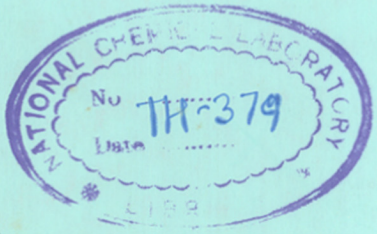
STUDIES ON

(I) BIOLOGICALLY ACTIVE COMPOUNDS AND THEIR ANALOGUES
(II) OXIRANES

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

BY

KRISHNA S. BHAT



DIVISION OF ORGANIC SYNTHESIS
NATIONAL CHEMICAL LABORATORY
PUNE–411 008. (INDIA)

1983

Dedicated to
my parents and brothers

COMPUTERISED

Certified that the work incorporated in the thesis "Studies on Biologically active compounds and their analogues (ii) Oxiranes" submitted by Shri Krishna S. Bhat was carried out under my supervision. Such materials as has been obtained from other sources were duly acknowledged in the thesis.

A. Somasekar Rao 14-2-83

(A. Somasekar Rao)
Supervisor

A C K N O W L E D G E M E N T

I take this opportunity to express my sincere gratitude to Dr. A. Somasekar Rao, Scientist, National Chemical Laboratory, Poona, for suggesting the problems tackled herein and offering me invaluable guidance and encouragement throughout the course of this work.

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I am grateful to the Director, National Chemical Laboratory, Poona, for providing all the facilities and allowing me to submit this work in the form of a thesis and to the Council of Scientific and Industrial Research, New Delhi, for the award of a fellowship.

(K.S. Bhat)

Poona-411008.

February, 1983.

C O N T E N T S

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All liquid samples whose b.p. are reported, were checked for purity on GLC.
3. All extracts were finally dried over anhydrous Na_2SO_4.
4. Pet.ether refers to the fraction boiling between 60-80°.
5. Alumina refers to neutral alumina made in this laboratory.
6. IR Spectra were recorded as liquid film or nujol mull on a Perkin-Elmer Infracord Spectrometer-model 137B or 599B; ν_{max} values are given in cm^{-1}.
7. NMR spectra were recorded on a Varian T-60 or WH-90 FT spectrometers, using TMS as internal standard (chemical shift in ppm).
8. Mass spectra were recorded on CEC-21-110B spectrometer.
9. Microanalyses were carried out in the micro analytical section of this laboratory.
10. TLC was performed on silica gel, made in this laboratory. R_f values refers to TLC using one of the following solvent systems: (A) pet.ether-acetone (4:1) (B) pet.ether-acetone (3:1) (c) pet.ether-acetone(1:4).
11. The numbers assigned to the charts and figures in each Chapter of this thesis refer only to that particular chapter.

CHAPTER-1

EPOXIDE AS INTERMEDIATE FOR KETONE TRANSPOSITION

SUMMARY

Methyl 4-keto-4-(4'-methylphenyl) butanoate (2) is transformed to methyl 3-keto-4-(4'-methylphenyl) butanoate (17) in three steps:

(i) $AlCl_3$ catalysed bromination of 2 is regio-selective and furnishes methyl 3-bromo-4-keto-4-(4'-methyl-phenyl)butanoate (7) in excellent yield.

(ii) $NaBH_4$ reduction of 7 in the presence of $NaHCO_3$ furnishes a mixture of cis-methyl 3,4-epoxy-4-(4'-methyl-phenyl) butanoate (10), methyl (E)-4-hydroxy-4-(4'-methyl-phenyl) but-2-enoate (13) in major quantities and lactone (16) and keto-ester (2) in minor quantities.

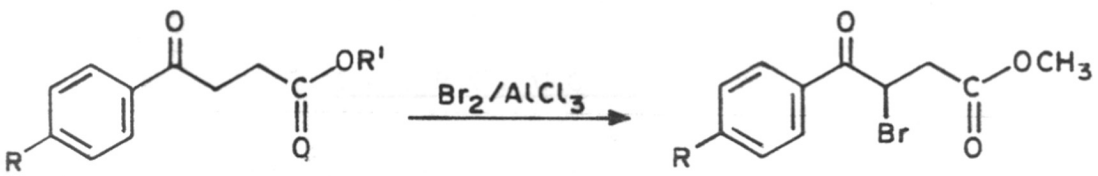
(iii) BF_3 etherate catalysed rearrangement of epoxide (10) furnishes β-keto-ester (17) in very high yield. Identity of 17 is further confirmed by converting it into ketone 19 by the action of alkali.

Thus the sequence of reactions, 2 → 7 → 10 → 17 constitutes an interesting example of ketone transposition and provides a convenient route for the preparation of 17 from the readily available 2.

Further hydroxy-ester (13) is transformed to starting keto-acid (1), on heating with NaOH-ethanol; keto-acid (1) is the starting material for the preparation of 2.

Similarly bromo-keto-esters (8) and (9) [prepared from keto-esters (4) and (6)] on sodium borohydride reduction furnish the epoxides (11) and (12). BF_3-etherate catalysed rearrangement of epoxide (11) furnishes β-keto-ester (18) in high yield.

CHART I



1 R = CH_3, R' = H

2 R = CH_3, R' = CH_3

3 R = R' = H

4 R = H, R' = CH_3

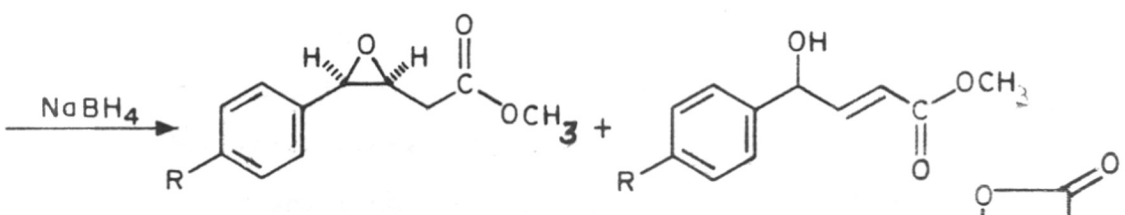
5 R = OCH_3, R' = H

6 R = OCH_3, R' = CH_3

7 R = CH_3

8 R = H

9 R = OCH_3



10 R = CH_3

11 R = H

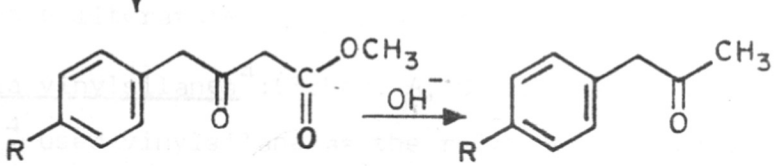
12 R = OCH_3

13 R = CH_3

14 R = H

15 R = OCH_3

16 R = CH_3



17 R = CH_3

18 R = H

19 R = CH_3

INTRODUCTION

The carbonyl group plays a pivotal role in bringing latitude to organic synthesis. In synthetic work it is often desirable to shift the position of a ketone carbonyl by one carbon atom, which is termed as "ketone-transposition". The importance of the carbonyl group makes the ability to relocate it within a molecule, a useful problem[1,2]; interest in efficient methods of carbonyl transposition remains high.

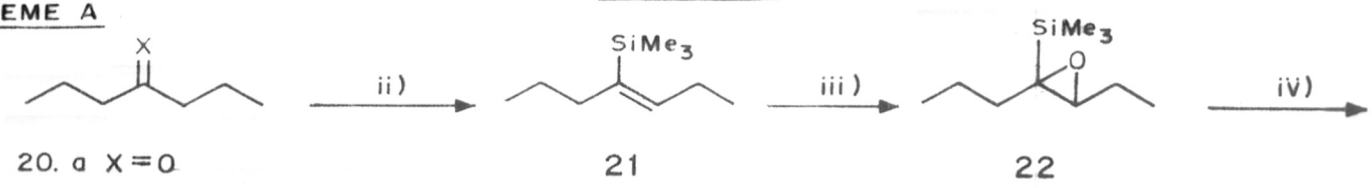
In this chapter, we furnish some examples of ketone transposition, involving the transformation of readily available keto-esters (2) and (4) to the β-keto-esters (17) and (18) by shifting the carbonyl group. Further, so transformed keto-ester (18) is a useful compound in synthetic work. In our laboratory methyl 3-keto-4-phenyl-butanoate (18) was used[3] as one of the starting materials in the conversion of $R\text{-}CH_2\text{-}X$(X = Br, I) to $R\text{-}CH_2\text{-}CH_2\text{-}CHO$.

Various procedures are available for effecting such site exchange of carbonyl group within a molecule; available literature methods are reviewed here.

(i) Via vinylsilanes[4]:(Scheme A, Chart II)- L.A.Paquette et al.[4] used vinylsilane as the relay intermediate for 1,2-carbonyl transposition. They transformed 4-oxo-n-hexane (20a) into 3-oxo-n-hexane (24): Vinyl carbanion

CHART—II

SCHEME A

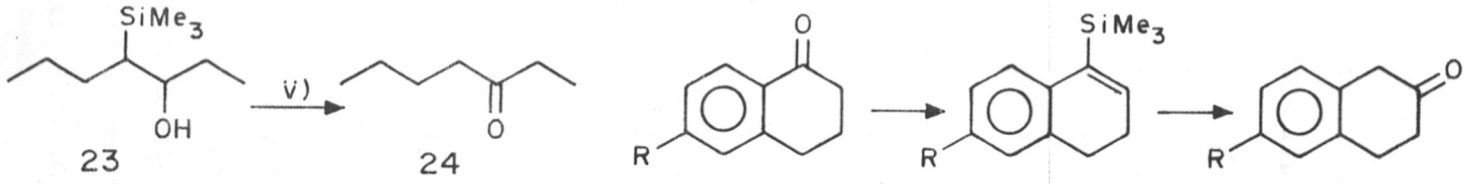


20. a X = O

b X = N·NH·$SO_2C_6H_5$

21

22



23

24

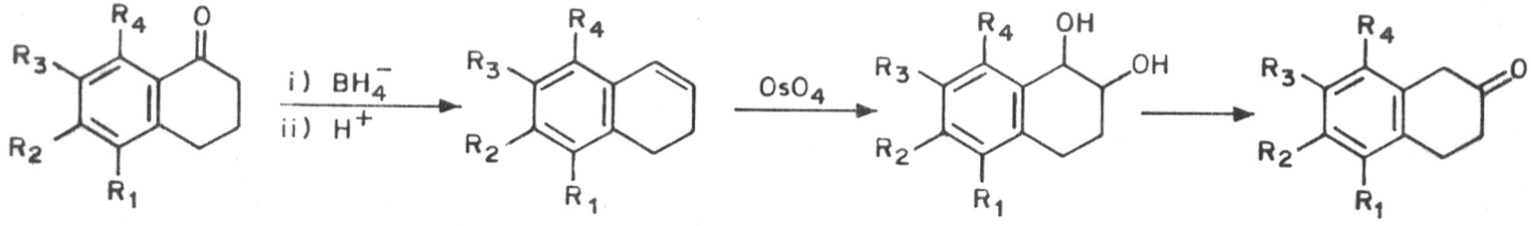
25 R = H
26 R = OCH_3

27 R = H
28 R = OCH_3

29 R = H
30 R = OCH_3

Reagent: i) alkyl lithium in TMEDA
ii) Chlorotrimethyl silane
iii) m—Chloroperbenzoic acid
iv) LAH
V) Chromic acid

SCHEME B[1]



31

32

33

34

a $R_1=R_2=R_3=R_4=H$

b $R_1=OCH_3$, $R_2=R_3=R_4=H$

c $R_1=R_3=R_4=H$, $R_2=OCH_3$

d $R_1=R_2=R_4=H$, $R_3=OCH_3$

generated through reaction of ketone arene sulfonyl hydrazone (20b) (prepared from 20a by the action of arene sulfonyl hydrazide) with alkyllithium reagent in tetramethylethylenediamine (TMEDA) solution was condensed with chlorotrimethylsilane to deliver vinylsilane (21), which on epoxidation with m-chloroperbenzoic acid furnished epoxide (22). Subsequent reduction of 22 with lithium aluminium hydride in THF at reflux temperature yielded β-silyl ethanol (23). Oxidation of 23 with stoichiometric quantity of chromic acid under two phase (ether/water) condition furnished pure transposed ketone (24).

Similarly, α-tetralone (25) and 6-methoxy α-tetralone (26) were transformed to the corresponding β-tetralones (29) and (30) respectively.

(2) Via reduction, dehydration and hydroxylation[1]:(Scheme B Chart II) - Frank M. Hauser et al.[1] transformed 1(2H)-tetralone (31a) to 2(1H)-tetralone (34a) in three steps. The first step was the conversion of 31a to 3,4-dihydro-napthalene (32a) by sodium borohydride reduction, followed by the dehydration of the alcohol intermediate in refluxing benzene with a catalytic amount of p-toluene-sulfonic acid. Second step was, hydroxylation of the olefinic moiety in 32a with a catalytic amount of osmium tetroxide/H_2O_2 to afford cis-diol (33a). Finally,

dehydration of 33a with catalytic amount of p-toluene-sulfonic acid and azeotropic removal of water yielded 2(1H)-tetralone (34a).

Using this strategy, 1 (2H)-tetralones (31b, 31c, 31d) were converted to 2(1H)-tetralones 34b, 34c, 34d).

Extension of this method for the conversion of 2 to β-keto-ester (17) is not feasible, as $NaBH_4$ reduction of 2 and subsequent acid catalysed dehydration would furnish lactone (16) instead of required olefin.

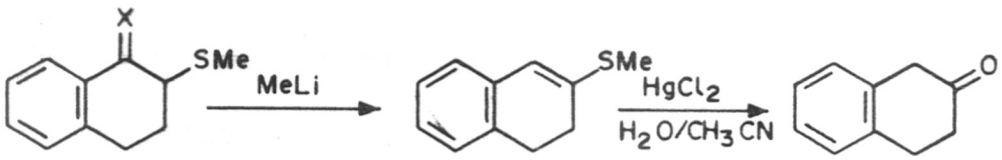
(3) Via sulphenylation of ketone

(a) S. Shibuya et al.[5] (Scheme C, Chart II), used -sulphenylated ketone as the key intermediate for the 1,2-transposition of carbonyl groups. For example, the toluene p-sulphenyl hydrazone (36) prepared from -tetralone (35) was treated with MeLi (6 mole equiv.) in ether at room temperature to afford vinyl sulphide (37). Hydrolysis of 37 with mercuric chloride in acetonitrile-water furnished -tetralone (38).

(b) B.M. Trost et al.[2] (Scheme D, Chart II), converted ethyl 3-phenyl propionate (39) to α-phenyl acetone (44). Reduction of α-sulfenylated compound 40 (prepared by sulphenylation of 39) with lithium aluminium hydride afforded hydroxy compound (41), which was dehydrated to enol-thio-ether (43) using thionyl chloride and potassium t-butoxide in DMSO. Hydrolysis of 43 with mercuric

CHART-II (contd.)

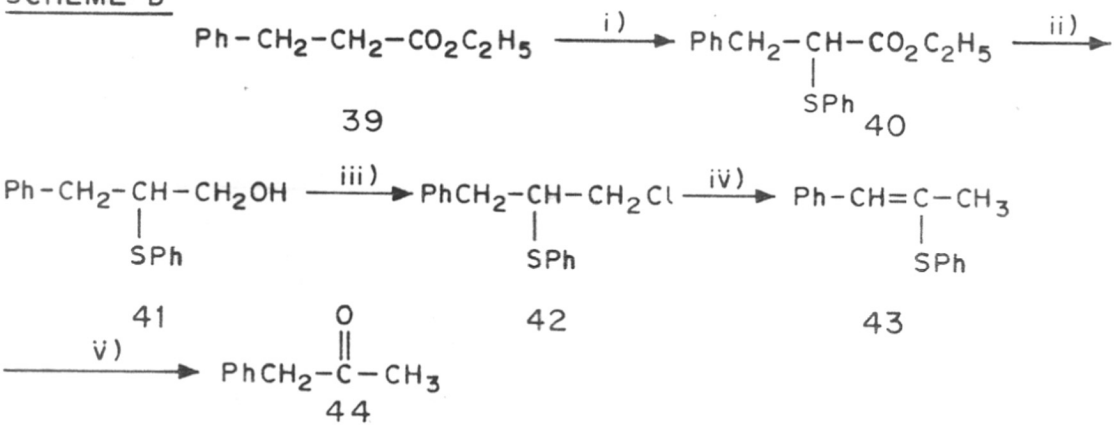
SCHEME C[5]



35 X=O 37 38

36 X=N-NH-$SO_2C_6H_4-CH_3$-P

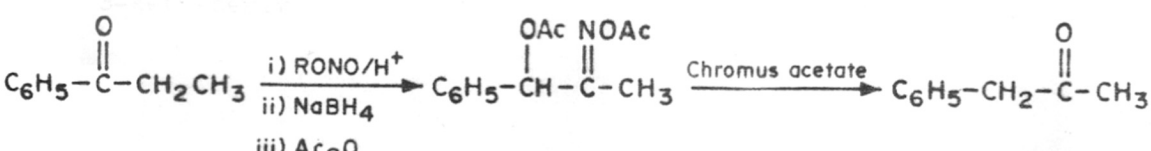
SCHEME D[2]



39 40 41 42 43 44

Reagent: i) LITHIUM N-CYCLOHEXYL-N-ISOPROPYL AMINE, THF, -78°, PhSSPh, HmDA, 0°. ii) $LiAlH_4$, iii) CH_3SO_2Cl, PYRIDINE, ROOM TEMPERATURE, iv) KOC_4H_9-t, DMSO, ROOM TEMPERATURE, v) $HgCl_2$, $3CH_3CN$, $1H_2O$, REFLUX.

