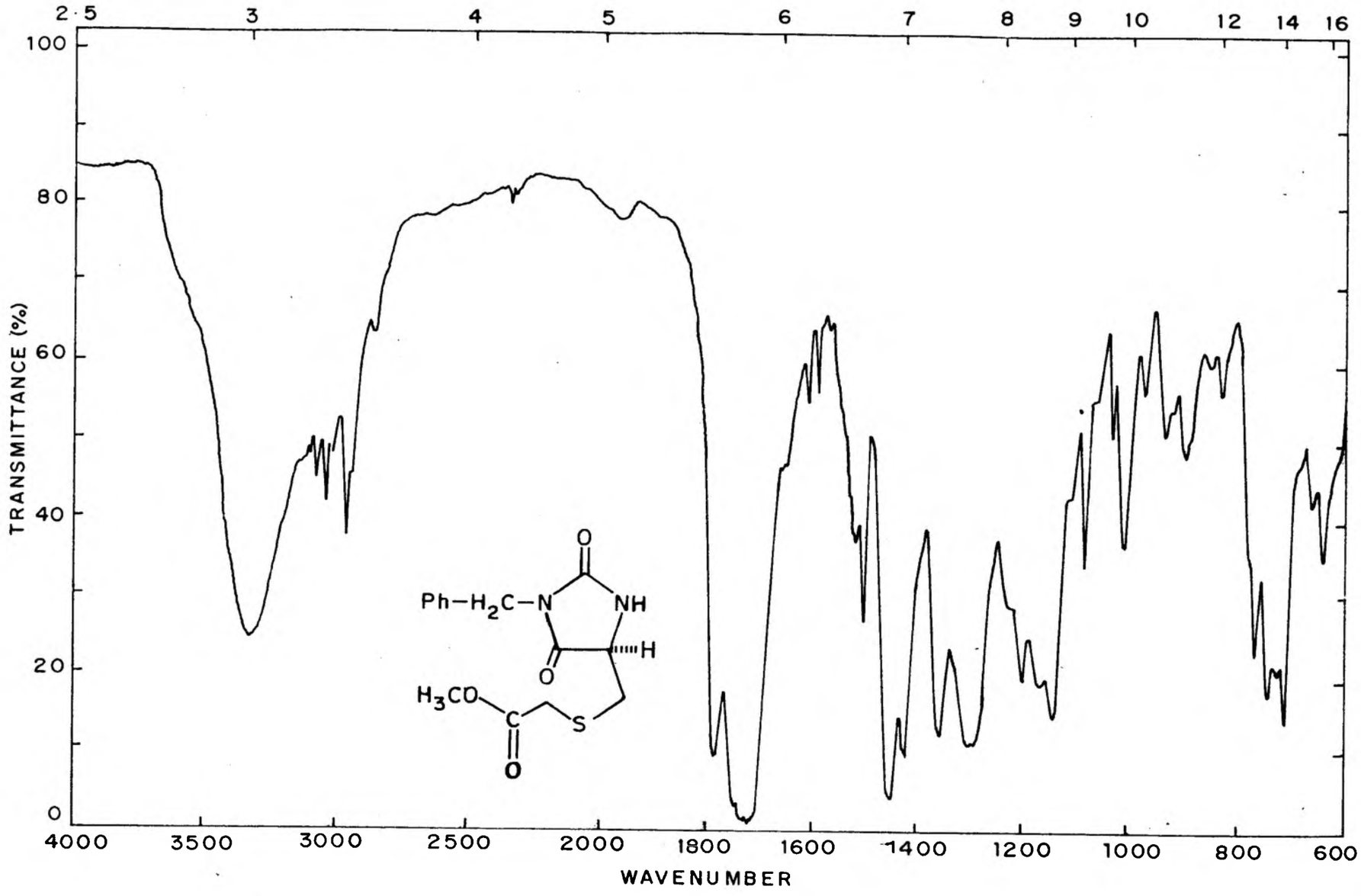

2·5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
Ph–H2C–N
NH
H
H3CO
C
S
O