SCHEME E[6]



45 46 47

chloride in acetonitrile-water system furnished transposed ketone (44).

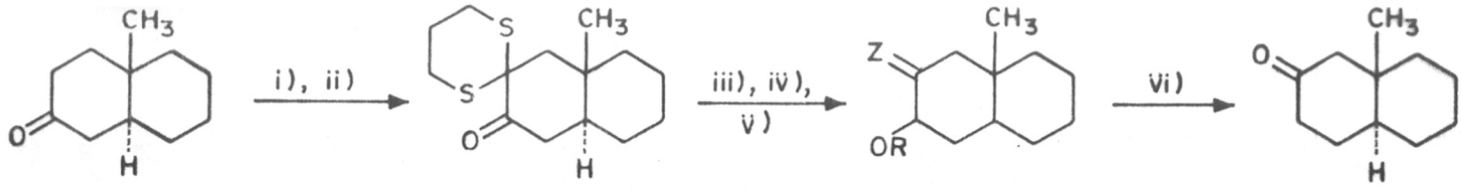
(4) Via oxime o-acetates[6]: (Scheme E, Chart II) E.J.Corey et al.developed a new method for the transposition of ketonic function on the basis of Cr(II) induced reductive deoximation with α-cleavage. Oximation of propiophenone (45) (using alkyl nitrite in presence of acid), followed by reduction with sodium borohydride and acetylation gave the α-acetoxy acetoxime (46), which upon treatment with excess chromous acetate in tetrahydrofuran-water (10:1) at 65° for 34 hr, afforded phenyl acetone (47).

(5) A non-oxidative method[7] (Scheme F, Chart II)- James A. Marshall et al.[7] converted 10r-methyl-(9Ht)-decal-3-one(48) into 10r-methyl-(9Ht)-decal-2-one (53): The hydroxy methylene derivative of ketone (48) afforded the thioketal-ketone (49), upon treatment with propane 1,3-dithiol-di-p-toluene sulfonate and potassium acetate in ethanol. Reduction of 49 with lithium aluminium hydride gave the alcohol (50), which was converted to the acetate (51) and resulting keto-acetate (52) was treated with calcium in ammonia to afford the desired ketone (53).

Similarly, 1c, 9c-dimethyl-7c-isopropenyl-(10Hr)-decal-2-one (54) was transformed to the corresponding 3-keto-derivative (55).

CHART – II (contd.)

SCHEME F[7]



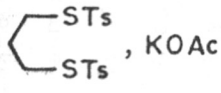
48 49 50 Z = $S(CH_2)_3S$, R = H 53

51 Z = $S(CH_2)_3S$, R = Ac

52 Z = O, R = Ac

Reagent:

i) $H{\cdot}CO_2Et$, NaH

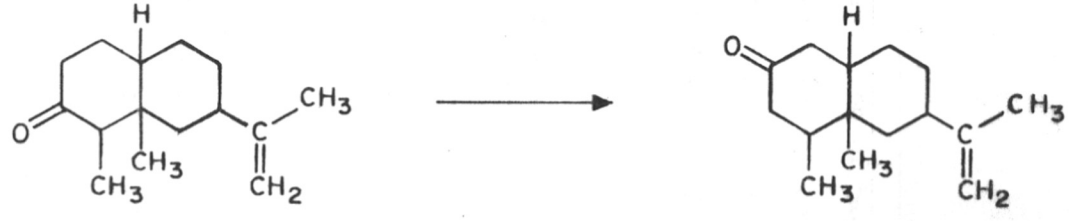
ii)  , KOAc

iii) $LiAlH_4$

iv) Ac_2O

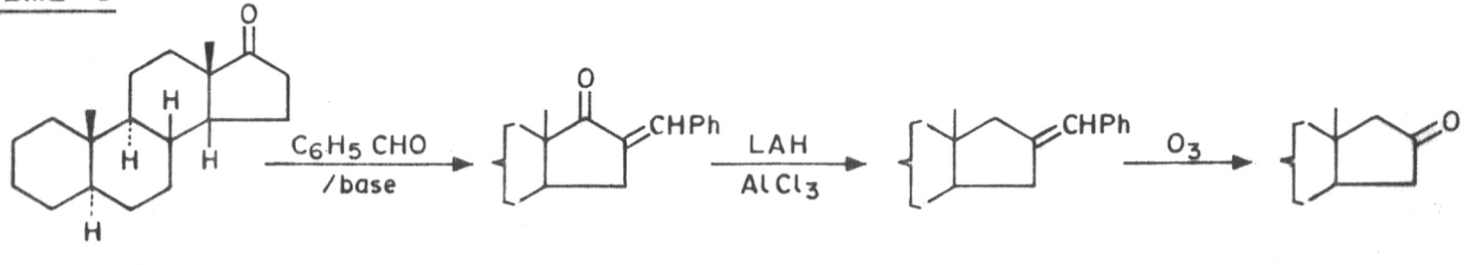
v) H_2O, $HgCl_2$

vi) Ca, NH_3



54 55

SCHEME G[8]



56 57 58 59

(6) Via conjugated benzylidene derivative[8] (Scheme G, Chart II)- Condensation of 5α-androstan-17-one (56) with benzaldehyde furnished the conjugated ketone (57), which was reduced with lithium aluminium hydride and aluminium chloride to 16-benzylidene derivative (58). Ozonolysis of 58 yielded the 5α-androstan-16-one (59).

This method of ketone-transposition is not feasible for converting keto-ester (2) to β-keto-ester (17), as LAH reduction of carbonyl group would reduce the ester function of 2 to corresponding alcohol.

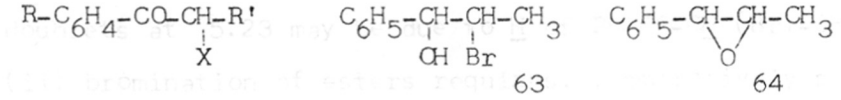
PRESENT WORK

In view of the importance of carbonyl group in organic synthesis, there is considerable interest in relocating it within a molecule. Hence an example of ketone transposition involving the transformation of readily available keto-ester (2) to the β-keto-ester (17) is presented in this chapter; β-keto-ester (17) was needed for some laboratory projects.

Literature study revealed that, benzylic epoxides are known to rearrange to carbonyl compounds (where carbonyl is homobenzylic) in the presence of BF_3-etherate[9,10]. We thought of making use of this strategy in the conversion of keto-ester (2) to β-keto-ester (17) via epoxide (10). We anticipated that the epoxide (10) is an intermediate which can be prepared readily on the basis of the following

literature reports.

It is reported in literature that, bromination[11] of



63 64

60. R = halogen, R' = - CH_2-COOH, X = H

61. R = halogen, R' = -CH_2-COOH, X = Br

62. R = H, R' = CH_3, X = Br.

keto-acid (60) regioselectively furnishes bromo-keto-acid (61); it is also reported that sodium borohydride reduction of 2-bromo-propiophenone (62) gives predominantly the bromohydrin (63), which is then converted into epoxide (64) in the presence of alkali[12]. On the basis of these literature data we expect smooth transformation of keto-ester (2) to β-keto-ester (17) and our observations are presented here.

Conventional esterification of keto-acid (1) (prepared from toluene and succinic anhydride in presence of anhydrous aluminium chloride) by CH_3OH-H_2SO_4 method furnishes the keto-ester (2) in very good yield.

$AlCl_3$ catalysed bromination[13] of 2 in ether is regioselective and furnishes exclusively 7 (where bromine atom is α to ketone carbonyl but not to ester carbonyl) in excellent yield. The conclusion drawn in favour of 7

is based on-

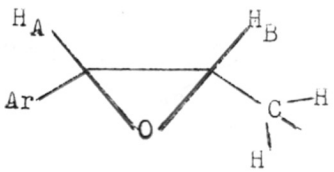
(i) PMR data: only one singlet at 3.60 for ester $C\underline{H}_3$ indicates the presence of one compound; 1H doublet of doublets at 5.23 may be due to $\underline{H}$ of Ph-CO-$C\underline{H}$ (Br)-CH_2-

(ii) bromination of esters requires, comparatively more drastic conditions than the ketonic compounds; hence we exepct bromination to go α to ketone carbonyl.

Sodium borohydride reduction of 7 in the presence of $NaHCO_3$ furnishes a mixture of the epoxide (10), hydroxy-ester (13), lactone (16) and keto-ester (2). Comparison of PMR spectrum of this mixture with the PMR spectra of authentic samples shows that, the mixture is composed of 34% of 10, 34% of 13, 10% of 16 and 6% of 2, which is in good agreement with the actual quantities of the pure components 10, 13, 16 and 2 isolated through column chromatography over grade II alumina.

Compound 10 analysed for $C_{12}H_{14}O_3$ and exhibits a band at 1736 cm^{-1} in its IR spectrum, assignable to ester C=O. Its PMR spectrum shows signals at δ 2.30 (m, 2H), 2.33 (s, 3H), 3.40 (m, 1H), 3.58 (s, 3H), 3.98 (d, 1H, J = 4 H_z) and 7 12 (s, 4H). Signals at 2.33, 3.58 and 7.12 are assigned to aromatic CH_3, ester $C\underline{H}_3$ and aromatic H, whereas 2H multiplet at 2.30 is assignable to -$C\underline{H}_2$- of -CH_2-$COOCH_3$; thus 12 protons have been accounted leaving signals in the region of 3.40 and 3.98 to be accounted for. The position and multiplicity of the

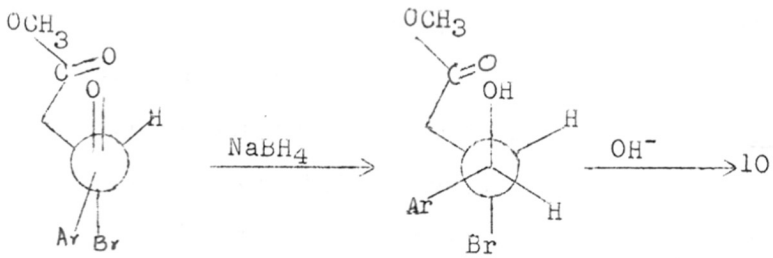
signals at 3.40 and 3.98 may be assignable to H_A and H_B of the oxirane system as shown below; doublet at 3.98



is compatable with the benzylic H (H_A), whereas multiplet at 3.40 is compatable with the homobenzylic H (H_B); coupling constant J = 4Hz for oxirane proton at 3.98 indicates the cis-geometry of the oxirane system. Hence compound (10) may be cis-methyl 3,4-epoxy-4-(4'-methylphenyl) butanoate. Thus assigned structure of compound 10 is further supported by its rearrangement to 17 with BF_3 etherate and to hydroxy acid (68) with NaOH-ethanol treatment, which has been discussed in detail (page No. 20)

The cis-stereochemistry is assigned to the 10, on the basis of coupling constant[14], J = 4 Hz of the benzylic H with the homobenzylic H. The formation of the cis-isomer (10) but not the trans-isomer during $NaBH_4$ reduction of bromo-ester (7) in alkaline medium can be rationalised as follows:

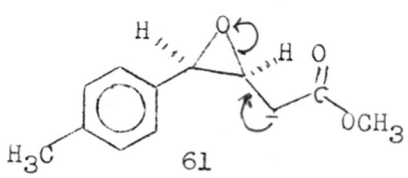
Cornforth et al.[15] suggested that for α-halo-carbonyl derivatives, the carbon-halogen and carbonyl dipoles prefer an anti conformation. On this basis the bromo-ester (7) is likely to be present predominantly in the conformation with the C-Br bond farthest away from C=O to minimise



7 60

dipole repulsion between C=O and C-Br bonds. Further for certain additions (e.g. of hydride or an organometallic) to the carbon-oxygen double bond of ketones containing an asymmetric α-carbon, Cram's rule[16] predicts that, the in coming group preferentially attacks on the side of the plane containing smaller group. Thus the hydride attack on the favoured conformer 7 can be anticipated to take place from the side trans to the bulky $-CH_2-COOCH_3$ substitutent to furnish exclusively the threo-bromohydrin (60). The alcoholate anion formed from 60 displaces Br by backside attack to furnish the cis-epoxide (10).

Further, compound (10) is a β,γ-epoxy-ester; the anion 61 may be expected to open as shown below; in agreement with our expectation, there are precedents in literature for similar type of elimination)[17]; treatment of 10 with NaOH-ethanol furnished the hydroxy acid (68),



61

identified by direct comparision (IR, PMR and mixed m.p.) with a sample prepared by an alternate route which will be presented later.

The structure assigned to hydroxy-ester (13) is based on its elemental analysis, mass-spectrum, IR and PMR spectral data. Elemental analysis and M^+ (206) fixed the molecular formula, $C_{12}H_{14}O_3$. IR spectrum exhibits bands at 3550, 1725 and 1665 cm^{-1}, assignable to hydroxy, ester carbonyl and C=C respectively. Its PMR spectrum shows signals at δ 2.30 (s, 3H), 3.40 (broad s, 1H), 3.63 (s, 3H), 5.07 (dd, 1H), 5.93 (dd, 1H), 6.70 (dd, 1H) and 7.03 (s, 4H). Signals at 2.30, 3.63 and 7.03 are assigned to aromatic $C\underline{H}_3$, ester $C\underline{H}_3$ and aromatic H respectively. Signal at 3.40, vanishes after D_2O treatment indicating the presence of hydroxyl H. Doublet of doublets at 5.93 and 6.70 are assignable to olefinic protons, which is also supported by the presence of C=C in IR spectrum. The remaining 1H at 5.07 is then assigned to benzylic as well as allylic H. Large coupling constant (J = 15 H_z) of olefinic H shows, the compound 13 has E-geometry. Thus assigned structure of 13 as methyl (E)-4-hydroxy-4-(4'-methylphenyl) but-2-enoate is further confirmed by MnO_2 oxidation.

Active MnO_2 is known to oxidise allylic alcohol to the corresponding carbonyl compound[18]. Hence we anticipate the oxidation of hydroxy-ester (13) to keto-ester

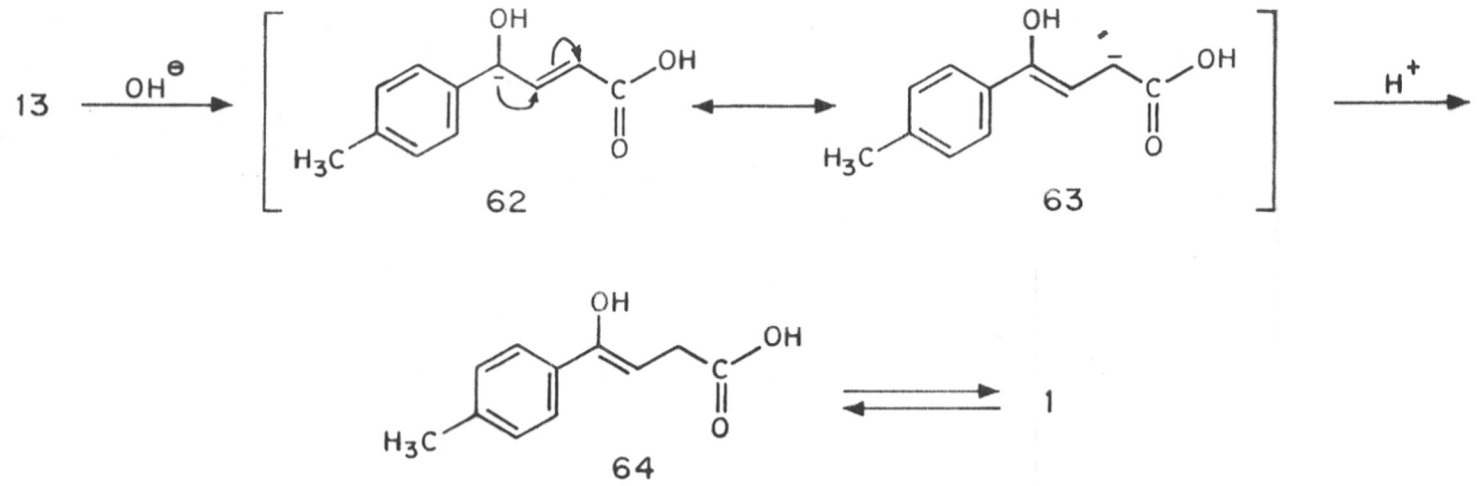
(70); according to our anticipation, oxidation of hydroxy-ester (13) with active MnO_2 readily furnishes the known keto-ester (70) identified by direct comparison (IR, PMR, TLC and VPC) with an authentic sample.