FIG. 4·2·6

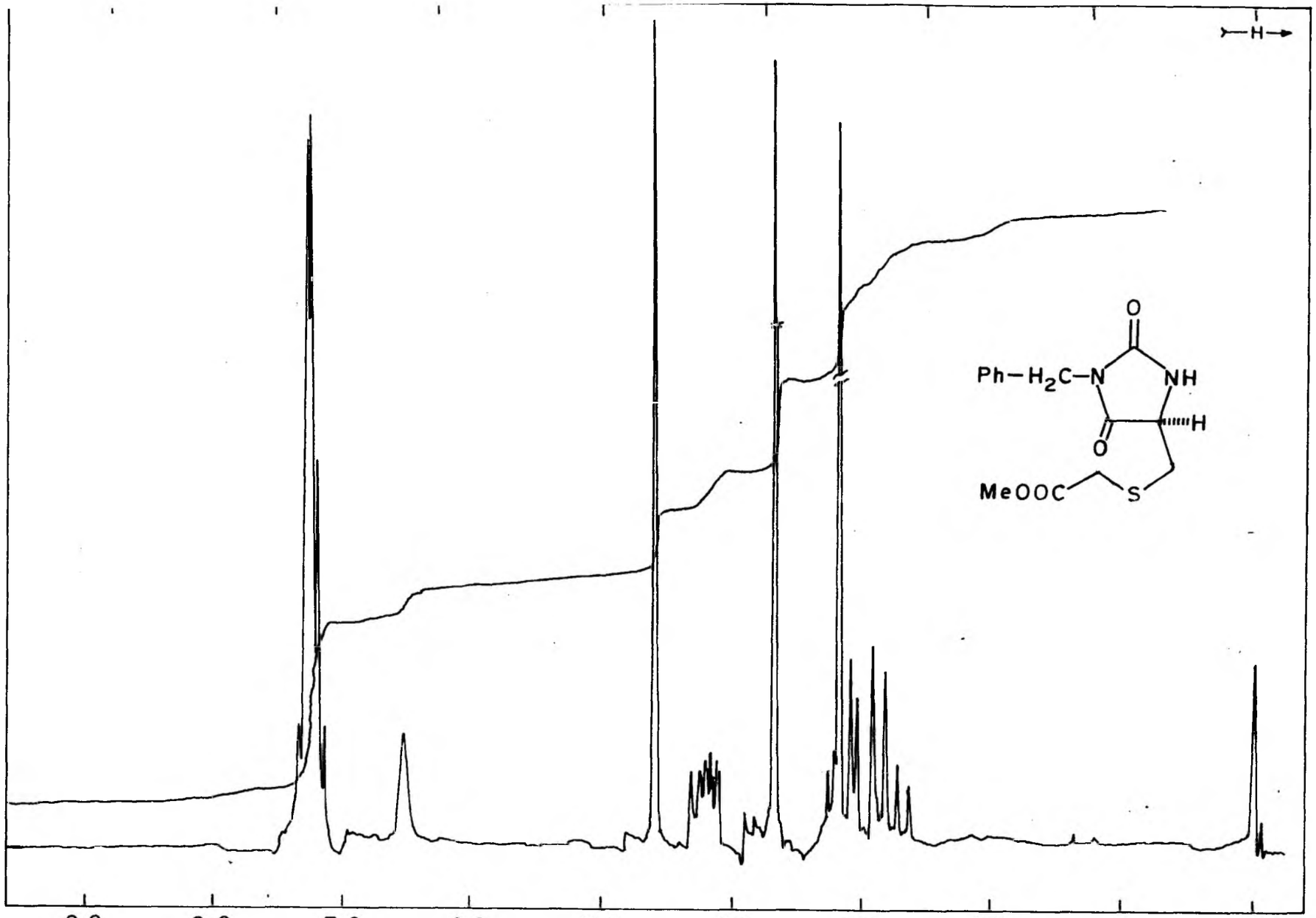


FIG. 4·2·7

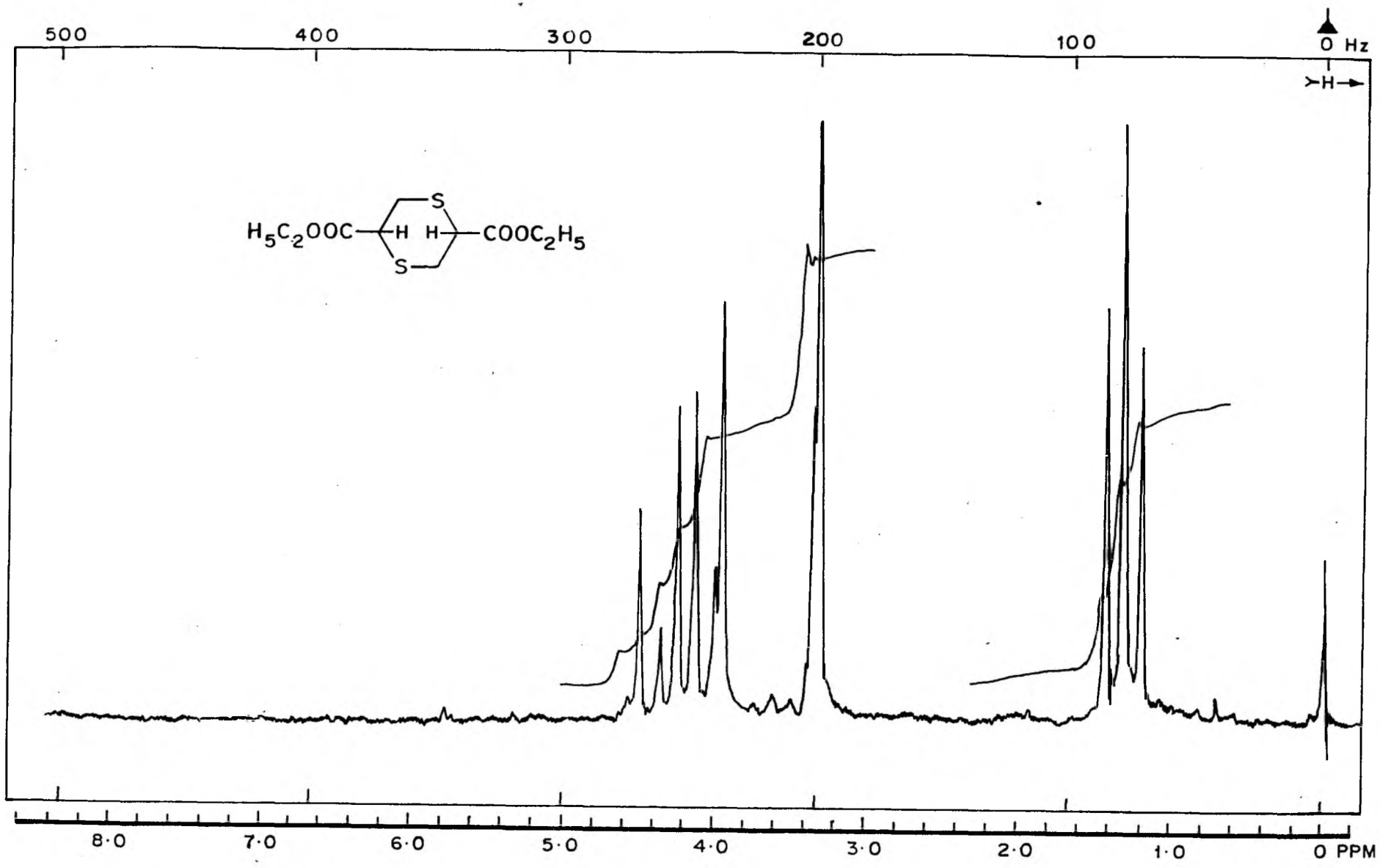

500
400
300
200
100
0 Hz
>H→
S
H
H
S
H_5C_2OOC
$COOC_2H_5$
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 4·2·8

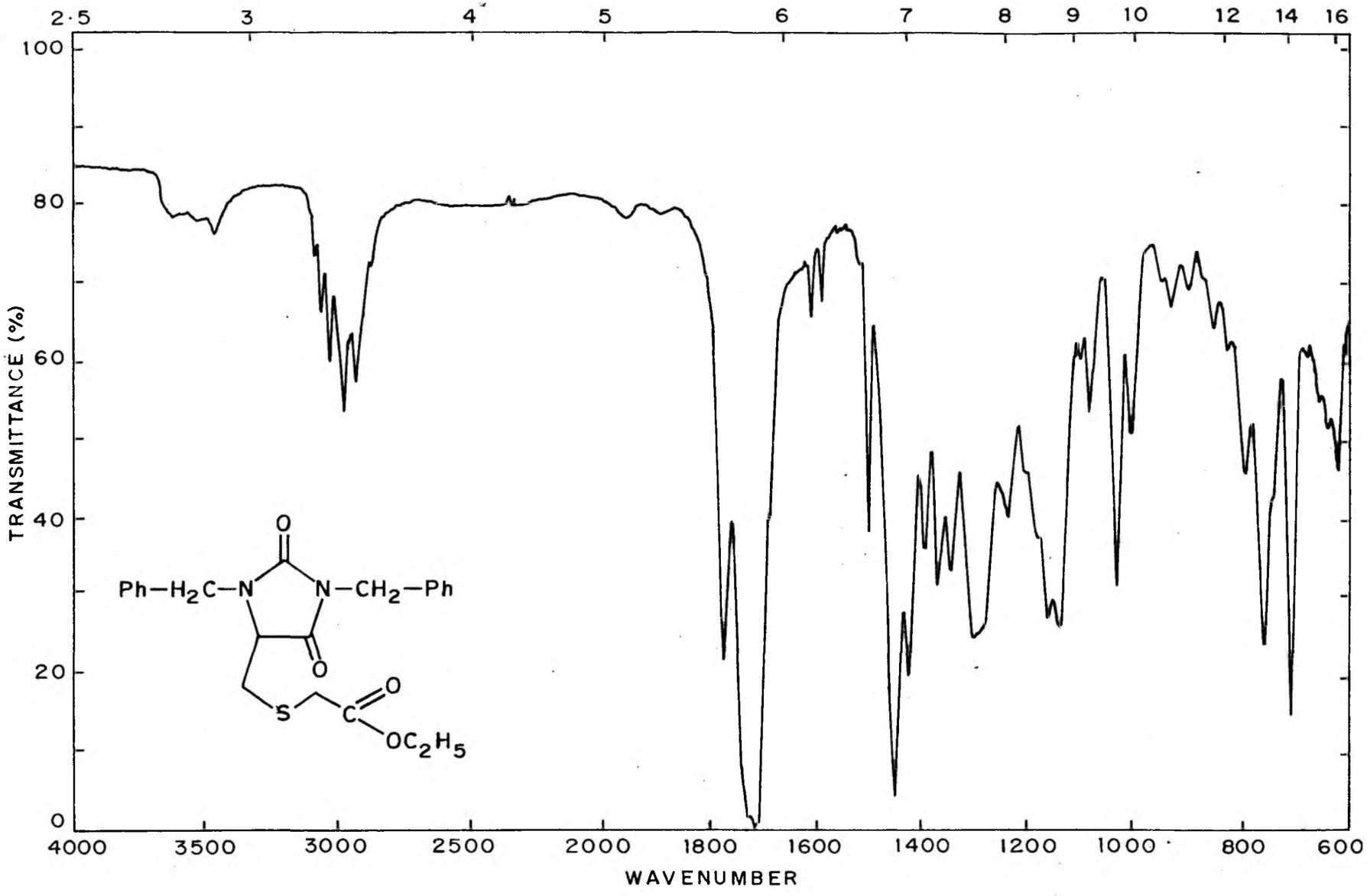

2·5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER
Ph–H2C–N
N–CH2–Ph
O
O
O
S
C
O
OC2H5

FIG. 4·2·9

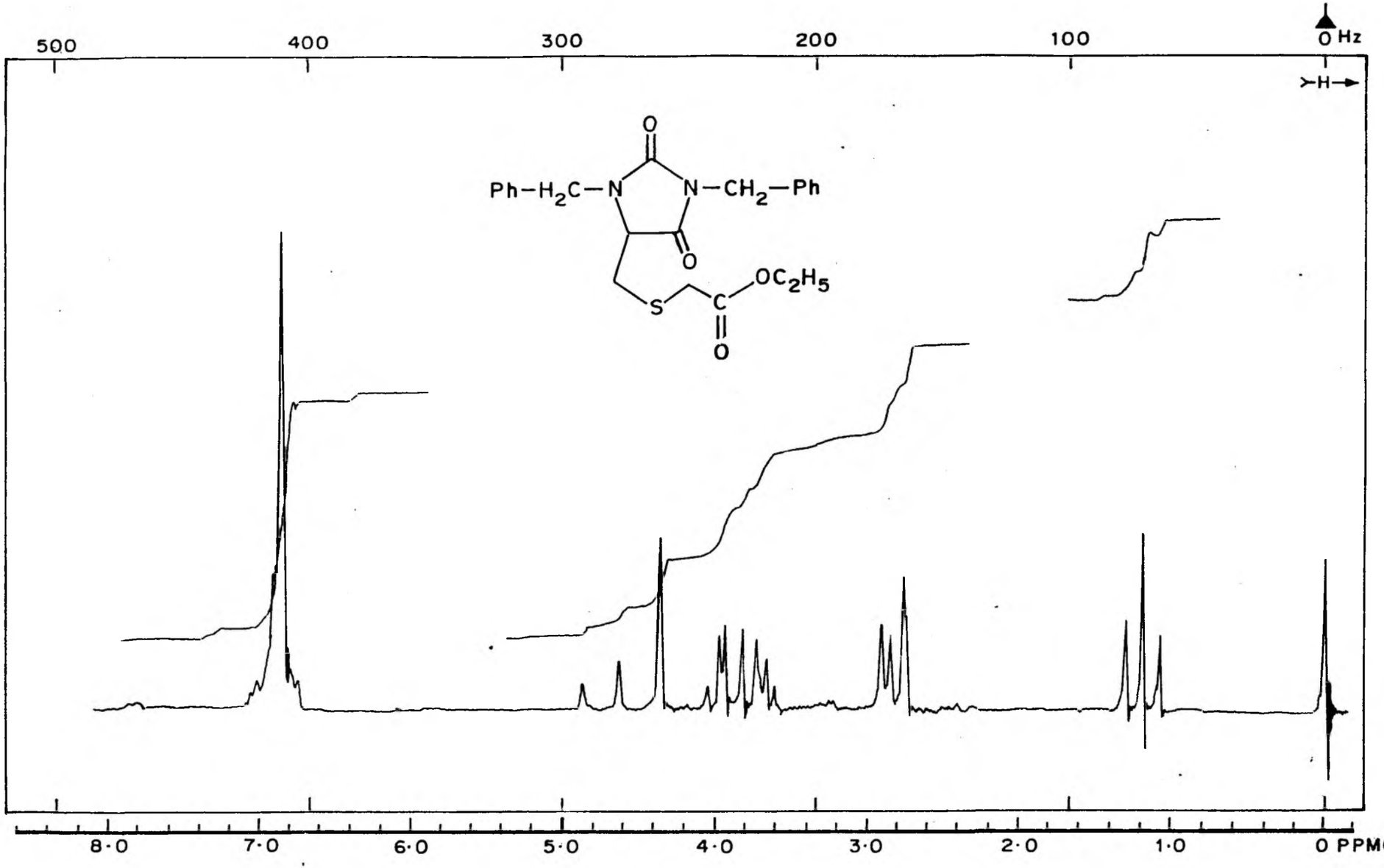

500
400
300
200
100
0 Hz
>H→
Ph–H2C–N
N–CH2–Ph
OC2H5
S
C
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(