Hydroxy-ester (13) is also prepared by $NaBH_4$ reduction of α,β-unsaturated keto-ester (70). But this method is not satisfactory in view of the poor yield of 13 due to the formation of side products e.g. lactone (16) and diol (71). The formation of lactone (16) can be anticipated by the 1,4-hydride attack on α,β-unsaturated keto-ester (13) to furnish keto-ester (2), which can easily transform to lactone (16) in presence of sodium borohydride. The formation of diol (71) might have resulted due to the reduction of ester function, which is very rare.

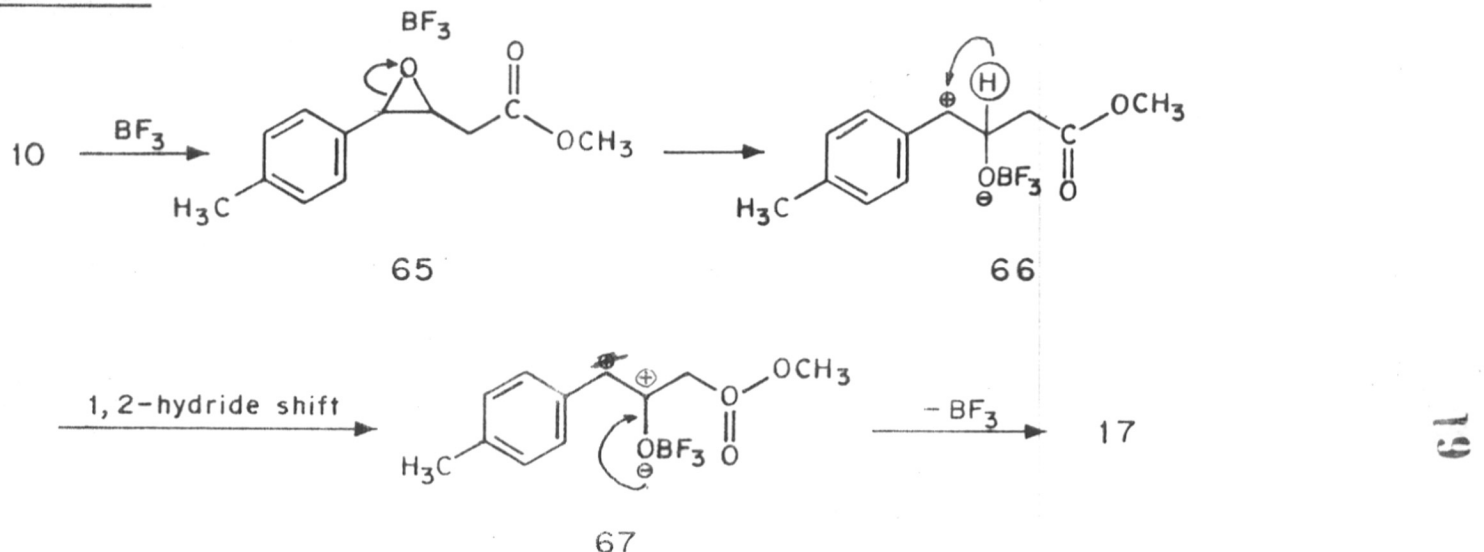
Saponification of 13 under carefully controlled conditions furnishes the hydroxy acid (68); however prolonged treatment of 13 with excess of alkali on a steam-bath furnishes the keto-acid (1). The isomerisation of 13 to 1 is an example of transformation of a γ-hydroxy-α,β-unsaturated carbonyl compound to 1,4-dicarbonyl compound, possible mechanism is shown in Scheme A, Chart III and there are precedents in literature for this type of rearrangement[19,20]. This observation is significant, since the hydroxy-ester (13) (obtained as a byproduct in the preparation of 10 from 7) can be

CHART-III

SCHEME A



SCHEME B



transformed to the keto-acid (1), which is the starting material for the preparation of 7.

The acid-catalysed isomerisation of trans hydroxy ester (13) to cis-hydroxy ester and subsequently the formation of conjugated lactone (72) was anticipated. But when 13 is treated with p-toluene sulfonic acid in benzene at room temperature for 20 hrs, instead of lactone (72), dimeric ether (73) is formed. This indicates that acid catalysed conversion of hydroxy-ester (13) to lactone (72) is not feasible.

Formation of β-keto-ester (17)

Three methods have been tried for the conversion of epoxide (10) to β-keto-ester (17).

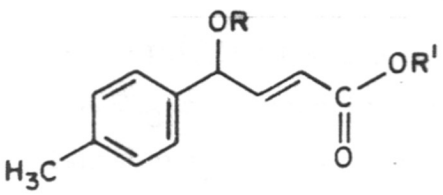
(i) Epoxides are known to rearrange to ketones (or aldehydes) in the presence of BF_3 etherate[9,10]. Hence epoxide (10) is treated with BF_3 etherate in benzene at room temperature, when epoxide (10) readily rearranges to furnish the β-keto-ester (17) in high yields; the possible mechanism is shown in scheme B, chart III. Structure assigned to 17 is in good agreement with the analytical data: Elemental analysis and M^+ shows the molecular formula $C_{12}H_{14}O_3$. IR shows bands at 1740 and 1725 cm^{-1} assignable to ester carbonyl and carbonyl which is not benzylic respectively. PMR spectrum shows signals at δ 2.37 (s, 3H), 3.27 (s, 2H), 3.60 (s, 3H), 3.70 (s, 2H) and

7.13 (s, 4H). Signals at 2.37, 3.60 and 7.13 are assigned to aromatic CH_3, ester CH_3 and aromatic H, whereas singlets at 3.27 and 3.70 are in good agreement with the benzylic $-C\underline{H}_2-$ and $-C\underline{H}_2-$ of $-C\underline{H}_2-COOCH_3$ respectively. The structure assigned to 17, as methyl 3-keto-4-(4'-methylphenyl)butanoate is further supported by its transformation to 19 on heating with NaOH-ethanol, here we assume first step is the formation of β-keto-acid which can decarboxylate[21] to furnish 19.

(ii) As styrene oxide has been thermally rearranged to phenylacetaldehyde[22], thermal rearrangement of epoxide (10) to β-keto-ester (17) is tried. However, 10 on thermal rearrangement furnishes a complex mixture; presence of 17 in this complex mixture is established by transforming it into 19 by treatment with alkali.

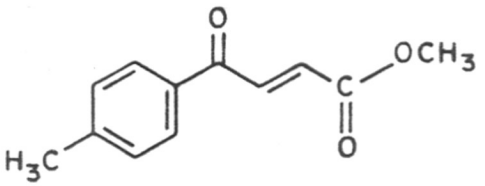
(iii) Epoxides are known to give chlorohydrins on treatment with hydrogen chloride[23]. On this basis, epoxide 10 is treated with hydrogen chloride; 10 furnishes a mixture of erythro and threo chlorohydrins (75). Assignment of erythro and threo isomers are based on PMR spectral data, which shows two singlets (4:3) at δ 3.56 and 3.66 for ester $C\underline{H}_3$ and two doublets (4:3) centered at 4.80 for benzylic $-C\underline{H}-$ adjacent to carbon atom bearing one proton. This mixture of erythro and threo-chlorohydrins (75) on heating with methanolic solution of pyridine furnishes 17 in low yield.

CHART-III (contd.)

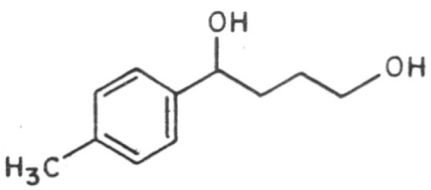


68 $R = R' = H$

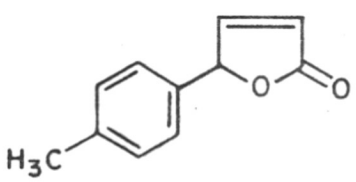
69 $R = -COCH_3$, $R' = CH_3$



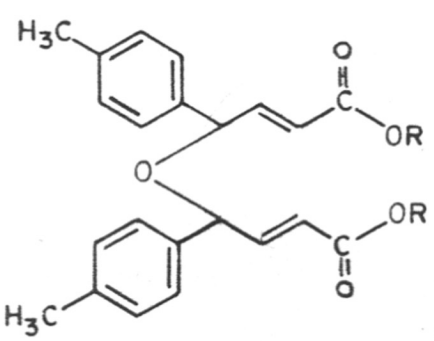
70



71

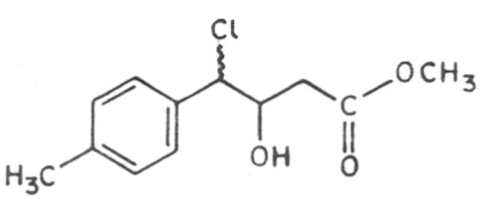


72



73 $R = CH_3$

74 $R = H$



75

Hence BF_3 etherate rearrangement of 10 to 17 can be considered as the best method for preparation of keto-ester (17) from 10..

$AlCl_3$ catalysed bromination of keto-ester (4) furnishes bromo-keto-ester (8), which on sodium borohydride reduction in presence of $NaHCO_3$, yields a mixture of epoxide (11) and hydroxy ester (14). Epoxide (11) on BF_3 etherate treatment, furnishes β-keto-ester (18) in good yield.

Similarly, $AlCl_3$ catalysed bromination of keto-ester (6) furnishes bromo-keto-ester (9). 9 on sodium borohydride reduction in presence of $NaHCO_3$, furnishes a mixture of epoxide (12) and hydroxy-ester (15).

EXPERIMENTAL

Methyl 4-keto-4-(4'-methylphenyl) butanoate (2)

Methylation of the keto-acid 1 by CH_3OH-H_2SO_4 method (the reflux) furnished the keto-ester (2) in good yield, m.p.42°; b.p.120°/0.5 mm (li.t[24] b.p.119-20°/0.5 mm); TLC, R_f 0.57 (solvent A); PMR : 2.37 (3H, s, Ar-CH_3), 2.60 (2H, t, J = 6 Hz, -CH_2-$COOCH_3$), 3.13 (2H, t, J = 6 Hz, Ar-CO-CH_2-), 3.60 (3H, s, -OCH_3), 7.13 (2H, d, J = 8 Hz, aromatic H ortho to CH_3), 7.76 (2H, d, J = 8 Hz, aromatic H meta to CH_3).

Methyl 3-bromo-4-keto-4-(4'-methylphenyl)butanoate (7)

To the mixture of 2 (10.30 g, 0.05 mol) and anhydrous $AlCl_3$ (100 mg) in dry ether (20 ml), bromine (8 g, 0.05 mol) in dry CCl_4 (10 ml) was added dropwise. The reaction mixture was stirred for 5 min, diluted with water, extracted with ether, the ether extract washed with water and dried. The residue obtained after the evaporation of solvent, furnished 7 (14.20 g); yield 100%; TLC: R_f 0.59 (solvent A); IR (liquid film): 1740 (ester C=O), 1678 (Ar-C=O); PMR: 2.37 (3H, s, Ar-CH_3), 3.10 (2H, m, -CH_2-$COOCH_3$), 3.60 (3H, s, -OCH_3), 5.23 (1H, dd, J = 6 Hz and 8 Hz, -CO-CHBr), 7.00 (2H, d, J = 8 Hz, aromatic), 7.60 (2H, d, J = 8 Hz, aromatic); MS: m/z 284 (M^+); (Found: C, 50.32; H, 4.74. $C_{12}H_{13}BrO_3$ requires C, 50.56; H, 4.59%).

$NaBH_4$ reduction of methyl 3-bromo-4-keto-4-(4'-methylphenyl) butanoate (7)

A mixture of 7 (14 g, 0.05 mol) in methanol (100 ml), $NaBH_4$ (1.9 g, 0.05 mol) in water (10 ml) and sodium bicarbonate (4.2 g, 0.05 mol) in water (50 ml) was stirred at 28° for 1.5 hr, diluted with water and extracted with ether. The ether extract was washed with water and dried. Evaporation of solvent furnished a mixture of cis-methyl 3,4-epoxy-4-(4'-methylphenyl) butanoate (10), methyl (E)-4-hydroxy-4-(4'-methylphenyl) but-2-enoate (13), 4-(4'-methylphenyl)-butanolide (16) and 2 (10.26 g). Comparison of PMR spectrum of the above residue with the PMR spectra of authentic samples of 10, 13, 16 and 2 showed that the residue was composed of 10 (34%), 13 (34%), 16 (10%), 2 (6%) and unidentified compounds (16%). The conclusion thus drawn was in good agreement with the actual quantities of the pure components 10, 13, 16 and 2 isolated through chromatography.

The above residue (10 g) was chromatographed on alumina (Gr. II, 200 g). The column was eluted successively with (i) pet.ether, (ii) 1% ethyl acetate + pet.ether, (iii) 2% ethylacetate + pet.ether, (iv) 4% ethylacetate + pet.ether, (v) 6% ethylacetate + pet.ether. Fraction (i) was composed predominantely of 10 (3.04 g); yield 31%; b.p.152-56° (bath temp.)/2 mm; TLC: R_f 0.64

(solvent A); PMR: 2.30 (2H, m, $-C\underline{H}_2-CO_2CH_3$), 2.33 (3H, s, $Ar-C\underline{H}_3$), 3.58 (3H, s, $-C\underline{H}_3$), 3.98 (1H, d, J = 4 Hz, benzylic, oxirane H), 7.12 (4H, s, aromatic); MS: m/z 206 (M^+); Found: C, 69.90; H, 6.75. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84% .

Fraction (ii), 0.7 g was a 1:1 mixture of 10 and 2 as revealed by PMR spectrum. Pure sample of 2 could be obtained from this mixture through preparative TLC.

Fraction (iii) was a 2:5:2:5 mixture of 2,16,13 and an unidentified compound according to its PMR spectrum and TLC behaviour. Pure sample of 16 was obtained from this mixture through preparative TLC, m.p.81°; TLC: R_f 0.54 (solvent A); IR (Nujol): 1780 (γ-lactone C=O); PMR: 2.40 (3H, s, $Ar-C\underline{H}_3$), 2.46 (4H, m, $-C\underline{H}_2-C\underline{H}_2-$), 5.23 (1H, m, Ar-C<u>H</u>), 7.00 (4H, s, aromatic).

Fraction (V) was composed predominantly of 13 (3.05 g); yield 31%; b.p.185° (bath temp.)/2 mm; TLC: R_f, 0.43; PMR: 2.30 (3H, s, $Ar-C\underline{H}_3$), 3.40 (1H, broad s, exchangable with D_2O, hydroxyl H), 3.63 (3H, s, $-OC\underline{H}_3$), 5.07 (1H, dd, J = 5 Hz and 2 Hz, $>C\underline{H}-OH$), 5.93 [1H, dd, J = 16 Hz and 2 Hz = $C\underline{H}(CO_2CH_3)$], 6.70 (1H, dd, J = 16 Hz and 5 Hz, olefinic H), 7.03 (4H, s, aromatic H); MS: m/z 206 (M^+); Found: C, 70.05; H, 6.97. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%.

Methyl 3-keto-4-(4'-methylphenyl)butanoate (17)

A mixture of 10 (0.57 g, 0.28 mmol) in dry benzene (15 ml) and BF_3 etherate (1 ml) was kept at room temperature for 1.5 hr. The benzene layer was washed with water until free from acid, dried and benzene was removed to furnish 17 (0.54 g); yield 95%; distillation yielded the analytical sample; b.p. 160-62° (bath temp.)/ 2 mm; TLC: R_f 0.58; IR (liquid film): 1740 (ester C=O), 1725 (C=O); PMR: 2.37 (3H, s, Ar-CH_3), 3.27 (2H, s, -CH_2-Ar), 3.60 (3H, s, -OCH_3), 3.70 (2H, s, -CH_2-$COOCH_3$), 7.13 (4H, s, aromatic); MS: m/z 206 (M^+); (Found: C, 70.01; H, 7.06. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%).