FIG. 4·2·10

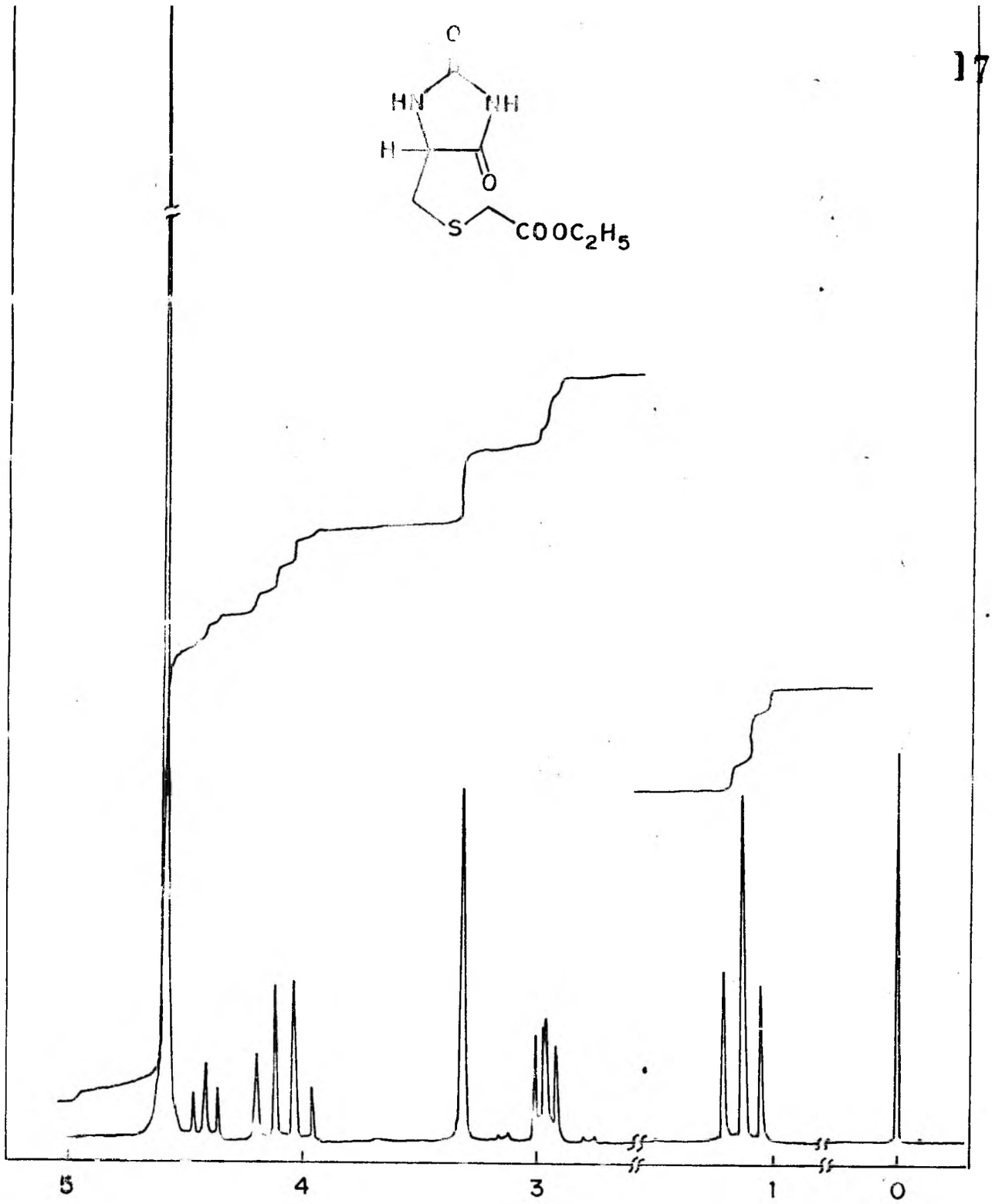


FIG. 4·2·11

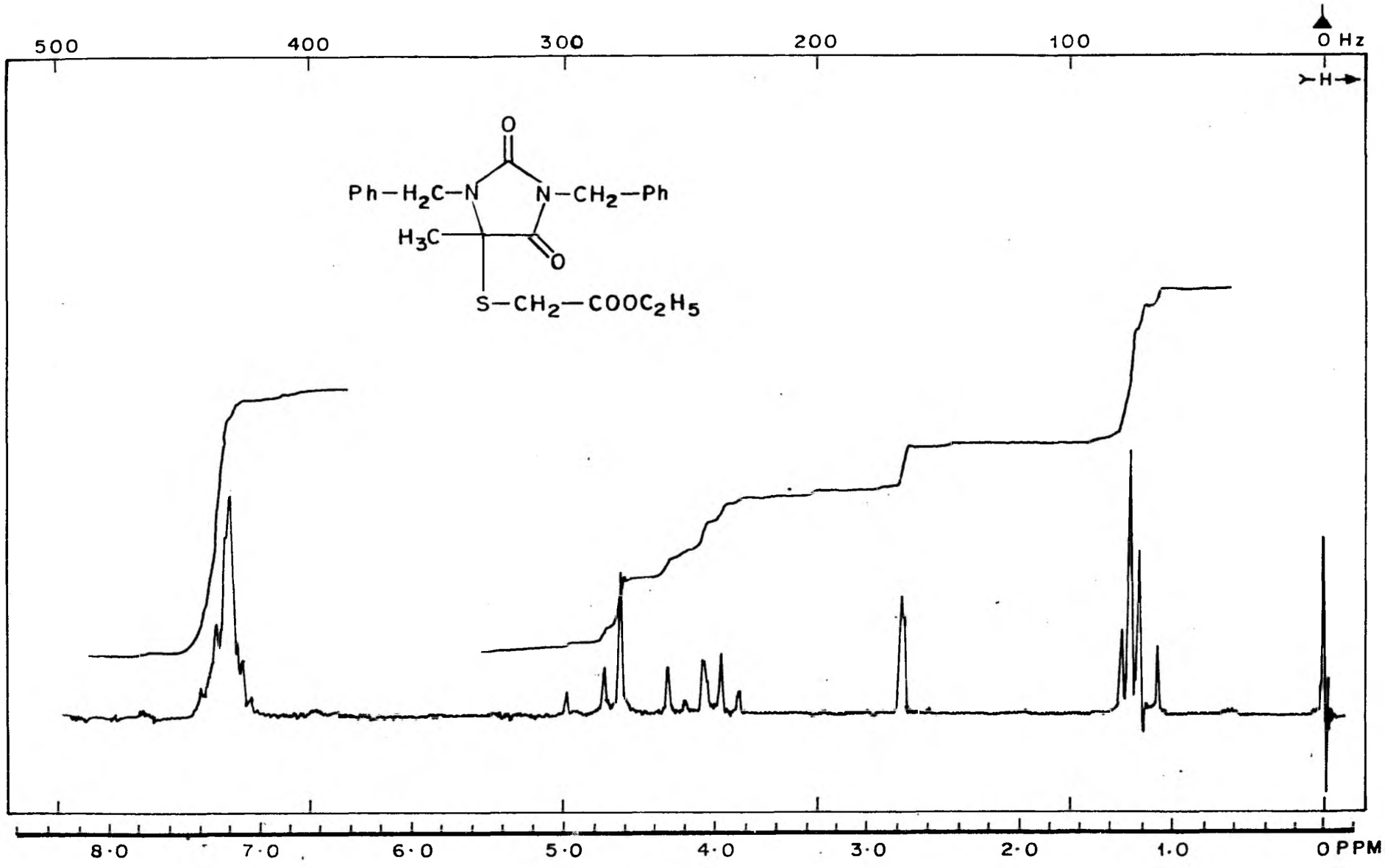

500
400
300
200
100
0 Hz
TMS
Ph–H2C–N
N–CH2–Ph
H3C
O
O
S–CH2–COOC2H5
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM

FIG. 4·2·12

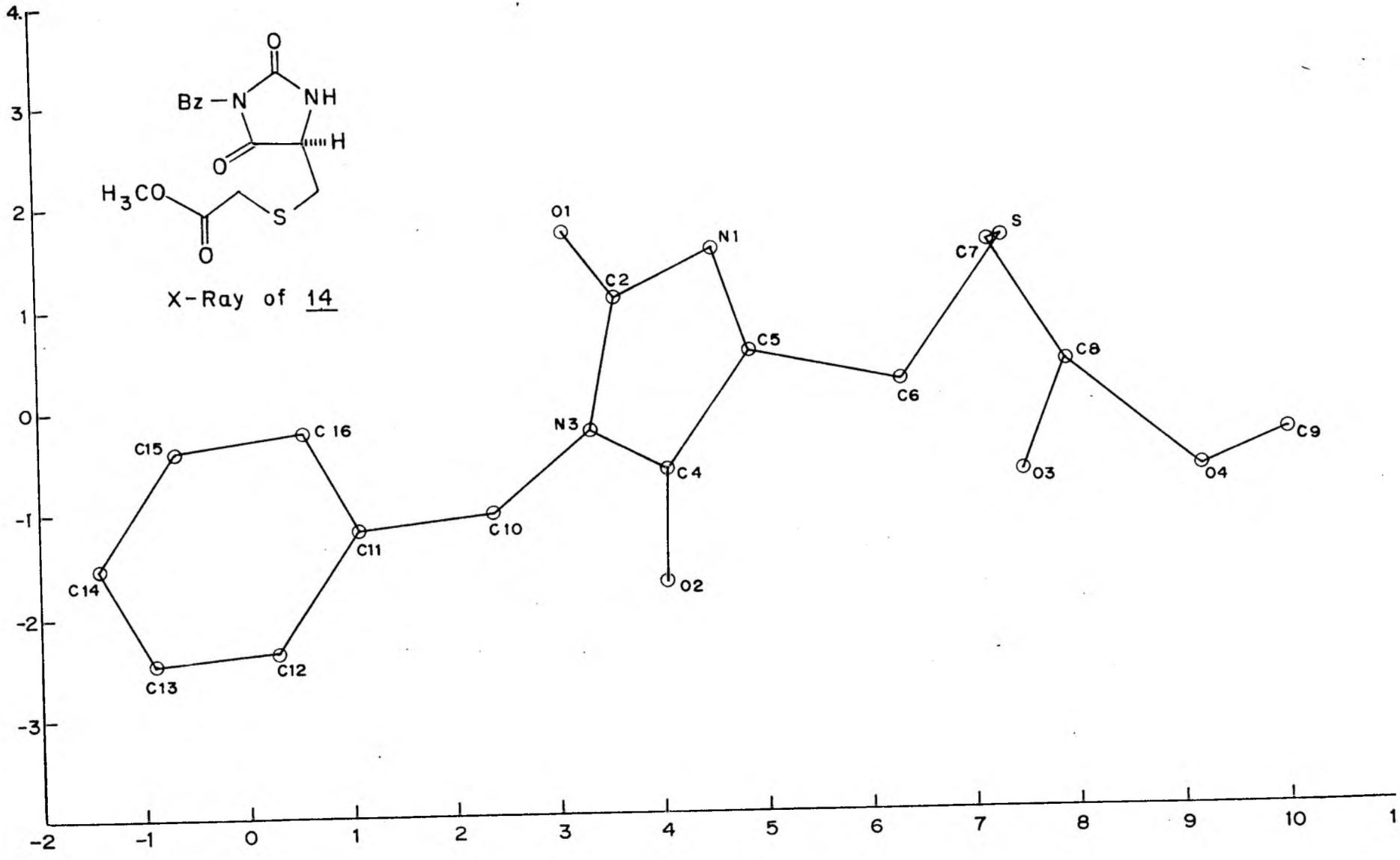
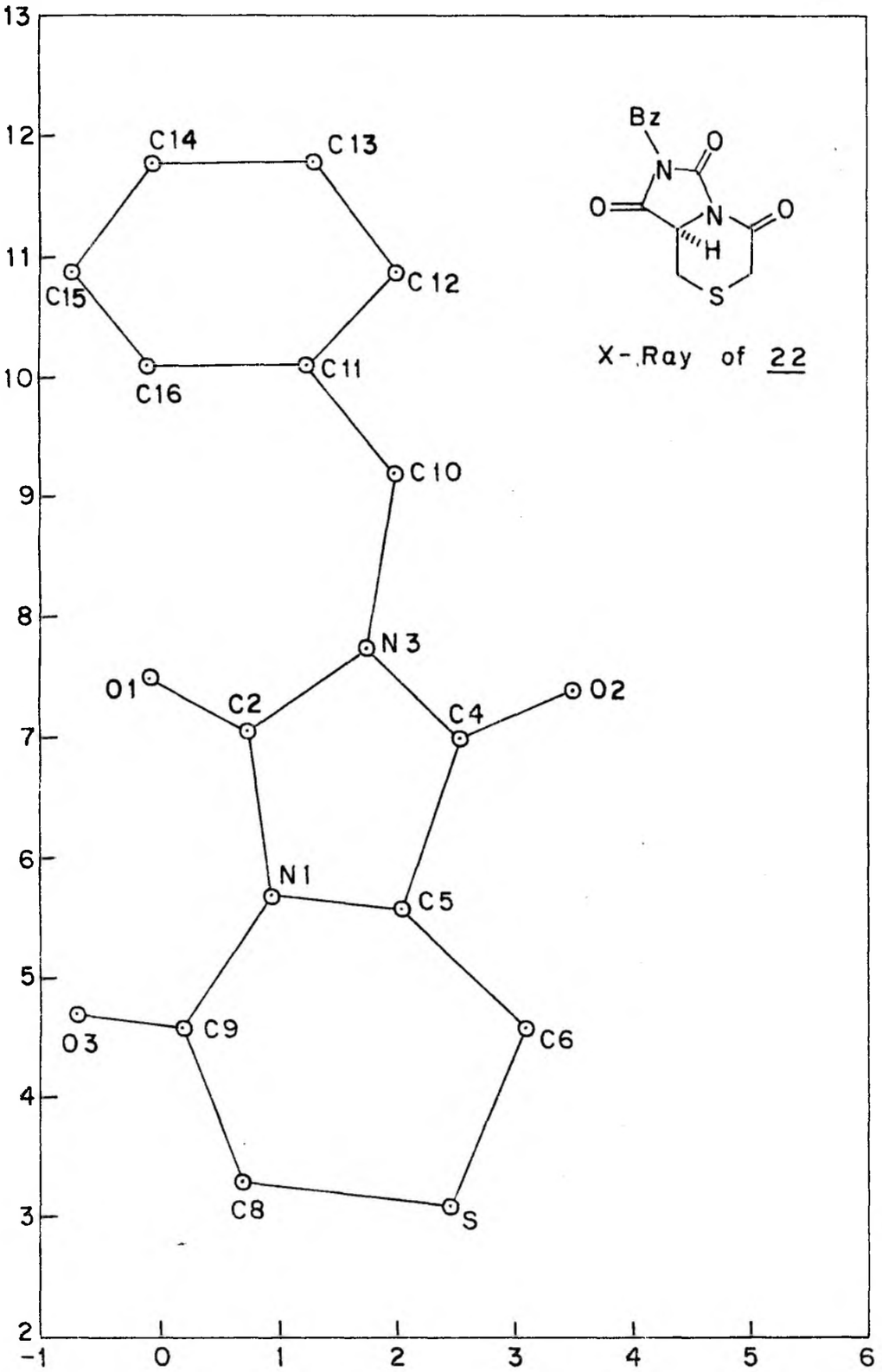

Bz – N
NH
H
O
H3CO
S
O
X-Ray of 14
O1
N1
C2
C5
C6
C7
S
C8
C9
O3
O4
N3
C4
O2
C10
C11
C12
C13
C14
C15
C 16
4
3
2
1
0
-1
-2
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
10
1

FIG. 4·2·13


Bz
O
N
O
N
O
H
S
X-Ray of 22
C14
C13
C12
C15
C11
C16
C10
N3
O1
C2
C4
O2
N1
C5
O3
C9
C6
C8
S
13
12
11
10
9
8
7
6
5
4
3
2
-1
0
1
2
3
4
5
6

FIG·4·2.14

4.3.0 REFERENCES

1 V.M. Berezovskii, S.D. Mikhno, N.S. Kulachkina, V.B. Zhuk and N.A. Preobrazhenskii
J. General Chemistry, USSR, 2815 (1963).

2 W.C. Hess
J. Am. Chem. Soc., 56, 1421 (1934).

3 J.V. Kavabinos and J.L. Szabo
J. Am. Chem.Soc., 66, 649 (1944).

4 Elimer
Chem. Rev., 46, 403-416 (1950).

5 P. Karrer and H. Schmid
Helv. Chim. Acta, 27, 125 (1944).

6 S. Murahashi, H. Yulki, K. Kosai and F. Doura
Bull. Chem. Soc., Japan, 39, 1559 (1966).

7 a) H. Gilman, W. Langham and F.W. Moore
J. Am.Chem. Soc., 62, 2327 (1940).

b) H. Gilman, J.A.Beel, C.G. Brannen, M.W. Bullock, G.E. Dunn and L.S. Miller
J. Am.Chem. Soc., 71, 1499 (1949).

c) H. Gilman and F.K. Cartedge
J. Organometallic Chem., 2, 447 (1964).

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A Stereoselective Synthesis of (±)-Biotin†

A V RAMA RAO*, T RAVINDRANATHAN, S V HIREMATH & D RAJAGOPALA REDDY
National Chemical Laboratory, Poona 411 008

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The key intermediate, 3,4-(1,3-dibenzyl-2-oxo-imidazolido)-thiophane (**2**) for the synthesis of biotin has been prepared starting from *cis*-but-2-ene-1, 4-diol.

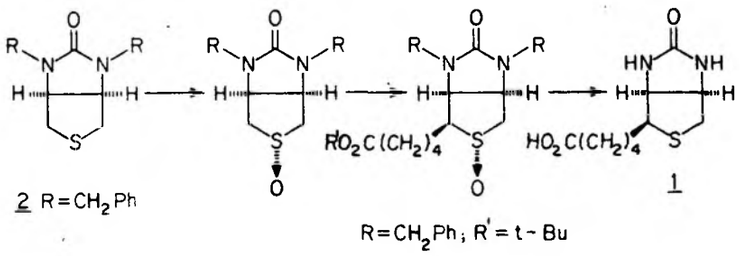
The intricate chemistry involved in the construction of all *cis* skeleton of biotin (**1**), as well as its importance in food and nutrition[1] have led to numerous elegant syntheses of this essential vitamin during the last decade[2a-o]. Some of these approaches have industrial bias. One such synthesis due to French workers[2f] involves stereoselective alkylation of a cyclic sulphoxide for the introduction of valeric acid side-chain characteristic of biotin (Scheme 1). This approach is versatile for the preparation of other biotin analogues, because the same intermediate can be alkylated to introduce different substituents. The desired key intermediate (**2**) was earlier obtained by four different approaches[2f,3]. We wish to report the synthesis of **2** starting from *cis*-but-2-ene-1, 4-diol (**3**) (Scheme 2). The significance of our approach is a one-step efficient conversion of the diurethane (**9**) to the imidazolidone (**16**) or dibenzylimidazolidone (**18**) as desired. The method is of general utility for the conversion of vicinal diamines into imidazolidones.

Oxidation of the dioxepin (**4**) (obtained from **3** in 80% yield)[4] with aqueous $KMnO_4$ (0°, 6 hr, followed by continuous Et_2O extraction) furnished the *cis*-diol (**5**) in 50% yield as a viscous oil.

Methanesulphonylation of **5** (CH_3SO_2Cl, pyridine, CH_2Cl_2, 0°, room temp. afforded the dimesylate (**6**) in 90% yield m.p. 129-31°; PMR ($CDCl_3$) δ 3.20 (*s*, 6H), 4.03 (*m*, 4H), 4.85 (*s*, 2H), 5.03 (*m*, 2H). (**6**) on treatment with sodium azide in DMF at 90° for 5 hr furnished the *cis*-diazide (**7**) in 85% yield; PMR ($CDCl_3$): δ 4.00 (*m*, 6H), 4.86 (*s*, 2H). Catalytic hydrogenation of **7** (Pd/C 10%, MeOH, room temp., 6 hr) gave the diamine (**8**) as a brownish liquid in almost quantitative yield, which was directly converted into the corresponding diurethane (**9**) (ClCOOEt, EtOH, room temp, 4 hr) in 85% yield; m.p. 75°; IR (nujol): 3460 (−NH) 1695 cm^{-1} (amide C=O); PMR ($CDCl_3$): δ 1.26 (*t*, 6H), 3.83 (*m*, 10H), 4.70 (*s*, 2H), 5.40 (*bd*, 2H). All efforts to convert the diamine (**8**) into the corresponding imidazolidone (**16**) by treatment with phosgene resulted mostly in polymeric products from which only small quantity of **16** could be obtained, m.p. 245-50° (d); M^+ 158.