Action of ethanolic NaOH on 17: Formation of 1-(4-methylphenyl)propan-2-one (19)

A mixture of 17 (0.5 g, 0.24 mmol), ethanol (25 ml), sodium hydroxide (0.8 g, 0.20 mmol) and water (25 ml) was kept at room temperature for 1 hr, heated under reflux for 30 min, cooled, diluted with water and extracted with ether. The ether extract was washed with water and dried. The solvent was removed and the residue was distilled under reduced pressure to furnish 19; yield 82%; b.p. 120-25° (bath temp.)/12 mm (lit.[25] b.p. 109-10°/12 mm); TLC: R_f 0.63 (solvent system A); IR (liquid film); 1725 (C=O); PMR: 2.0 (3H, s, -CO-CH_3), 2.30 (3H, s, Ar-CH_3),

3.53 (2H, s, benzylic), 7.10 (4H, s, aromatic).

Methyl 4-chloro-3-hydroxy-4-(4'-methylphenyl)butanoate (75)

Through a solution of 10 (0.74 g) in dry ether (50 ml) dry HCl gas was passed for 30 min. Solvent was removed under reduced pressure, and residue was extracted with ether. Ether extract was washed with water, dried and concentrated to furnish 75 (0.78 g); yield: 91%; TLC: R_f 0.41 (solvent system A); IR: 3545 (OH), 1738 (ester C=O); PMR: 2.37 (3H, s, Ar-C<u>H</u>$_3$), 2.73 (2H, m, -C<u>H</u>$_2$-COOCH$_3$), 3.02 1H, broad s, exchangable with D_2O), 3.56 and 3.66 (3H, s, -COOC<u>H</u>$_3$), 4.27 (1H, m, >C<u>H</u>-OH), 4.80 (1H, two d, J = 5 H., Ar>C<u>H</u>-Cl), 7.10 (4H, m, aromatic). Found: C, 60.16; H, 6.58. $C_{12}H_{15}ClO_3$ requires C, 59.87; H, 6.23%.

Action of methanolic pyridine on 75: Formation of 17

A mixture of 75 (0.6 g, 0.29 mmol), methanol (20 ml) and pyridine (0.26 g, 0.36 mmol) was heated under reflux for 5 hr. Solvent was removed under reduced pressure, the residue extracted with ether. Ether extract was washed with water, dried and the solvent removed. Residue (0.48 g) was chromatographed on alumina (Gr. II, 10 g). Fraction eluted with 5% ethylacetate + pet.ether furnished 17 (0.14 g), identified through TLC, IR and NMR; yield 26%.

Thermal rearrangement of (10)

10 (0.3 g, 0.14 mmol) was heated at 195-200° for 45 min under nitrogen atmosphere. Residue(complex mixture by TLC analysis) was cooled and heated with a mixture of NaOH (0.60 g) water (15 ml) and ethanol (15 ml) for 1 hr. Work up of the reaction mixture furnished 19 (0.05 g), identified through TLC, IR and PMR; yield: 21%.

Action of alkali on 10

A mixture of 10 (0.30 g, 0.15 mmol), sodium hydroxide (0.08 g, 0.019 mmol), ethanol (10 ml) and water (10 ml) was stirred at room temperature for 2 hr, diluted, acidified and extracted with ether. Ether extract was washed with water, dried, concentrated and the residue recrystallised to furnish (E)-4-hydroxy-4-(4'-methyl phenyl)but-2-enoic acid (68) (0.21 g); m.p.95-97; IR (Nujol): 3500 (OH), 1700 (C=O); PMR ($CDCl_3$); 2.33 (3H, s, Ar-CH_3), 5.12 (1H, dd, J = 5 Hz and 2 Hz, >CH-OH), 5.89 (1H, dd, J = 16 Hz and 2 Hz, =C<H), 6.66 (2H, m, exchangable with D_2O; acidic H and hydroxyl H), 7.01 (5H, m, Ar-H and vinyl H); MS: m/z 192 (M^+);(Found: C, 68.39; H, 6.38. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%).

MnO_2 oxidation of 13

A mixture of 13 (0.3 g) and active MnO_2 (5.0 g) in dichloromethane (20 ml) was stirred at room temperature for 3 hr, filtered. Filtrate was concentrated and the

residue recrystallised (pet.ether) to furnish methyl (E)-4-keto-4-(4'-methylphenyl) but-2-en-oate (70) (0.27 g); yield: 91%; m.p.44-45° (lit.[26] m.p.45.5 - 46°); IR: 1730 (ester C=O), 1667 (benzylic C=O); PMR: 2.40 (3H , s, Ar-CH_3), 3.80 (3H, s, -$COOCH_3$), 6.66 (1H, d, J = 16 H_z, olefinic H α to ester C=O), 7.16 (2H, d, J = 8 H_z, aromatic H meta to benzylic C=O), 7.76 (3H, m, aromatic H ortho to benzylic C=O and olefinic H).

Action of ethanolic sodium hydroxide on 13:

(i) With excess of sodium hydroxide

A mixture of 13 (0.25 g, 0.12 mmol), sodium hydroxide (0.25 g, 0.62 mmol), ethanol (5 ml) and water (5 ml) was heated under reflux for 1 hr, cooled, diluted to 50 ml, acidified and extracted with ether. Ether extract was washed with water, dried and the solvent evaporated. Residue after recrystallisation furnished 1 (0.18 g); yield 78%; m.p.128-29° (lit.[24] m.p.129°); identity of 1 was established through IR, PMR and m.mp. determination with an authentic sample.

(ii) With equimolecular quantity of sodium hydroxide

A mixture of 13 (0.25 g, 0.12 mmol), sodium hydroxide (0.060 g, 0.15 mmol), ethanol (10 ml) and water (10 ml) was stirred at room temperature for 2 hr, diluted with water to 50 ml, acidified and extracted with ether. Ether extract was washed with water, dried and

concentrated. Residue after recrystallisation (pet.ether + ethylacetate (5:1) furnished E-4-hydroxy-4-(4'-methylphenyl)but-2-enoic acid (68) (0.186 g); yield 78%; m.p.96-98°; the acid (68) thus obtained was identical (IR, NMR and m.m.mp) with the sample obtained through an alternate route described above.

Methyl (E)-4-acetoxy-4-(4'-methylphenyl)but-2-enoate (69)

A mixture of 13 (0.30 g), pyridine (4 ml) and acetic anhydride (4 ml) was kept overnight. Work-up of the reaction mixture furnished 25 (0.32 g); TLC: R_f 0.63 (solvent A); IR: 1735 (broad, C=O); PMR: 2.02 (3H, s, -O-COC$\underline{H}_3$), 2.30 (3H, s, Ar-C$\underline{H}_3$), 3.65 (3H, s, -OC$\underline{H}_3$), 5.90 ⌈1H, dd, J = 16 Hz and 2 Hz, =CH (COOMe)⌋, 6.27 (1H, dd, J = 6 Hz and 2 Hz, >C$\underline{H}$OAc), 7.08 (5H, m, aromatic H and vinyl H); MS: m/z 248 (M^+);(Found: C, 67.88;H, 6.85. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%).

Action of p-toluene sulphonic acid on 13

A mixture of 13 (0.58 g), p-toluenesulphonic acid (0.06 g) and benzene (20 ml) was stirred at room temperature for 20 hr. The benzene layer was successively washed with aq. $NaHCO_3$, water and dried. Evaporation of benzene furnished ether 73 (0.45 g); TLC: R_f 0.65 (solvent system A); IR (liquid film): 1738 (ester C=O); PMR: 2.30 (6H, s, Ar-C$\underline{H}_3$), 3.63 (6H, s, -OC$\underline{H}_3$), 4.76 (2H, m, >CH-O-CH<), 5.93 ⌈2H, dd, J = 16 Hz and 2 Hz, = C$\underline{H}$(COOCH$_3$)⌋, 7.03

(10H, m, Ar-H and vinylic H);(Found: C, 73.24; H, 6 65. $C_{24}H_{26}O_5$ requires C, 73.07; H, 6.64%).

Action of ethanolic sodium hydroxide on 73

A mixture of 73 (0.25 g), sodium hydroxide (0.08 g), ethanol (10 ml) and water (10 ml) was stirred at room temperaturefor 5 hr. The reaction mixture was diluted to 50 ml, acidified,extracted with ether. Ether extract was washed with water, dried and concentrated. Residue after crystallisation (pet.ether) furnished 74 (0.18 g); m.p.174-79°; IR (Nujol): 3350 (broad, carboxylic OH), 1695 (C=O);(Found: C, 72.23; H, 5 70. $C_{22}H_{22}O_3$ requires C, 72.11; H, 6.05%).

Methyl 4-keto-4-phenylbutanoate (4)

Esterification of 4-keto-4-phenylbutanoic acid (3) m.p.114° (lit.[27] m.p.116°) using CH_3OH-H_2SO_4 method (reflux) furnished the keto-ester (4) in good yield. b.p.184°/30 mm (lit.[28] b.p.187°/30 mm); TLC: R_f, 0.58 (solvent system A) PMR: 2.60 (2H, t, J = 6 Hz, $-CH_2-COOCH_3$), 3.12 (2H, t, J = 6 Hz, $Ar-CO-CH_2-$), 3.62 (3H, s, $-OCH_3$), 7.12 to 7.70 (5H, m, aromatic H).

Methyl 3-bromo-4-keto-4-phenylbutanoate (8)

To the mixture of (4) (9.6 g, 0 05 mol) and anhydrous $AlCl_3$ (100 mg) in dry ether (20 ml), bromine (8 g, 0 05 mol) in dry CCl_4 (10 ml) was added dropwise. The reaction mixture was stirred for 10 min, diluted with water and

extracted with ether. The ether extract was washed with water and dried. The residue obtained after the evaporation of solvent furnished 8 (13.5 g); yield 100%; TLC: R_f 0.60 (solvent system A); IR (liquid film): 1740 (ester C=O), 1678 (benzylic C=O); PMR: 3.10 (2H, m, $-\underline{CH}_2-COOCH_3$), 3.60 (3H, s, $-OCH_3$), 5.23 (1H, dd, J = 6 H_z and 8 H_z, $-COC\underline{H}Br$), 7.40 (3H, m, aromatic H), 7.86 (2H, m, aromatic H ortho to carbonyl);(Found : C, 48.52; H, 4.27. $C_{11}H_{11}BrO_3$ requires C, 48.71; H, 4.06%).

NaBH$_4$ reductionof methyl 3-bromo-4-keto-4-phenylbutanoate(8)

A mixture of 8 (13.5 g) in methanol (100 ml), $NaBH_4$ (1.9 g) in water (10 ml) and sodium bicarbonate (4.2 g) in water (50 ml) was stirred at 28° for 1.5 hr, and worked up as in the case of 7, to furnish a mixture of cis-methyl 3,4-epoxy-4-phenylbutanoate (11), methyl (E)-4-hydroxy-4-phenylbut-2-enoate (14), 4-phenylbutanolide and 4 (9.6 g). Comparison of PMR spectrum of the above mixture with the PMR spectra of authentic samples of 11 and 14 showed 32% of 11 and 30% of 14. The conclusion thus drawn was in good agreement with the actual quantities of the pure components 11 and 14 isolated through chromatography.

The above mixture was chromatographed on alumina (Gr. II; 200 g). The column was eluted with successively with (i) pet.ether, (ii) 1% ethylacetate + pet.ether

(iii) 2% ethylacetate + pet.ether, (iv) 4% ethylacetate + pet.ether, (v) 6% ethylacetate + pet.ether and 10% ethyl acetate + pet.ether. Fraction (i) furnished 11 (2.8 g); b.p.150-52° (bath temp.)/2 mm; TLC: R_f 0.65 (solvent system A) IR (liquid film): 1738 (ester C=O); PMR: 2.30 (2H, m, $-C\underline{H}_2-CO_2CH_3$), 3.58 (3H, s, $-OC\underline{H}_3$), 3.96 (1H, d, J = 4 Hz, benzylic oxirane H), 7.16 (5H, s, aromatic H); (Found: C, 68.57; H, 6.40. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%).

Fraction (V), eluted with 6% ethylacetate + pet.ether furnished 14 (2.7 g); b.p 170-72° (bath temp.)/1 mm; TLC: R_f, 0.43 (solvent system A); IR (liquid film): 3530 (OH), 1725 (ester C=O); PMR: 3.53 (3H, s, $-COOC\underline{H}_3$), 3.90 (1H, broad s, exchangable with D_2O, hydroxyl H), 5.13 (1H, dd, J = 5 Hz and 2 Hz, $C\underline{H}-OH$), 5.93 (1H, dd, J = 16 H and 2 H , $=C\underline{H}(COOCH_3)$, 6.86 (1H, dd, J = 16 Hz and 5 H , olefinic H), 7.16 (5H, s, aromatic H), MS: m/z 206 (M^+); (Found: C, 68.62; H, 6.42. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%.

Methyl 3-keto-4-phenylbutanoate (18)

A mixture of 11 (0.5 g) in dry benzene (15 ml) and BF_3 etherate (1 ml) was kept at room temperature for 1.5 hr. The benzene layer was washed with water until free from acid, dried and benzene removed to furnish 18 (0.45 g). Yield 95%; b.p.150-60°(bath temp.)/2 mm, (lit.[29] b.p.125°/3 mm); TLC: R_f, 0.59 (solvent system A): IR: 1740 (esterC=O),

1725 (C=O); PMR: 3.28 (2H, s, $-C\underline{H}_2-Ar$), 3.62 (3H, s, $-OC\underline{H}_3$), 3.72 (2H, s, $-C\underline{H}_2-COOCH_3$), 7.11 (5H, s, aromatic).

Methyl 4-keto-4-(4'-methoxyphenyl) butanoate (6)

Esterification of 4-keto-4-(4'-methoxyphenyl)butanoic acid (5) m.p.144° (lit.[30] m.p.144.5 - 146.5°) furnished 6 b.p.195-200° (bath temp.)/1 mm; IR: 1740 (ester C=O), 1675 (Ar-C=O); PMR: 2.60 (2H, t, J = 6 Hz, $-C\underline{H}_2-COOCH_3$), 3.14 (2H, t, J = 6 Hz, $Ar-CO-C\underline{H}_2-$), 3.60 (3H, s, $-COOC\underline{H}_3$), 3.83 (3H, s, $Ar-OC\underline{H}_3$), 6.80 (2H, d, J = 8 Hz, aromatic H ortho to $-OCH_3$), 7.80 (2H, d, J = 8 Hz, aromatic H meta to $-OCH_3$).

Methyl 3-bromo-4-keto-4-(4'-methoxyphenyl) butanoate (9)

Bromination of 6 (11.1 g) with bromine (8.0 g) in presence of anhydrous aluminium chloride (100 mg) as per the above procedure furnished 9 (15 g); yield: 100%; TLC: R_f, 0.57 (solvent system A); IR: 1738 (ester C=O), 1680 (Ar-C=O); PMR: 3.10 (2H, m, $-C\underline{H}_2-COOCH_3$), 3.60 (3H, s, $-COOCH_3$), 3.83 (3H, $Ar-OC\underline{H}_3$), 5.24 (1H, dd, J = 6 Hz and 8 Hz, $-COC\underline{H}Br$), 6.80 (2H, d, J = 8 Hz, aromatic H ortho to $-OCH_3$), 7.80 (2H, d, J = 8 Hz, aromatic H meta to $-OCH_3$).

$NaBH_4$ reduction of methyl 3-bromo-4-keto-4-(4'-methoxyphenyl) butanoate (9)

Sodium borohydride reduction of 9 (10.00 g) in the presence of sodiumbicarbonate as per the above procedure furnished 21% of cis-methyl 3,4-epoxy-4-(4'-methoxyphenyl)

butanoate (12) and 38% of methyl (E)-4-hydroxy-4-(4'-methoxyphenyl)but-2-enoate (15), after chromatography over grade II alumina.

Pet.ether fraction furnished 12: TLC: R_f 0.62 (solvent system): IR (liquid film): 1738 (C=O); PMR: 2.31 (2H, m, $-C\underline{H}_2-CO_2CH_3$), 3.59 (3H, s, $-COOC\underline{H}_3$), 3.80 (3H, s, $Ar-OC\underline{H}_3$), 3.94 (1H, d, J = 4 Hz, benzylic oxirane H), 7 04 (4H, m, aromatic H).

8% Ethylacetate + pet.ether fraction yielded 15; TLC: R_f 0.40 (solvent system A); IR (liquid film): 3555 (OH), 1722 (ester C=O); PMR: 3.60 (3H, s, $-COOC\underline{H}_3$), 3.75 (3H, s, $Ar-OC\underline{H}_3$), 5.03 (1H, dd, J = 5 Hz and 2 Hz, $C\underline{H}-OH$), 5.95 [1H, dd, J = 16 Hz and 2 Hz, $=C\underline{H}(CO_2CH_3)$], 7.00 (5H, m, aromatic H and vinyl H).