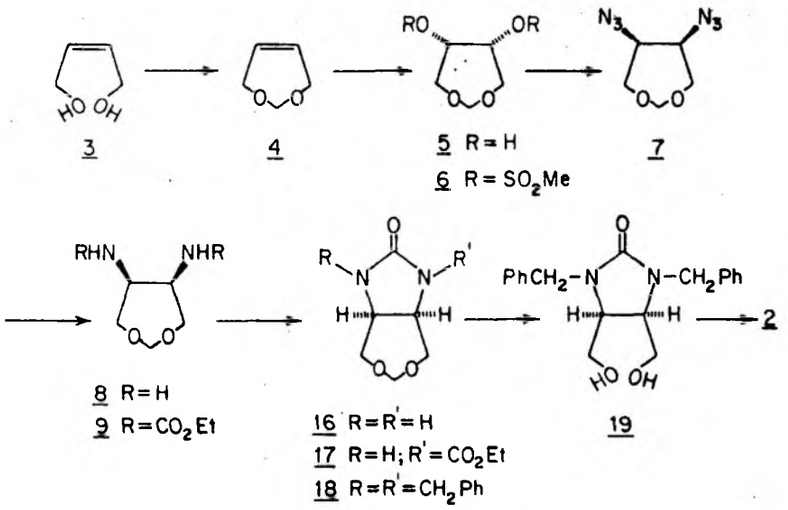
The diurethane (**9**) was also prepared by a different route starting from dioxepin (**4**) as shown in Scheme 3. Epoxidation of **4** (*m*-chloroperbenzoic acid, CH_2Cl_2, 0°, 12 hr)[5] followed by ammonolysis of **10** (sat. NH_3 in MeOH, 120°, 6 hr, steel bomb) furnished the amino alcohol (**11**) which was converted without purification into the urethane alcohol (**12**) (ClCOOEt, EtOH, room temp., 6 hr), m.p. 110-12°; M^+ 205. **12** was smoothly converted into **13** (methanesulphonyl chloride-Py-dioxane, room temp., 48 hr) in 90% yield; m.p. 92°; PMR ($CDCl_3$): δ 1.26 (*t*, 3H), 3.16 (*s*, 3H), 4.00 (*m*, 6H), 4.13 (*q*, 2H), 4.76 (*s*, 2H), 5.53 (*d*, 1H). **13** on treatment with sodium azide in HMPA at 50° for 24 hr gave the azide (**14**). Hydrogenation of **14** (Pd/C 10%, EtOH 30 psi, room temp., 5 hr) resulted in the formation of **15** which was characterised as its diurethane derivative (**9**), identical with the product obtained in the earlier approach (Scheme 2).

As our efforts to convert the diamine (**8**) into the imidazolidone (**16**), did not result favourably in good yields, we submitted the diurethane (**9**) to sodium hydride treatment (3 eq) in dry benzene (room temp., 24 hr) which interestingly resulted in the formation of **16** exclusively (95% yield) and not **17** as was

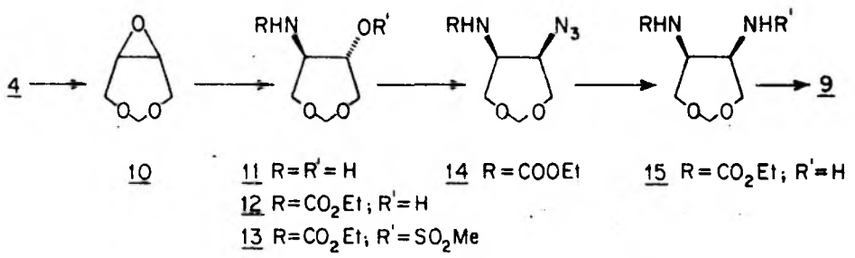


Scheme 1

†NCL Communication No. 3147.



Scheme 2



Scheme 3

anticipated. **16** was converted into the corresponding N,N'-dibenzyl derivative (**18**) in 80% yield [benzyl bromide, NaH; (3 eq), DMF, room temp., 12 hr, reflux 2 hr], m.p. 132 : M^+ 338; IR (nujol, cm^{-1}): 1680 (amide C = O); PMR ($CDCl_3$): δ 3.69 (*d*, 4H), 3.88 (*m*, 2H), 4.08 and 4.96 (*AB*, *J* = 15 Hz, 4H), 4.61 and 4.84 (*AB*, *J* = 6 Hz, 2H), 7.24 (*s*, 10H). Alternatively **9** could be smoothly converted into **18** in one pot reaction by reacting the former with benzyl bromide in the presence of excess of NaH in dry benzene for 12 hr at room temperature followed by refluxing for 2 hr (80% yield). The conversion of **18** into the desired **2** was achieved by sequential acid hydrolysis, methanesulphonylation and finally treating with sodium sulphide in ethanol[2f]. The compound (**2**)' was identical in all properties with those reported earlier[2f].

As the conversion of **2** into (±)-biotin was earlier reported[2f], our new synthesis of **2** in effect constitutes a total synthesis of **1**.

References

1 (a) Blair R & Whitehead C, *Feedstuffs*, **48** (1976) 30; (b) McCormick D B, *Nutr Rev*, **33** (1975) 97; (c) Anderson J O & Warnick R E, *Poult Sci*, **49** (1970) 569; (d) Bonjour J P, *Int J Vitam nutr Res*, **47** (1977) 107.

2 (a) Whitney R A, *Can J Chem*, **59** (1981) 2650; (b) Ohrui H & Emoto S, *Tetrahedron Lett*, (1975) 2765; (c) Zav'yalov S I *et al*, *Bull Acad Sci USSR Div chem Sci*, **24** (1975) 1533; (d) Confalone P N, Pizzolato G, Baggiolini E G, Lollar D & Uskokovic M R, *J Am chem Soc*, **97** (1975) 5936; (e) Confalone P N, Pizzolato G & Uskokovic M R, *Helv chim Acta*, **59** (1976) 1005; *J org Chem*, **42** (1977) 135; *J org Chem*, **42** (1977) 1630; (f) Lavielle S, Bory S, Moreau B, Luche M J & Marquet A, *J Am chem Soc*, **100** (1978) 1558; (g) Marx M, Marti F, Reisdorff J, Sandmaier R & Clark S, *J Am chem Soc*, **99** (1977) 6754; (h) Ogawa T, Kawano T & Matsui M, *Carbohydr Res*, **57** (1977) C31; (i) Ohrui H, Sueda N & Emoto S, *Agri biol Chem*, **42** (1978) 865; (j) Confalone P N, Pizzolato G, Baggiolini E G, Lollar D & Uskokovic M R, *J Am chem Soc*, **99** (1977) 7020; (k) Confalone P N, Lollar D, Pizzolato G & Uskokovic M R, *J Am chem Soc*, **100** (1978) 6292; (l) Vasilevskis J, Gualtieri J A, Hutchings S D, West R C, Scott J W, Parrish D R, Bizzarro F T & Field G F, *J Am chem Soc*, **100** (1978) 7423; (m) Kotake H, Inomata K, Murata Y & Kinoshita H, *Chem Lett*, **10** (1976) 1973; (n) Fliri A & Hohenlohe-Oehringen K, *Chem Ber*, **113** (1980) 607; (o) Rossy Ph, Vogel F G M, Hoffmann W, Paust J & Nurrenbach A, *Tetrahedron Lett*, **22** (1981) 3493.

3 (a) Baker B R, Querry M V, Safir S R, McEwen W L & Bernstein S, *J org Chem*, **12** (1947) 174; (b) Takaya T, Yoshimoto H & Imoto E, *Bull chem Soc Japan*, **40** (1967) 2636; (c) Hiroshi K, Katsuhiko I, Yasue M, Hydeki K & Masahiro K, *Chem Lett*, (1976) 1073.