Sodium borohydride reduction of methyl (E)-4-keto-4-(4'-methylphenyl)but-2-enoate (70)

To a mixture of 70 (0.50 g) in methanol (15 ml), sodium borohydride (0.1 g) in water (5 ml) was added dropwise at 5-10° (bath temperature). Reaction mixture was slowly warmed to room temperature at interval of 30 min. and stirred at room temperature for 1 hr. Reaction mixture was diluted with water and extracted with ether. Ether extract was washed with water, dried and concentrated. Residue furnished a mixture of 13, 16 and 4-(4'-methylphenyl)-butane-1,4-diol (71). Comparison of PMR spectrum

of the above residue with the PMR spectra of authentic samples of 13, 16 and 71 showed that the residue was composed of 1:1:1 mixture of 13, 16 and 71. The conclusion thus drawn was in good agreement with the actual quantities of the pure components 13, 16 and 71 isolated through chromatography over grade II alumina (1:20 ratio).

Fraction eluted with 12% ethylacetate + pet.ether furnished 71. IR: 3550 (OH); PMR: 1.63 (4H, m, $-C\underline{H}_2-C\underline{H}_2-CH_2-OH$), 2.36 (3H, s, $Ar-C\underline{H}_3$), 3.50 (2H, m, $-C\underline{H}_2-OH$), 4.13 (2H, m, exchangable with D_2O, hydroxyl H), 4.56 (1H, m, $Ar>C\underline{H}.OH$), 7.2 (4H, s, aromatic H).

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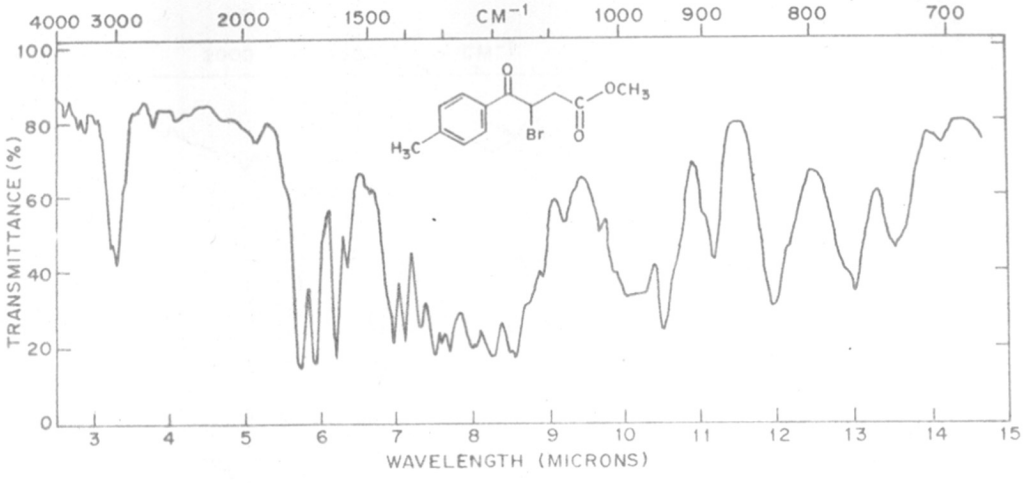
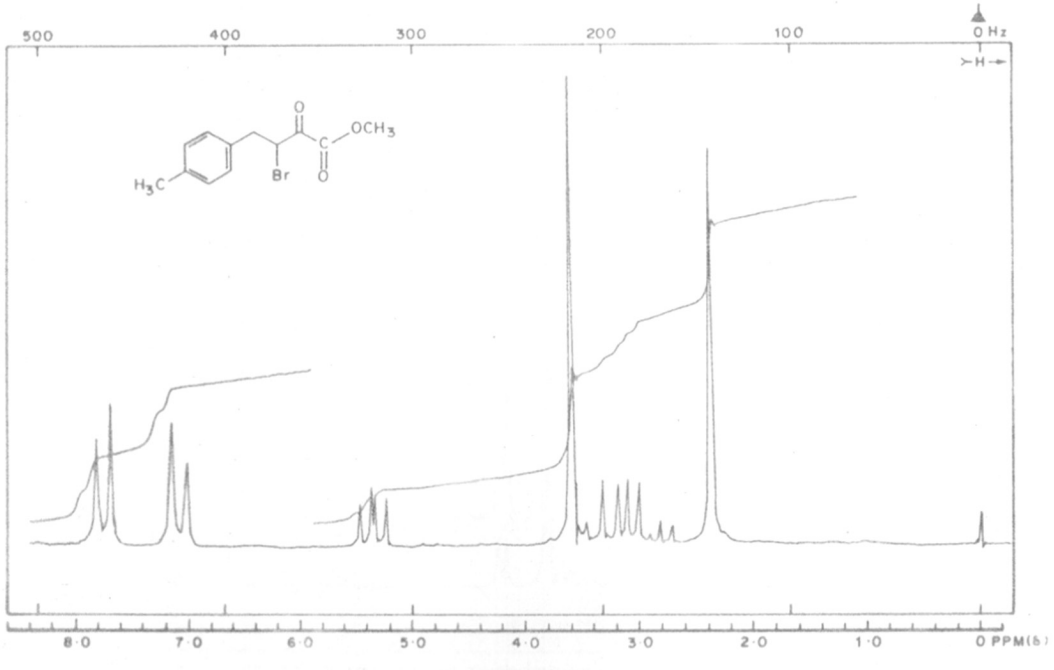
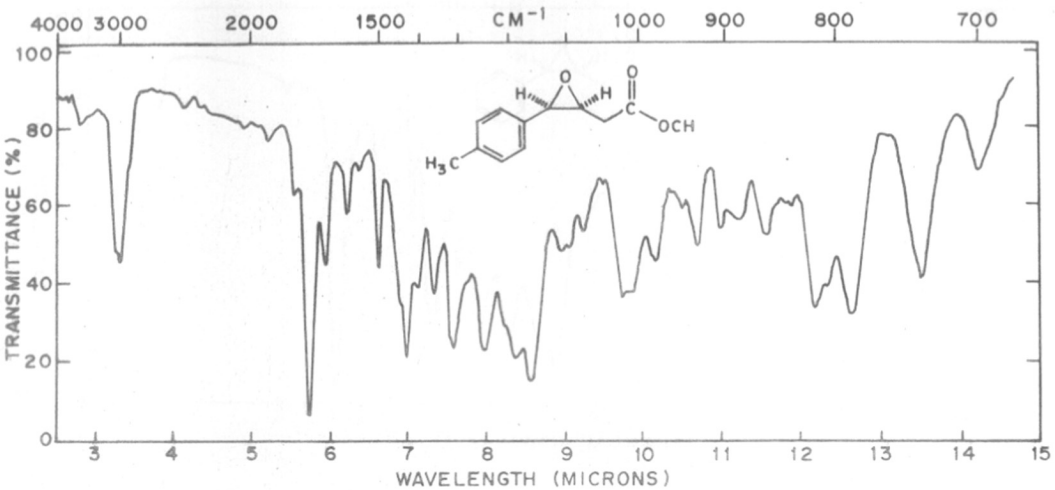
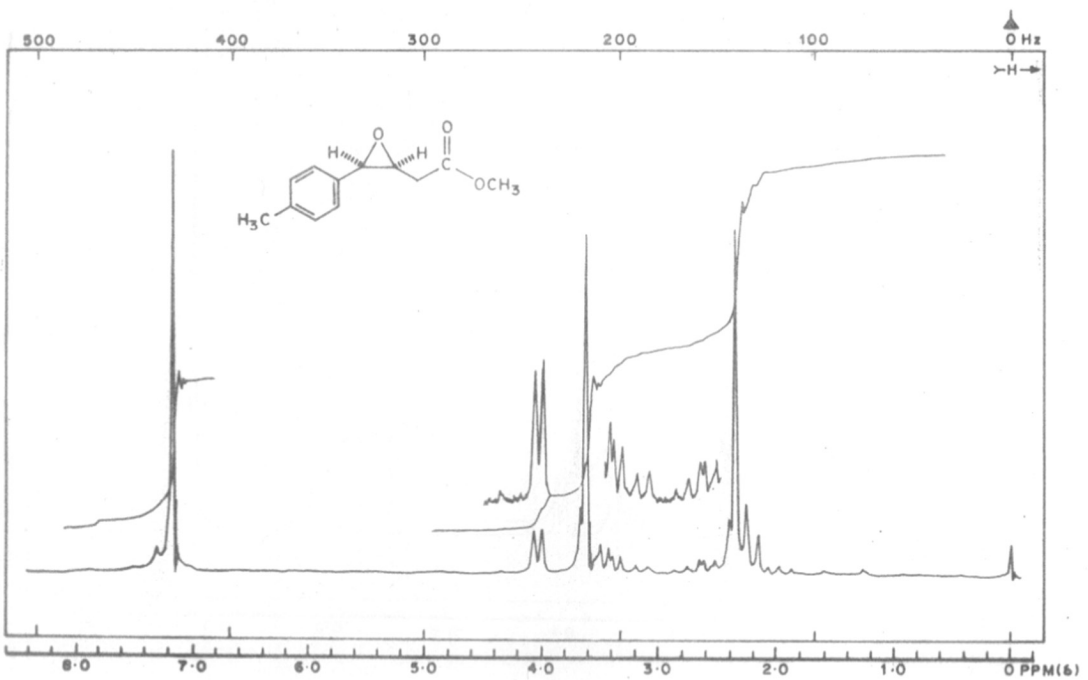




IR & NMR OF METHYL 4-KETO-4-(4'-METHOXYPHENYL) BUTANOATE (7)





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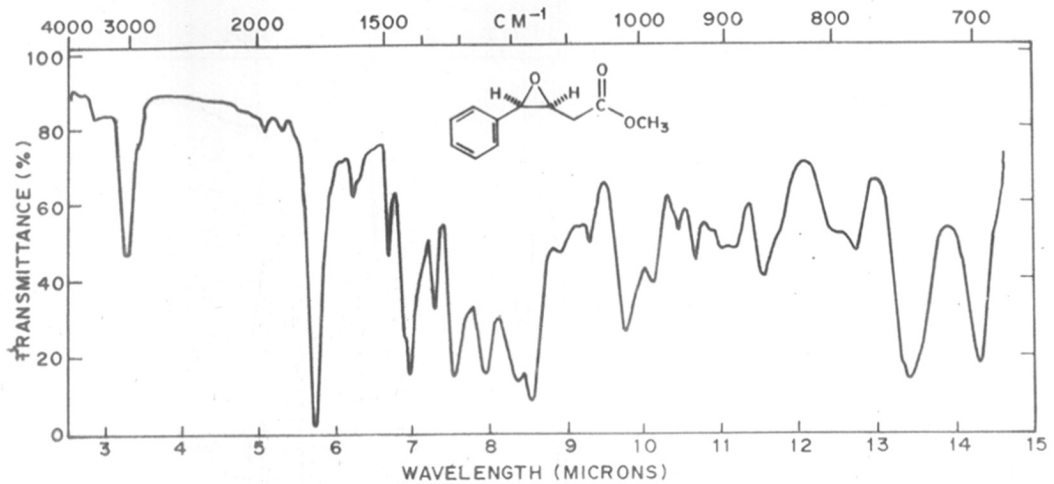

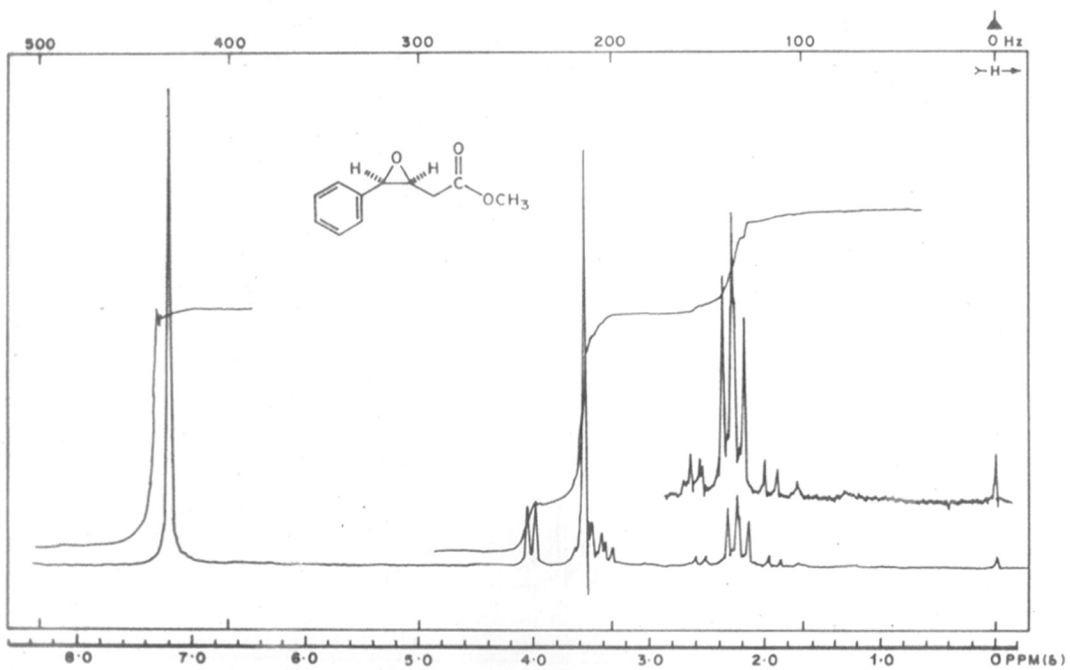

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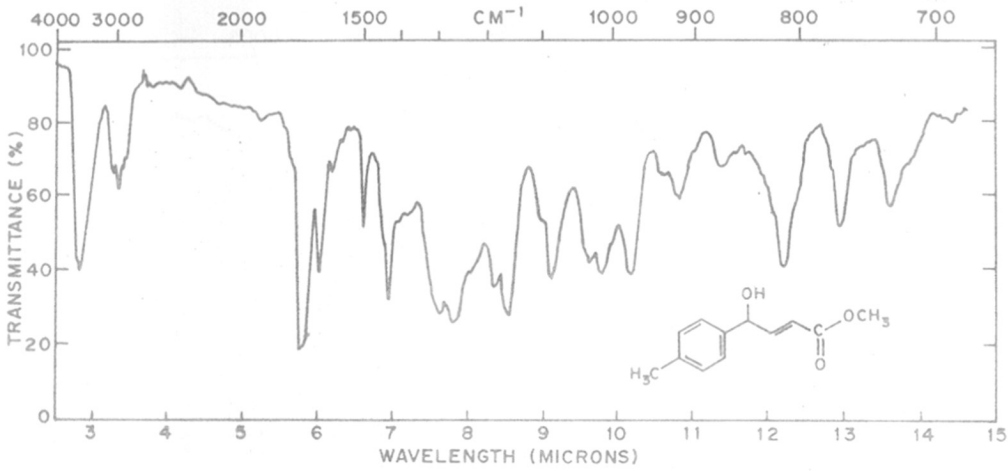

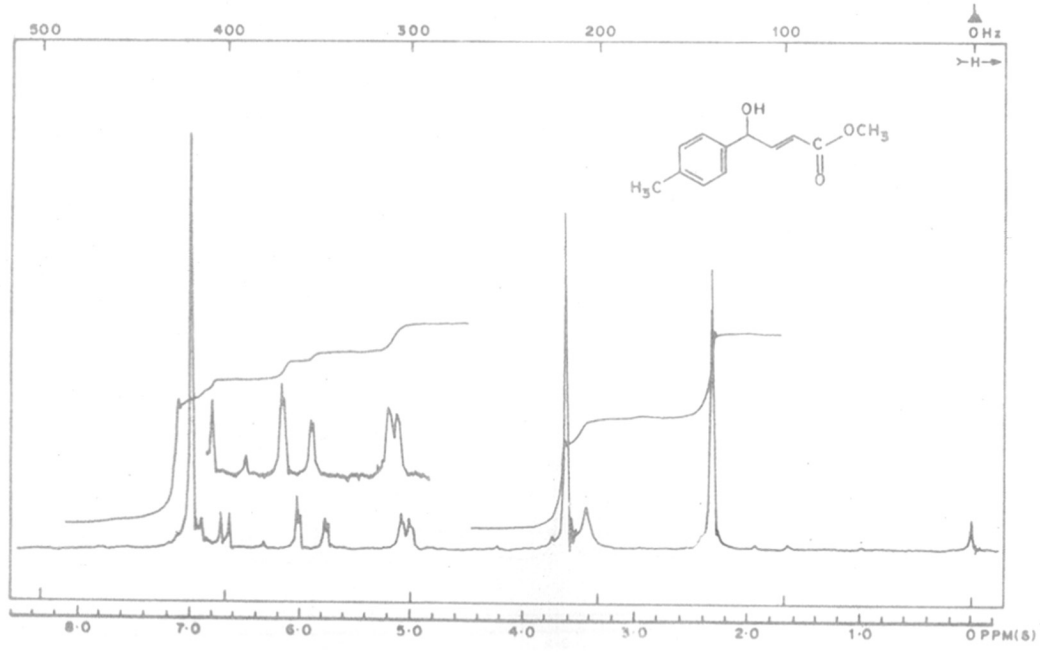

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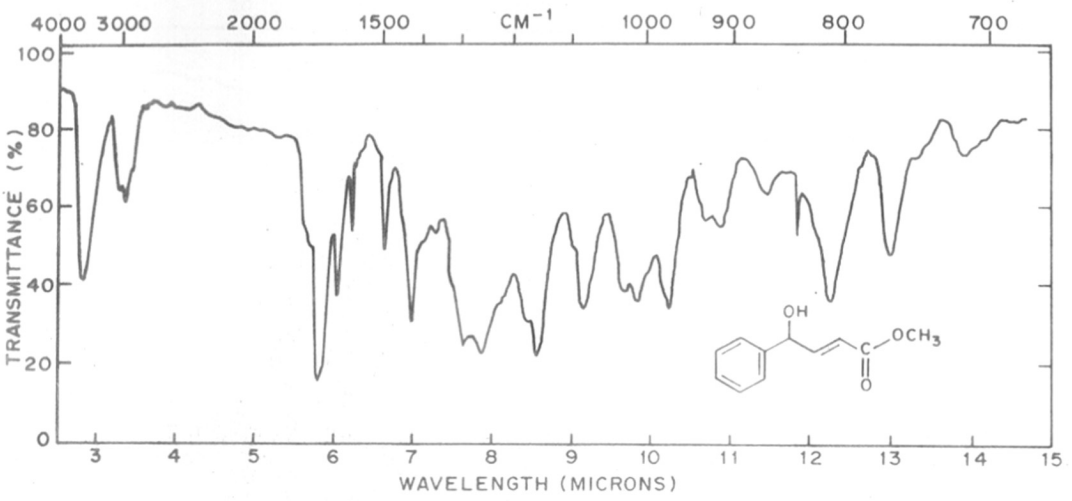