4 Brannock K C & Lappin G R, *J org Chem*, **21** (1956) 1366.

5 Miller M W, *Tetrahedron Lett*, (1969) 2545.

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Note

A modified synthesis of (+)-biotin from D-glucose†

T. RAVINDRANATHAN, SHIVAJAT V. HIREMATH, D. RAJAGOPALA REDDY, AND A. V. RAMA RAO
National Chemical Laboratory, Poona 411008 (India)
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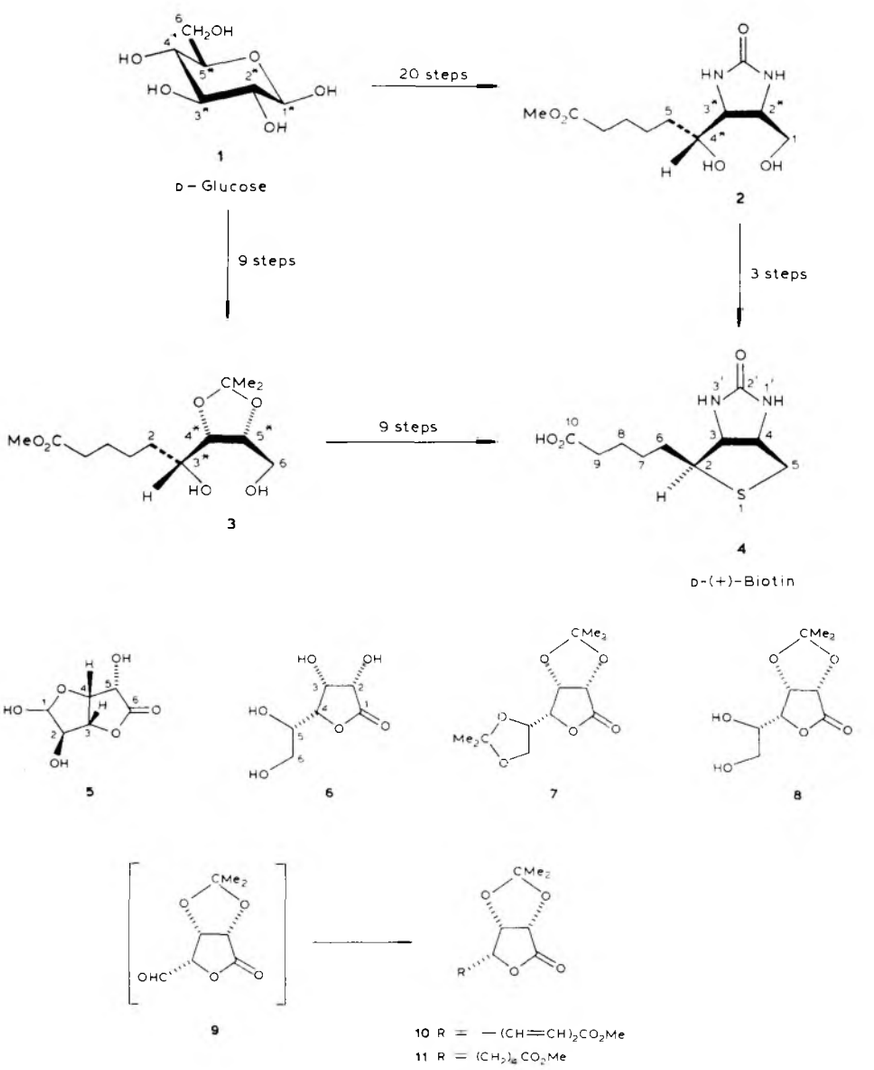
Four syntheses of (+)-biotin (**4**), using sugars as chiral substrates, have been reported[1–4]. In one of these syntheses[2], D-glucose (**1**) was converted into (+)-biotin in 23 steps where C-1/5 of D-glucose became C-5,4*,3*,2*,6 of (+)-biotin (biotin numbering) *via* the intermediate diol **2**. We now report a shorter synthesis whereby C-2/6 of D-glucose become C-6,2*,3*,4*,5 of **4** *via* the key intermediate **3**, which has also been prepared from D-mannose[1] and D-arabinose[4].

D-Glucurono-6,3-lactone[5] (**5**) was catalytically reduced to L-gulono-1,4-lactone†† (**6**) using Raney nickel[6]. Compound **6** was converted into the 2,3:5,6-di-*O*-isopropylidene derivative[7] (**7**) which was selectively hydrolysed to the 2,3-*O*-isopropylidene derivative (**8**) using methanol–hydrochloric acid. Periodate oxidation of **8** in acetone–water at 0° furnished the aldehyde **9** which, on treatment with excess of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane[8] in dichloromethane afforded the crystalline, unsaturated lactone **10** (10%). Hydrogenation[1,3] of **10** over 10% Pd-C gave a very poor yield of the desired saturated lactone **11**. However, when the borohydride-reduced palladium catalyst[9] was used at 0° and atmospheric pressure, **11** was obtained in almost quantitative yield. Borohydride reduction of **11** in methanol at 0° then gave the required intermediate diol **3** (80%) as a syrup. The ^{1}H-n.m.r. data of **3** accorded with those reported[4].

Since the yield of the lactone **10** in the Wittig reaction was poor, **3** was prepared by another route starting from **7**. Treatment of **7** with sodium borohydride in methanol at 0° gave the lactol **12** which, with benzoyl chloride in pyridine, furnished the crystalline benzoate **13** (96%). Selective hydrolysis of **13** with methanol–hydrochloric acid afforded the diol **14** (95%), periodate oxidation of which in acetone–water at 0° gave the aldehyde **15**. Application of the Wittig reaction to **15**,

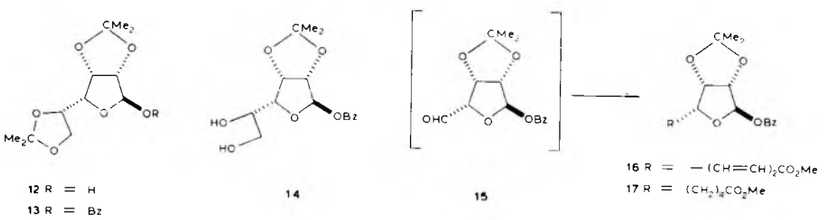
†NCL Communication No. 3505.
††L-Gulono-1,4-lactone and its mono- and di-*O*-isopropylidene derivatives had optical rotations lower than expected, possibly because of partial epimerisation at C-1 of D-glucuronolactone during the hydrogenation.

0008-6215/84/$ 03.00



using excess of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane in dichloromethane, gave the unsaturated lactol benzoate **16** (79%). Catalytic hydrogenation (borohydride-reduced palladium catalyst) of **16** then furnished the saturated lactol benzoate[1] **17** in quantitative yield.

Since the conversions **17**→**3**→**4** have been reported[1,4], this work constitutes the total synthesis of (+)-biotin (**4**) from D-glucose.



12 R = H
13 R = Bz

14

15

16 R = —(CH=CH)$_2$CO$_2$Me
17 R = (CH$_2$)$_4$CO$_2$Me

EXPERIMENTAL

All melting points are uncorrected. Optical rotations were measured with a Jasco DiP 181 digital polarimeter. I.r. spectra were recorded with a Perkin–Elmer Infrared-683 spectrophotometer with sodium chloride optics. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian FT-80A or WH-90 Bruker spectrometer.

Commercial D-glucurono-6,3-lactone was converted into 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone by literature procedures[6,7].

2,3-O-Isopropylidene-L-gulono-1,4-lactone (**8**). — A solution of 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (**7**, 5.2 g) in methanol (100 mL) containing conc. hydrochloric acid (1 mL) was stirred at room temperature for 0.5 h, neutralised with conc. ammonia, and concentrated under reduced pressure. The residue was extracted with dry acetone, the extract was concentrated, and the residue was crystallised from ethyl acetate–light petroleum to give **8** (2.4 g, 48%), m.p. 143–146°, $[\alpha]_D^{26}$ +30° (*c* 2, ethanol).

Anal. Calc. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.23; H, 6.58.

(2S,3S,4R)-2,3-Isopropylidenedioxy-4-[(1E,3E)-4-methoxycarbonyl-1,3-butadienyl]-4-butanolide (**10**). — To a solution of **8** (1.744 g, 8 mmol) in acetone–water (60 mL, 1:1) at 0° was added dropwise during ~5 min a solution of sodium metaperiodate (27 mL, 0.7M), and the mixture was stirred at 0° for 0.5 h. Ethylene glycol (2.5 mL) was then added and stirring continued for 0.5 h at 0°. Ethanol (150 mL) was added and the resulting solid was collected. The filtrate was concentrated to ~5 mL under reduced pressure at 25–30° and extracted with dichloromethane (5 × 20 mL). The combined extracts were dried (Na_2SO_4) and added dropwise to a solution of (3-methoxycarbonyl-2-propenylidene)triphenylphosphorane (5.77 g, 16 mmol) in dichloromethane (30 mL). The mixture was stirred for 4 h, and then concentrated under reduced pressure at room temperature. The residue was eluted from a column (75 g) of silicic acid with light petroleum–ethyl acetate (1:1) to give **10** (0.195 g, 9.28%), m.p. 137–138°, $[\alpha]_D^{25}$ +2° (*c* 1.4, chloroform); ν_{max}^{Nujol} 1790 and 1720 cm^{-1} (lactone and ester C=O, respectively). ^{1}H-N.m.r. data: δ 1.38 and 1.48 (2 s, 6 H, CMe_2), 3.74 (s, 3 H, CO_2Me), 4.82 (d, 1 H, $J_{6,7}$ 3.15, $J_{7,8}$ 0 Hz, H-7), 4.84 (s, 1 H, $J_{8,7}$ 0 Hz, H-8), 5.43 (dd, 1 H, $J_{6,7}$ 3.15, $J_{6,5}$ 8.66 Hz, H-6), 5.94 (dd, 1 H, $J_{5,6}$ 8.66, $J_{5,4}$ 11.02 Hz, H-5), 6.02 (d, 1 H, $J_{2,3}$ 15.7 Hz, H-2), 6.42 (dd, 1 H, $J_{4,3}$ 11, $J_{4,5}$ 11 Hz, H-4), and 7.48 (dd, 1 H, $J_{3,4}$ 11, $J_{3,2}$ 15.7 Hz, H-3).