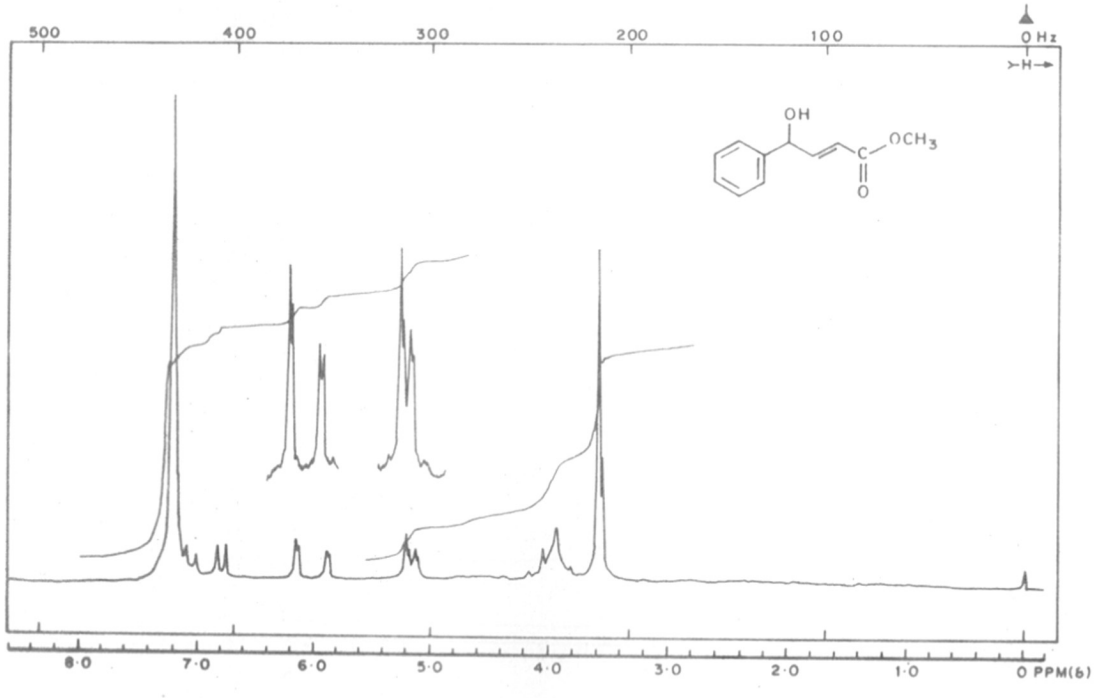

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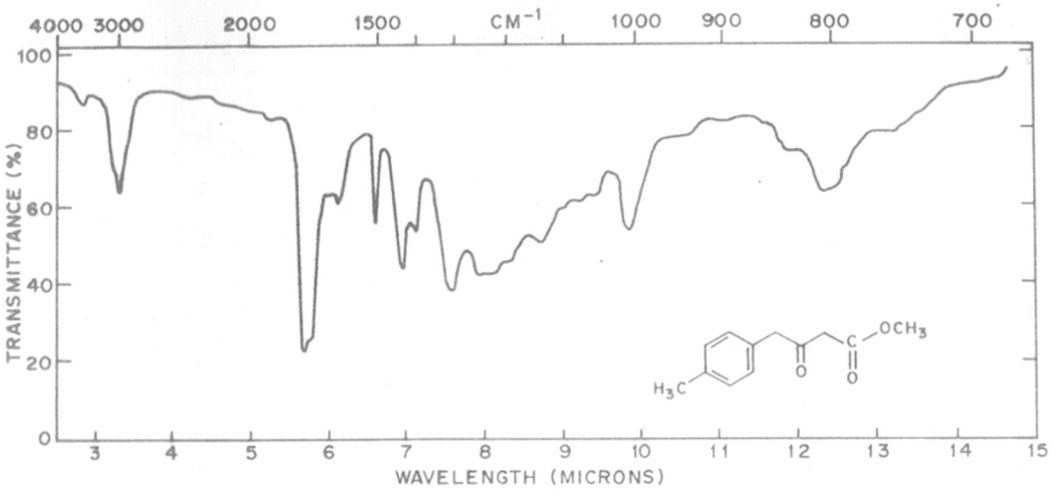

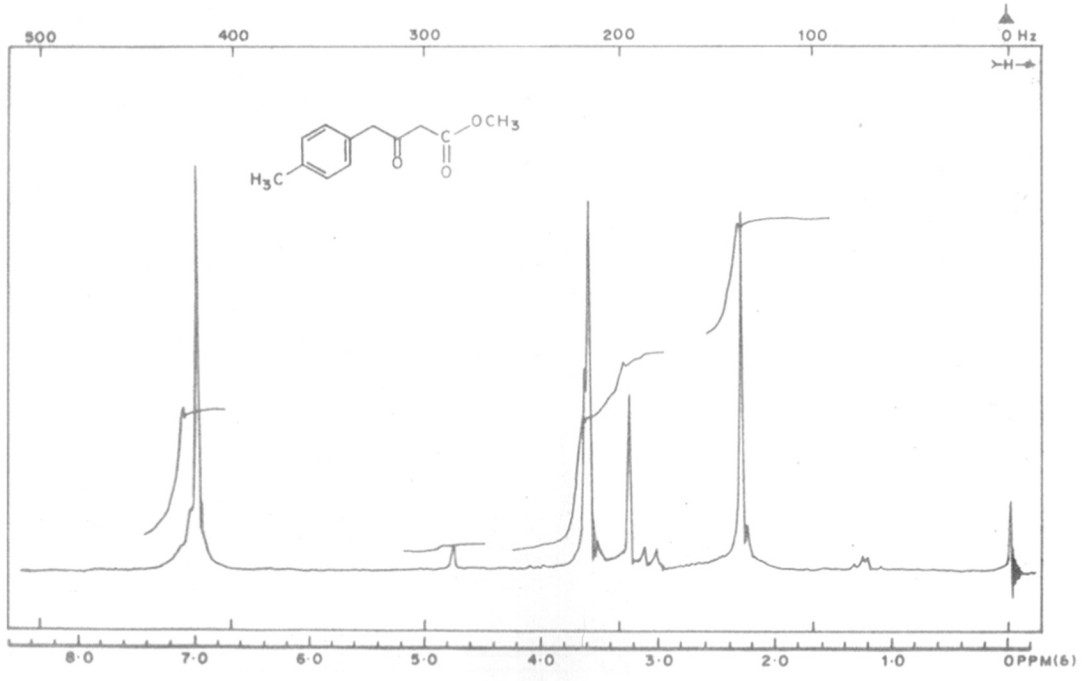

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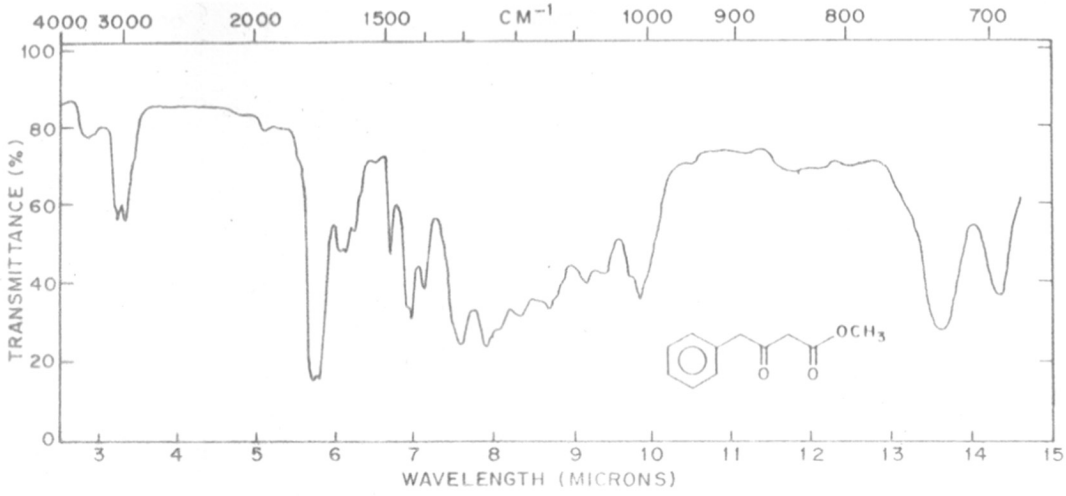

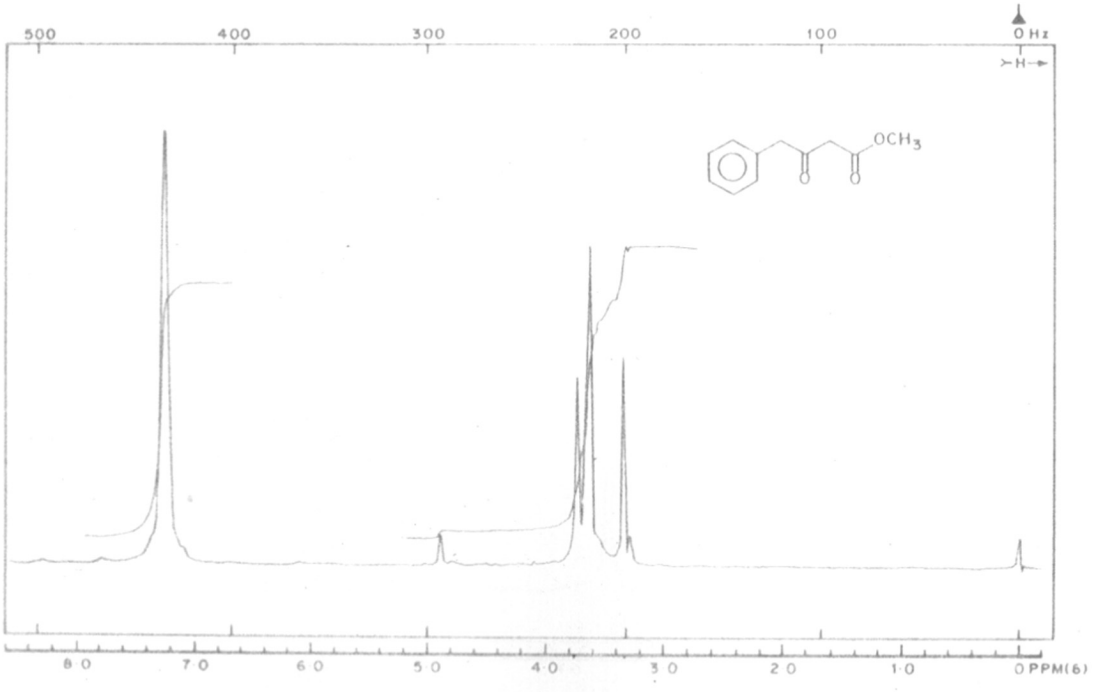

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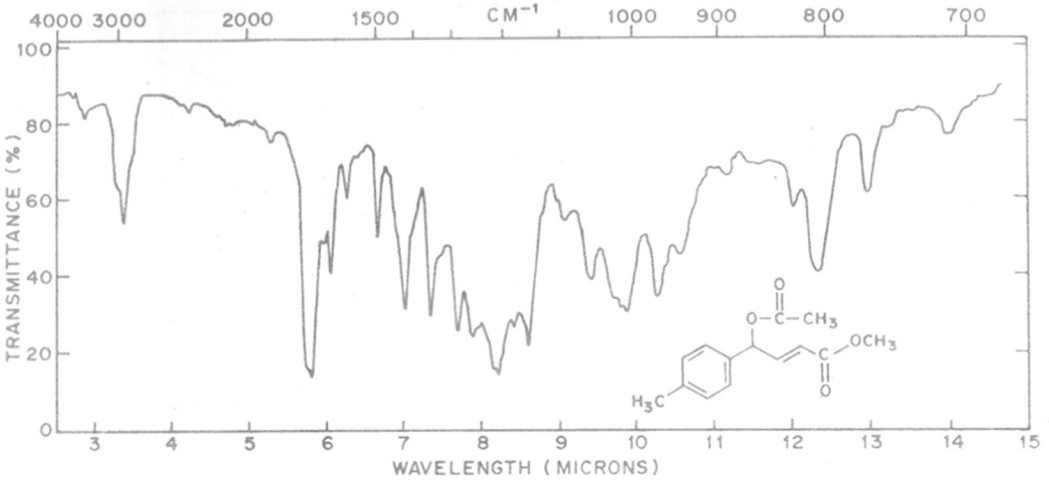
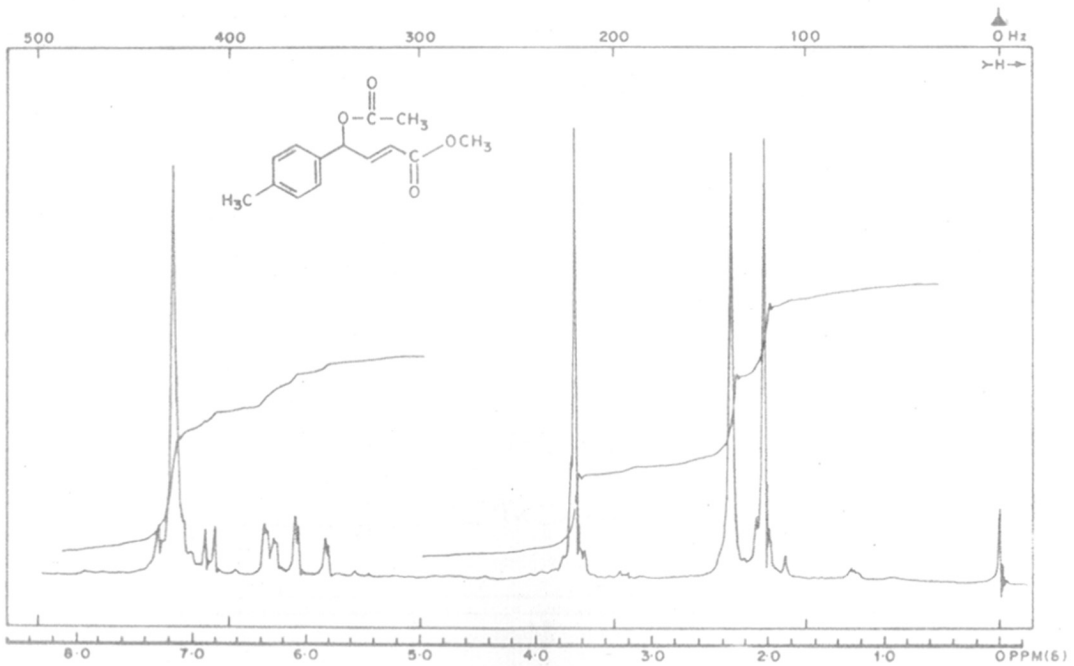
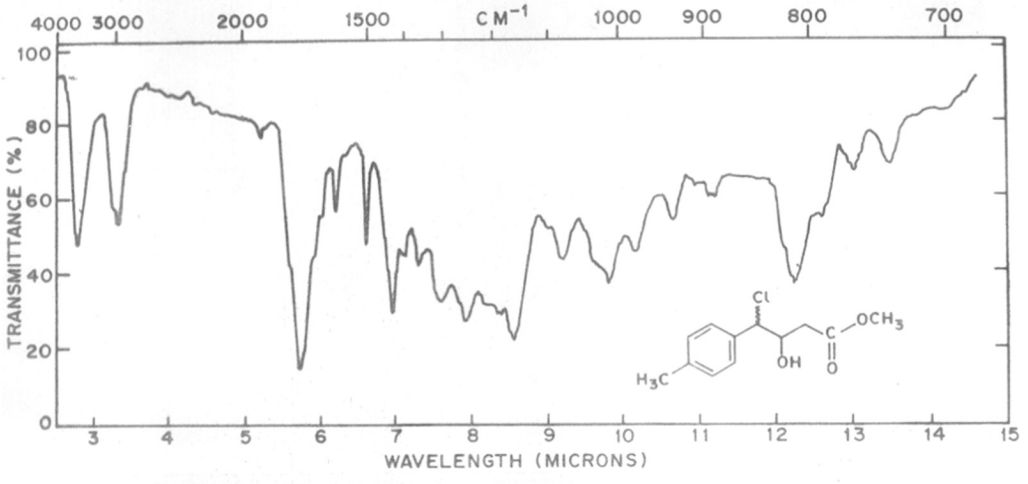
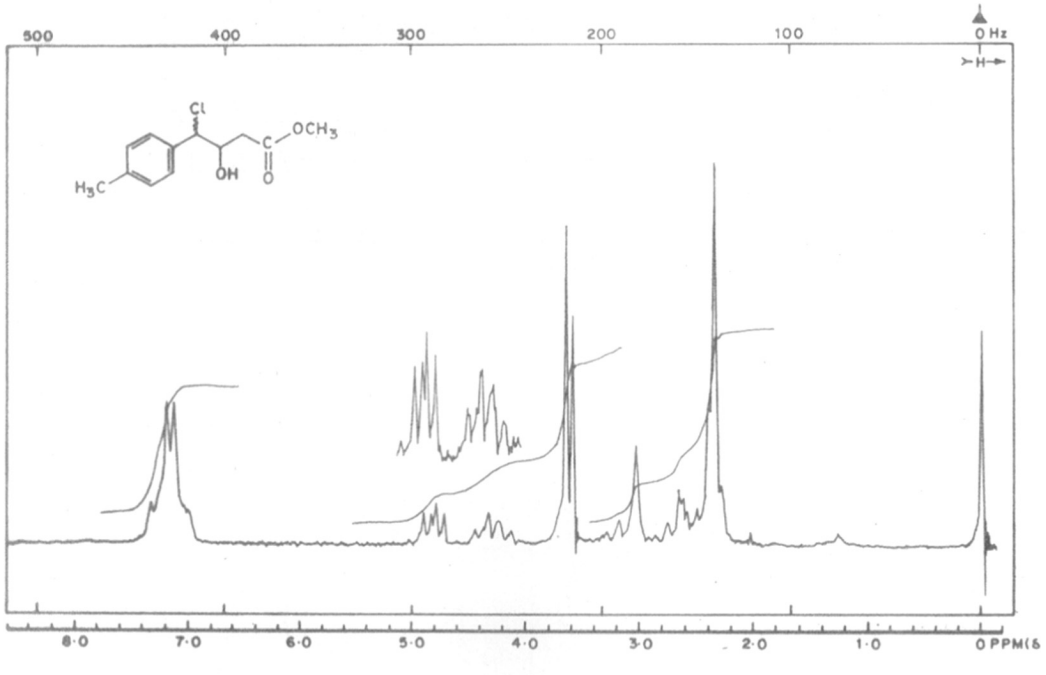




IR & NMR OF METHYL (E)-4-ACETOXY-4-(4'-METHYL PHENYL) BUT-2-ENOATE (69)





IR & NMR OF METHYL 4-CHLORO-3-HYDROXY-4-(4'-METHYL PHENYL) BUTANOATE (75)

CHAPTER-2

SYNTHESIS OF 2-DEOXY-DL-ERYTHRO PENTOSE AND 2-DEOXY-DL-ERYTHRO-PENTITOL

SUMMARY

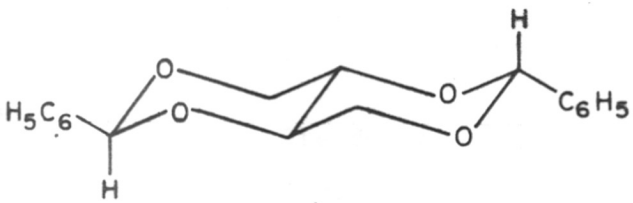
Synthesis of deoxy-sugars, 2-deoxy-(DL)-erythro-pentose and 2-deoxy-(DL)-erythro-pentitol are presented in this chapter.

Action of N-bromosuccinimide on 1,3:2,4-di-O-benzylidene-erythritol (1) furnishes 3-O-benzoyl-2,4-O-benzylidine-1-bromo-1-deoxy-DL-erythritol (2), which on reaction with sodium cyanide is transformed into 4-O-benzoyl-3,5-O-benzylidene-2-deoxy-DL-erythro-pentononitrile (3). Reduction of 3 with Raney nickel-sodium hypophosphite in the presence of N,N'-diphenylethylene-diamine gives (±)-3-O-benzoyl-2,4-O-benzylidene-1-deoxy-1-(1,3-diphenyl-2-imidazolidyl)-erythritol (4). Deblocking of 4 first in alkaline condition and then in acid condition furnishes 2-deoxy-DL-erythro-pentose (7), characterised as its diacetate (8). Acid hydrolysis of 3 furnishes lactone (9), characterised as diacetate (10), which on LAH reduction furnishes 2-deoxy-DL-erythro-pentitol (11) characterised as tetraacetate (12).

Preparation of starting material, erythritol (13) and its diastereomer, threitol (15) are described.

It is shown that PMR spectrum can be used to distinguish erythritol (13) and threitol (15).

CHART I



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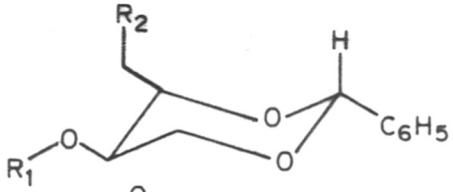
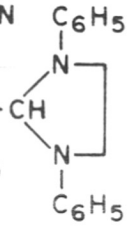
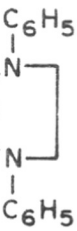


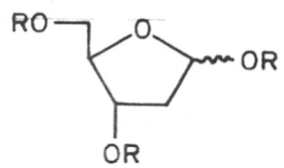
2. $R_1 = C_6H_5-\overset{O}{\overset{\|}{C}}-$, $R_2 = Br$

3. $R_1 = C_6H_5-\overset{O}{\overset{\|}{C}}-$, $R_2 = CN$

4. $R_1 = C_6H_5-\overset{O}{\overset{\|}{C}}-$, $R_2 =$ 

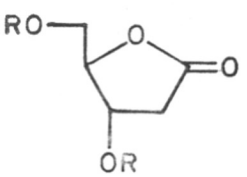
5. $R_1 = H$, $R_2 =$ 

6. $R_1 = CH_3-\overset{O}{\overset{\|}{C}}-$, $R_2 = CN$



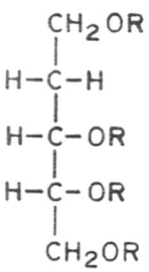
7. $R = H$

8. $R = -\overset{O}{\overset{\|}{C}}-CH_3$



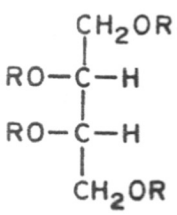
9. $R = H$

10. $R = -\overset{O}{\overset{\|}{C}}-CH_3$



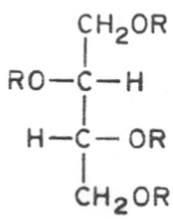
11. $R = H$

12. $R = -\overset{O}{\overset{\|}{C}}-CH_3$



13. $R = H$

14. $R = -\overset{O}{\overset{\|}{C}}-CH_3$



15. $R = H$

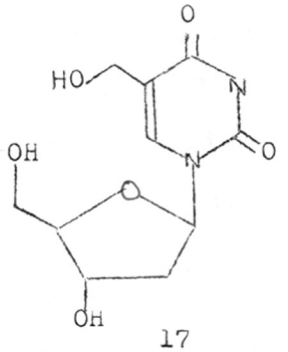
16. $R = -\overset{O}{\overset{\|}{C}}-CH_3$

INTRODUCTION

The deoxy sugars, long known as components of natural products, are an important class of carbohydrates. Unlike other classes, many deoxy sugars confer unique biological properties on the natural products of which they are a part. The commonly recognized members that have received attention from the biological stand-point have been the terminal-deoxy and 2-deoxy sugars occurring as components of cardiac glycosides and as antigenic determinants in bacterial polysaccharides. Several unusual deoxy sugars have been isolated from other natural products in recent years[1]. Moreover, 2-deoxy-pentoses form the carbohydrate component of the deoxy-nucleic acids and are therefore of particular biological importance[2]. In particular, 2-deoxy-D-erythro-pentose (7) (2-deoxy-D-ribose)* one of the members of this class has been extensively investigated since (i) it occurs naturally as the carbohydrate component of DNA and

*Here we have shown, 2-deoxy-erythro-pentose (7) in the furanose form for the sake of convenience, since in complex natural products 7 is present in furanose form. However, it is to be noted that the parent sugar 7 can exist in pyranose as well as furanose modifications ref.: R.V. Lemieux, I.D. Stevens, Can. J. Chem., 44, 249 (1966).

(ii) nucleosides derived from it show antiviral and antineoplastic activity. For example[3], 5-hydroxymethyl-



17

2'-deoxyuridine (17) inhibits the replication of Escherichia Coli 15T⁻, the reproduction of Ehrlich ascites carcinoma cells as well as a number of other mammalian cells, and the propagation of vaccinia and herpes simplex viruses. Further 5-hydroxymethyl-2'-deoxyuridylate competitively inhibits both prokaryotic and eukaryotic thymidylate synthetase and has been found in the DNA of several bacillus substilis phages in place of thymidine.

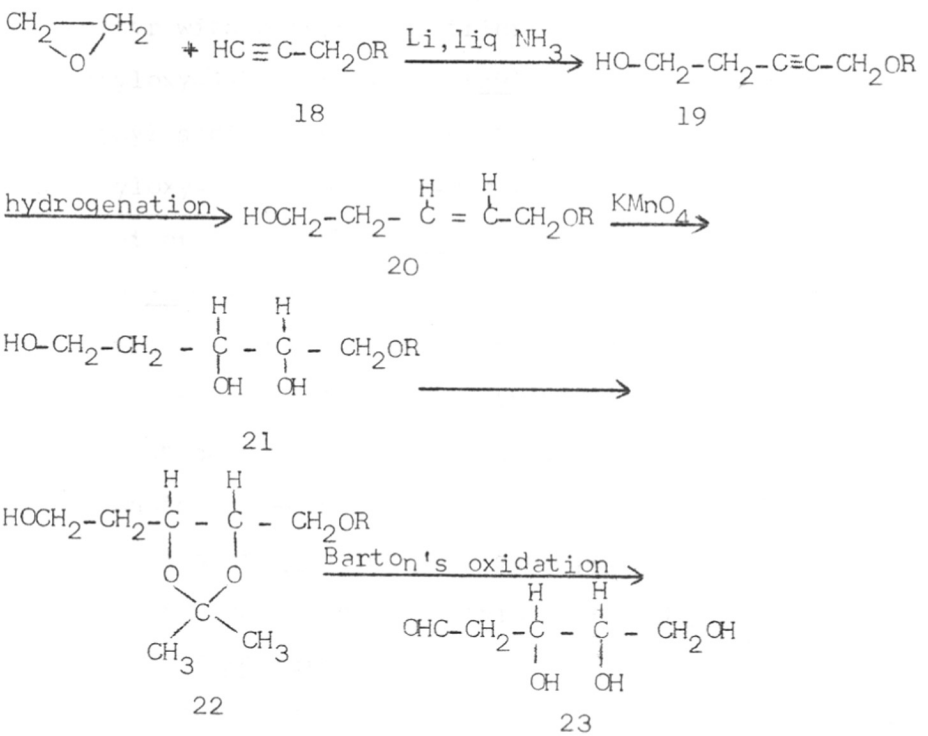
Some of the available approaches in literature for the synthesis of 2-deoxy-DL-ribose are presented here.

1. M. Nakagawa et al.[4] prepared 2-deoxy-DL-erythro-pentose (23) starting from ethylene oxide and propargyl alcohol (Scheme A). The reaction of lithium acetylide of propargyl alcohol derivative (18) in refluxing liquid ammonia with ethylene oxide gave C_5-acetylenic compound (19). A half-reduction of 19 by means of

Lindlar catalyst afforded C_5-cis-ethylenic compound (20). 20 was treated with potassium permanganate to cause cis-hydroxylation of the cis-ethylenic bond to furnish triol (21), which on reaction with acetone and anhydrous cupric sulfate yielded 22. The Barton's oxidation of the crude 22, followed by acid hydrolysis of the protective groups resulted in 23.

In another route (Scheme B), 23 was prepared by the hydroboration of DL-erythro-4-pentyn-1,2,3-triol (27) followed by hydrogen peroxide oxidation. Reaction between epichlorohydrin (25) and sodium acetylide (24) furnished trans-2-pentene-4-yn-1-ol (26), which on trans-hydroxylation by means of performic acid yielded DL-erythro-4-pentyn-1,2,3-triol (27). Triol 27 was treated with excess of bis (1,2-dimethylpropyl)borane and the reaction product was oxidised with hydrogen peroxide under careful addition of 1N sodium hydroxide solution to furnish 23.