Anal. Calc. for $C_{13}H_{16}O_6$: C, 58.20; H, 5.96. Found: C, 58.55; H, 5.82.

(2S,3S,4R)-2,3-Isopropylidenedioxy-4-(4-methoxycarbonylbutyl)-4-butanolide (**11**). — A solution of **10** (0.2 g) in methanol (10 mL) was hydrogenated at 1 atmosphere and 0° for 0.5 h using borohydride-reduced Pd catalyst (5 mg). The mixture was then filtered and concentrated to furnish **11** as a syrup (0.195 g), $[\alpha]_D^{25}$ +74° (*c* 1, chloroform); ν_{max}^{liquid} 1790 and 1740 cm^{-1} (lactone and ester C=O, respectively). ^{1}H-N.m.r. data: δ 1.41 and 1.48 (2 s, 6 H, CMe_2), 1.5–1.9 (m, 6 H, CH_2-3,4,5), 2.36 (t, 2 H, $COCH_2$), 3.7 (s, 3 H, CO_2Me), 4.3–4.5 (m, 1 H, H-6), and 4.68–4.86 (m, 2 H, H-7,8).

Methyl (6R,7S,8R)-6,9-dihydroxy-7,8-(isopropylidenedioxy)nonanoate (**3**). — To a solution of **11** (0.2 g) in methanol (15 mL) at 0° was added sodium borohydride (0.2 g) in portions. The mixture was stirred for 4 h at 0°, poured into cold water, and extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with saturated aqueous ammonium chloride, dried, and concentrated, and the residual liquid (0.19 g) was eluted from a column of silicic acid with light petroleum–ethyl acetate (1:1) to furnish **3** (0.165 g, 81.3%), $[\alpha]_D^{26}$ +14° (*c* 1, chloroform) {lit.[1,4] $[\alpha]_D^{20}$ +12.3° (*c* 2, chloroform)}; ν_{max}^{film} 3430 (OH) and 1745 cm^{-1} (CO_2Me). ^{1}H-N.m.r. data: δ 1.3 and 1.43 (2 s, 6 H, CMe_2), 2.28 (m, 2 H, $COCH_2$), 1–1.9 (m, 6 H, CH_2-3,4,5), and 3.6 (s, 3 H, CO_2Me).

Anal. Calc. for $C_{13}H_{24}O_6$: C, 56.52; H, 8.69. Found: C, 56.28; H, 8.90.

2,3:5,6-Di-O-isopropylidene-L-gulose (**12**). — To an ice-cold solution of **7** (2.58 g) in methanol (25 mL) was added sodium borohydride (0.39 g) slowly with stirring. After 0.5 h, the solvent was removed under vacuum and the residue was crystallised from ethyl acetate–light petroleum to give **12** (2.4 g, 92%), m.p. 113–115° (lit.[10] 114–115°), $[\alpha]_D^{24}$ +51° (*c* 1, chloroform).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69. Found: C, 55.63; H, 8.06.

1-O-Benzoyl-2,3:5,6-di-O-isopropylidene-L-gulose (**13**). — To an ice-cold mixture of pyridine (1.6 mL, 0.02 mol) and dry dichloromethane (5 mL) was added with stirring a solution of benzoyl chloride (1.8 mL, 0.015 mol) in dichloromethane (10 mL). After 5 min, a solution of **12** (2.64 g, 0.01 mol) in dichloromethane (15 mL) was added dropwise. The mixture was stirred at 0° for 4 h and then poured into ice–water, the aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined extracts and dichloromethane layer were washed with water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Recrystallisation of the residue from ethyl acetate gave **13** (3.6 g, 96%), m.p. 127–128°, $[\alpha]_D^{25}$ +13° (*c* 1.6, chloroform).

Anal. Calc. for $C_{19}H_{24}O_7$: C, 62.63; H, 6.59. Found: C, 62.34; H, 6.60.

1-O-Benzoyl-2,3-O-isopropylidene-L-gulose (**14**). — A solution of **13** (3.6 g) in methanol (50 mL) containing conc. hydrochloric acid (0.5 mL) was stored at room temperature for 1.5 h, neutralised with conc. ammonia, and concentrated under vacuum at room temperature. The residue was extracted with dry ethyl acetate, the extract was concentrated to 20 mL, and light petroleum (b.p. 60–80°) was added to slight turbidity. On cooling, **14** (3.1 g, 95%) separated; m.p. 174–175°,

$[\alpha]_D^{25}$ +91° (*c* 1,2, ethanol); ν_{max}^{Nujol} 3390 (OH) and 1730 cm^{-1} (benzoate C=O).

Anal. Calc. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.17. Found: C, 59.55; H, 6.23.

*Methyl 1-O-benzoyl-5,6,7,8-tetradeoxy-2,3-O-isopropylidene-*D-lyxo-*non-5,7-dienofuranuronate* (**16**). — The procedure was essentially similar to that described above for **10**, and gave **16** (79.6%), m.p. 89–90°, $[\alpha]_D^{25}$ −33° (*c* 1.46, chloroform); lit.[1] m.p. 91–92°, $[\alpha]_D^{20}$ −33.6° (*c* 0.3, chloroform). ^{1}H-N.m.r. data: δ 1.34 and 1.5 (2 s, 6 H, CMe_2), 3.78 (s, 3 H, CO_2Me), 4.89 (m, 2 H, H-2,3), 5.13 (d, 1 H, H-4), 5.85–6.5 (m, 4 H, H-1,5,6,8), 7.3–7.7 (m, 4 H, 3 Ar-H, H-7), and 8.08 (m, 2 H, 2 Ar-H).

Anal. Calc. for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88. Found: C, 64.50; H, 5.88.

*Methyl 1-O-benzoyl-5,6,7,8-tetradeoxy-2,3-O-isopropylidene-*D-lyxo-*nono-furanuronate* (**17**). — A solution of **16** (200 mg) in methanol (20 mL) was hydrogenated at room temperature and atmospheric pressure over borohydride-reduced Pd catalyst (5 mg). After hydrogen absorption ceased (~0.5 h), the solution was decanted and concentrated to furnish **17** (0.195 g) as a liquid which crystallised on storage; m.p. 66–67°, $[\alpha]_D^{25}$ +30° (*c* 3.2, chloroform). ^{1}H-N.m.r. data: δ 1.0–1.8 (m, 6 H, CH_2-5,6,7), 1.28 and 1.43 (2 s, 6 H, CMe_2), 2.3 (t, 2 H, $-CH_2CO_2Me$), 3.6 (s, 3 H, CO_2Me), 4.1 (m, 1 H, H-4), 4.75 (m, 2 H, H-2,3), 6.3 (s, 1 H, H-1), and 7.25–8.05 (2 m, 5 H, Ph).

REFERENCES

1 H. Ohrui and S. Emoto, *Tetrahedron Lett.*, (1975) 2765–2766.
2 T. Ogawa, T. Kawano, and M. Matsui, *Carbohydr. Res.*, 57 (1977) c31–c35.
3 H. Ohrui, N. Sueda, and S. Emoto, *Agric. Biol. Chem.*, 42 (1978) 865–868.
4 R. R. Schmidt and M. Maier, *Synthesis*, 9 (1982) 747–748.
5 T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 37 (1980) 115–119.
6 M. Ishidate, Y. Imai, Y. Hirasaka, and K. Umemoto, *Chem. Pharm. Bull.*, 11 (1965) 173–176.
7 H. Ogura, H. Takakashi, and T. Itoh, *J. Org. Chem.*, 37 (1972) 72–73.
8 E. Buchta and F. Amdree, *Chem. Ber.*, 92 (1959) 311–316.
9 T. W. Russell and D. M. Duncan, *J. Org. Chem.*, 39 (1974) 3050–3052.
10 R. K. Hulyalkar, *Can. J. Chem.*, 44 (1966) 1594–1596.