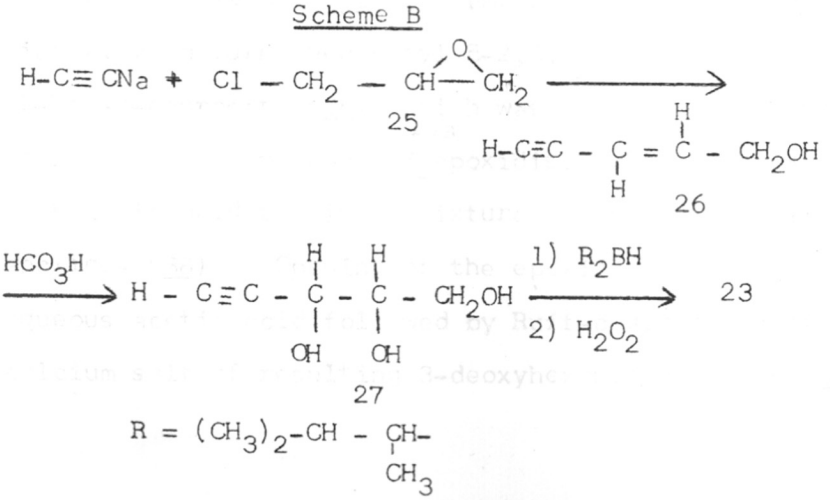
Scheme A



18 19 20 21 22 23

R = tetrahydropyranyl

Scheme B



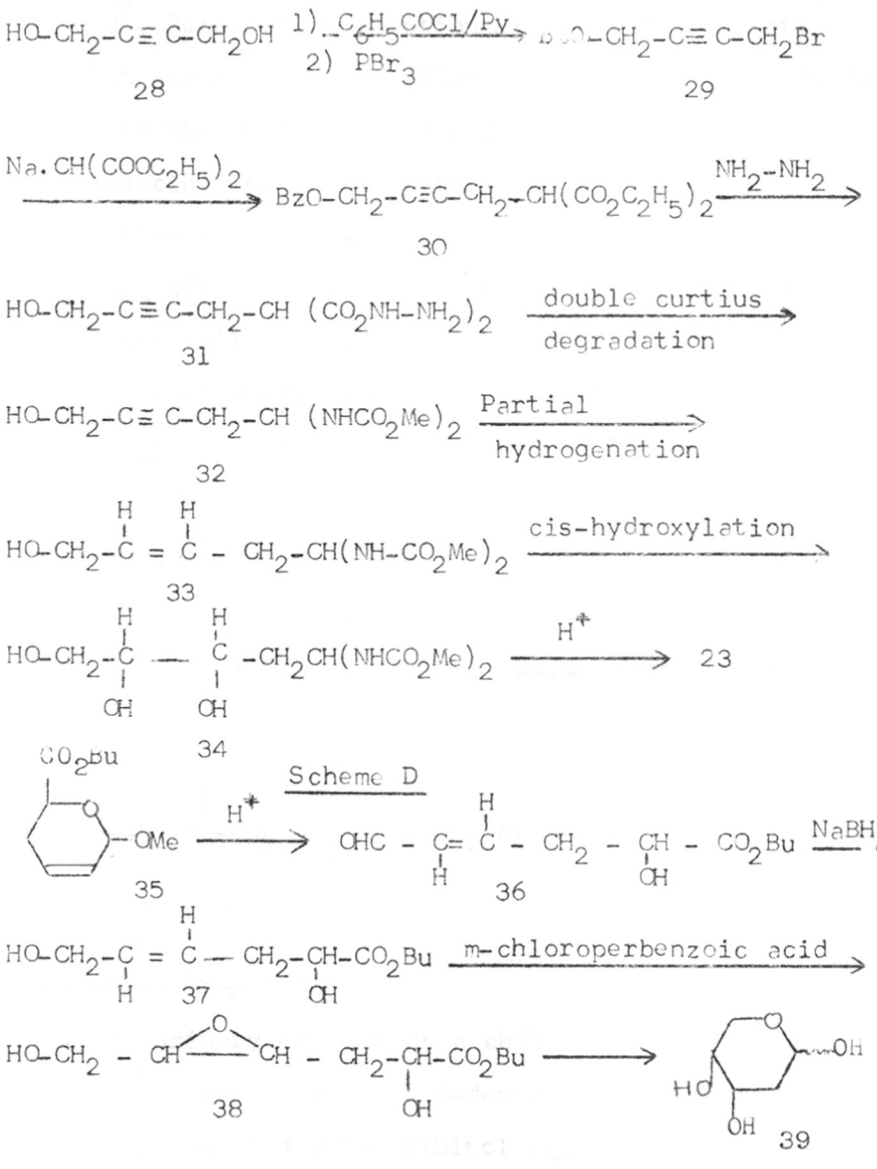
25 26 27 23

R = $(CH_3)_2-CH-\underset{CH_3}{CH}-$

2. This method involved[5] the conversion of but-2-yne-1,4-diol (28) into 2-deoxy-DL-ribose (23) (Scheme C). Monobenzoylation of 28 and treatment of the resulting half-ester with phosphorous tribromide furnished 1-benzoyloxy-4-bromobut-2-yne(29). The bromo-compound (29) with ethyl sodiomalonate gave the expected ethyl 5-benzoyloxy-pent-3-yne-1:1-dicarboxylate (30). Treatment of hydrazine on 30 yielded dihydrazide (31). Compound 31 was subjected to double Curtius degradation with nitrous acid, followed by treatment of the resulting diazide with methanol produced the acetylenic diurethane (32), which on partial catalytic hydrogenation gave the corresponding cis-ethylenic diurethane (33). Cis-hydroxylation of 33 using potassium permanganate or osmium tetroxide-hydrogen peroxide yielded 34. Acid hydrolysis of 34 furnished 23.

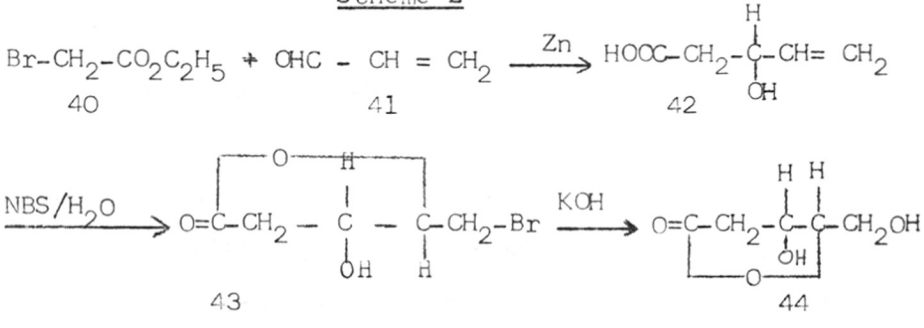
3. M.Chmielewski[6] reported a synthesis of 2-deoxy-DL-ribose (39) starting from butyl 2-methoxy-5,6-dihydro-2H-pyran-6-carboxylate (35) (Scheme D). Compound 35 with mineral acid furnished butyl E-2,3,4-tri-deoxy aldehydo-DL-hex-2-enuronate (36), which was easily reduced to diol (37). Compound 37 was epoxidised with m-chloro-perbenzoic acid to give a mixture of stereoisomeric epoxides (38). Opening of the epoxide ring of 38 with aqueous acetic acid followed by Ruff-degradation of the calcium salt of resulting 3-deoxyhexonic acid gave 39.

Scheme C


HO-CH2-C≡C-CH2OH
1) C6H5COCl/Py
2) PBr3
BzO-CH2-C≡C-CH2Br
28
29
Na.CH(COOC2H5)2
BzO-CH2-C≡C-CH2-CH(CO2C2H5)2
NH2-NH2
30
HO-CH2-C≡C-CH2-CH (CO2NH-NH2)2
double curtius degradation
31
HO-CH2-C≡C-CH2-CH (NHCO2Me)2
Partial hydrogenation
32
cis-hydroxylation
33
H+
23
34
CO2Bu
OMe
35
Scheme D
OHC - C= C - CH2 - CH - CO2Bu
NaBH4
36
m-chloroperbenzoic acid
37
38
39

4. This method of preparation of 2-deoxy-DL-ribose (23) involved[7], Reformatsky reaction of ethylbromoacetate (40) with acrolein (41), followed by alkaline hydrolysis to furnish DL- -hydroxy acid (42), which on treatment with N-bromosuccinimide in water followed by chromatographic purification on silica-gel yielded bromo-lactone 43. Lactone 43 with aqueous 1N potassium hydroxide at room temperature followed by standing at pH 1 for 24 hr afforded 2-deoxy-erythro-penteno-γ-lactone (44). Lactone (44) was reduced by the use of bis (1,2-dimethyl-propyl) borane (disiamylborane) to furnish 23; reaction sequence is shown in scheme E.

Scheme E



The urinary extract of a child with strabismus contained[8] large amounts of 2-deoxy-erythro-penteno-1,4-lactone (9) and 2-deoxy-D-ribitol (11) (2-deoxy-D-erythro-pentitol). 9 and 11 were not detected in normal urine.

The accumulation of these compounds may result from a defect in 2-deoxy-D-ribose catabolism.

Further, literature reports the use of 2-deoxy-D-ribitol as important intermediate for organic synthesis, some of the examples are given below:

1. Some of the ketoses exhibit biological activity and they are constituents of some antibiotics; hydrazones of ketoses inhibit nucleo-and proteo-synthesis in tumorous cells[9]. 2-Deoxy-D-ribitol (11) was used in the preparation of one of the such ketoses[10], 4-deoxy-L-glycero-2-pentulose.

2. 2-Deoxy-D-ribitol was used in the preparation of tetrahydrofuran derivative[11], by the acid catalysed dehydration.

Usually 2-deoxy-D-ribitol (11) is prepared[11] by sodium borohydride reduction of 2-deoxy-D-ribose (7) in alkaline condition.

Erythritol (13), used as starting material in the synthesis of 2-deoxy-DL-ribose (7) (which is presented in this chapter) is an optically inactive, meso compound, having very sweet taste. It was obtained microbiologically from sugars by means of various species of fungi, by yeasts of the zygosaccharomyces class and by various osmophilic yeasts. Erythritol was prepared-

(i) by chemical conversion of glucose to erythrose using LTA, followed by reduction[12] (ii) by LAH reduction

of ester of meso-tartaric acid[13] (iii) by hydration of meso 1,2:3,4-diepoxybutane[14] (iv) by cis hydroxylation of cis-2-butene-1,4-diol using hydrogen peroxide in the presence of osmium tetroxide[15] (v) by the action of potassium acetate and acetic acid mixture on bromohydrin obtained from cis-but-2-ene-1,4-diol-diacetate[16]. But in this method, besides erythritol, considerable quantity of threitol is also formed.

Threitol (15) exists in D and L form, having sweet taste but is not found in nature. The action of the wood-rotting fungus, armillaria mellea on glucose leads to D-threitol[17]. The two enantiomorphs were prepared by reduction of D- and L-threose respectively. Trans-hydroxylation of cis-but-2-ene-1,4-diol furnished DL-threitol[16].

PRESENT WORK

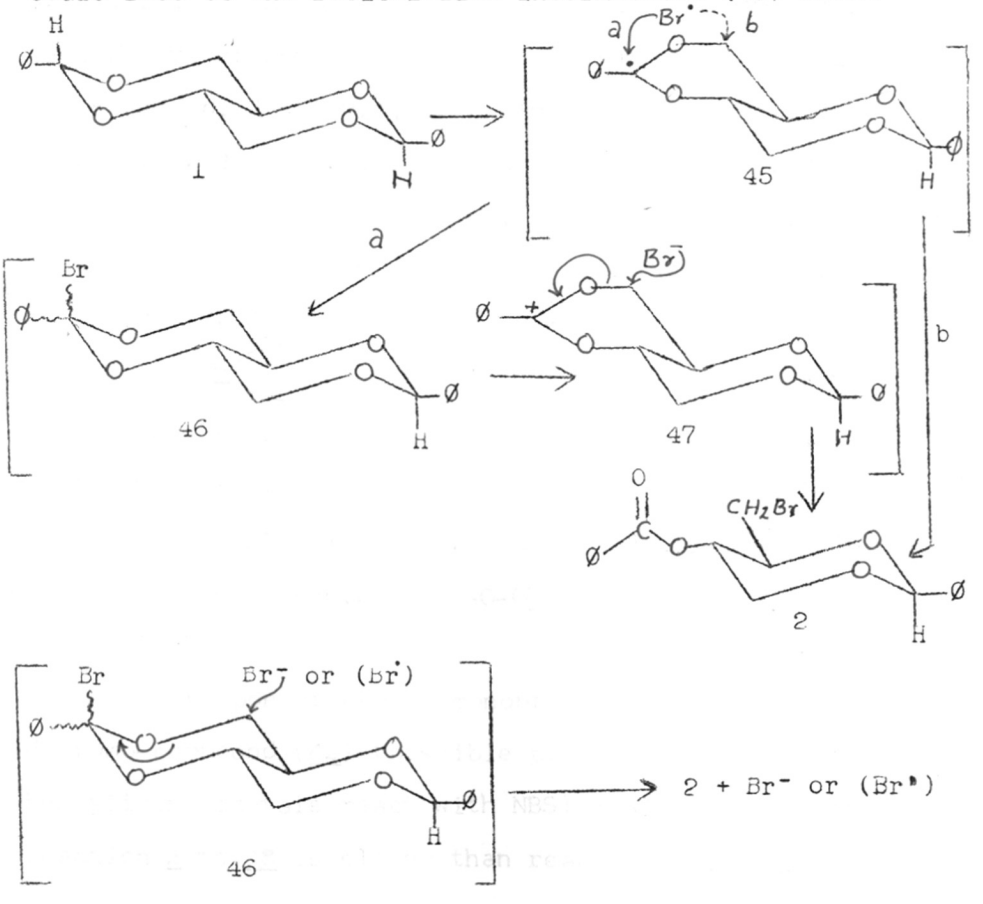
A synthesis of 2-deoxy-DL-erythro-pentose (7) and 2-deoxy-DL-erythro-pentitol (11) starting from erythritol (13) is described. Convenient, modified routes for preparation of erythritol (13) (in connection with above synthesis) and its diastereomer, threitol (15) are elaborated. It is shown that PMR spectrum can be used to distinguish erythritol (13) and threitol (15).

1,3:2,4-Di-O-benzylidene-erythritol (1) is prepared according to literature method[12] using erythritol (13) and benzaldehyde. Literature reports[19] that 1,3:2,4-di-O-benzylidene-erythritol must have the bicyclic structure (1) which is related to trans-decalin and has two equatorial phenyl groups, a thermodynamically very stable structure. Further 1 is an interesting example of the group of compounds which are optically inactive because of a centre of symmetry; the product of partial hydrolysis is a DL-mixture.

The action of N-bromosuccinimide (NBS) on benzylidene acetals has been extensively studied by Hanessian[20] and is known to give bromo-benzoates; we have utilised this strategy to transform 1 into bromo-compound (2). Thus reaction of 1 with equimolecular quantity of NBS and catalytic amount of benzoyl peroxide in CCl_4 at 76° furnished the bromo-compound (±)-2 in 55% yield; however

yield when corrected for recovered starting material (1) was 75%.

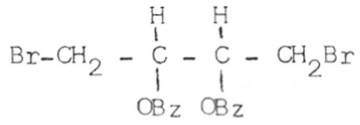
Based on the investigation of Hanessian[21], we can predict two pathways for the reaction of dibenzylidene acetal (1) with NBS under the above experimental conditions: an overall free-radical mechanism and a rdical hydrogen abstraction step followed by a concerted-type or ionic termination reaction. The initial hydrogen abstraction could lead to the radical-like intermediate (45) which



then reacts by pathways a or b. The pathway a could give a bromo-acetal intermediate 46 which could disproportionate into the benzoxonium ion 47 and bromide ion. Attack of the bromide ion at the least hindered C-6 position in 47 would give 2. The product 2 could also be formed by a direct attack of a bromine atom via pathway b or by a concerted attack (ionic or radical) via 46.

The bromo-compound (2) is analysed for $C_{18}H_{17}BrO_4$. IR spectrum shows band at 1735 cm^{-1} assigned to carbonyl of benzoate. PMR spectrum shows signals at 3.58 (2H, d, J = 6 Hz), 3.76 (1H, t, J = 10 Hz), 4.18 (1H, m), 4.53 (1H, dd, J = 5 and 10 Hz), 5.14 (1H, dt, J = 5 and 10 Hz), 5.61 (1H, s), 7.40 - 8.00 (10H, m). The 2H doublet at 3.58, 1H singlet at 5.61 and 10H multiplet at 7.40 to 8.00 are assigned to $-C\underline{H}_2Br$, benzylic H of the system Ø - $C\underline{H}(O-)(O-)$ and aromatic H respectively, whereas 1H triplet at 3.76 and 1H doublet of doublets at 4.53 are assignable to axial and equatorial H of $-OC\underline{H}_2$. The remaining 1H multiplet at 4.18 and 1H doublet of triplets at 5.14 are compatable with $-O-C\underline{H}-CH_2-Br$ and $-C\underline{H}-OBz$ respectively.

The preponderance of monobromo-compound (2) over dibromo-compound (42) (possible product when both benzylidene acetals react with NBS) indicates that the reaction 2 to 48 is slower than reaction 1 to 2.



48

However, reaction of 1 with two moles of NBS and catalytic amount of benzoylperoxide in CCl_4 furnished dibromo-compound (48) characterised by analytical data.

Following the earlier reports[22], the primary bromide (±)-2 is reacted with sodium cyanide in dimethyl sulfoxide to furnish cyano-compound (±)-3 in 67% yield. Compound 3 is characterised by spectral data: IR spectrum shows bands at 2240 and 1735 cm^{-1} assignable to -C≡N and C=O respectively. PMR shows signals at 2.78 (2H, d, J = 6 Hz), 3.78 (1H, t, J = 10 Hz), 4.22 (1H, m), 4.53 (1H, dd, J = 5 and 10 Hz), 5.04 (1H, dt, J = 5 and 10 Hz), 5.59 (1H, s) and 7.20 to 8.10 (10, m). The 2H doublet at 2.78 1H singlet and 5.59 and 10H multiplet at 7.20 to 8.10 are assigned to $-C\underline{H}_2-CN$, $\emptyset - C\underline{H}\begin{matrix}O-\\O-\end{matrix}$ and aromatic H respectively. The 1H triplet at 3.78 having J = 10 Hz and 1H doublet of doublets at 4.53 having J = 5 and 10 Hz are assignable to axial and equatorial H of $-OC\underline{H}_2-$, whereas 1H multiplet at 4.22 and 1H doublet of triplets at 5.04 are consistant with $-OC\underline{H}-CH_2CN$ and $-C\underline{H}-OBz$).

Compound 3 has been transformed to 4-O-acetyl-3,5-O-benzylidene-2-deoxy-DL-erythro-pentononitrile (6): Cyano-compound (±)-3 is hydrolysed in alkaline condition at

room temperature. Crude product after work-up shows bands at 3545 and 2240 cm^{-1} assignable to hydroxy and -C≡N which indicates the complete hydrolysis of benzoate moiety; above crude product is acylated using a mixture of pyridine and acetic anhydride to furnish (±)-6. IR spectrum of (±)-6 shows bands at 2240 and 1745 cm^{-1} assigned to -C≡N and acetate carbonyl. PMR spectrum of (±)- 6 shows signals at 2.1 (s, 3H), 2.78 (d, 2H, J = 6 Hz), 3.73 (t, 1H, J = 10 Hz), 4.12 (m, 1H), 4.48 (dd, 1H, J = 5 and 10 Hz), 4.98 (dt, 1H, J = 5 and 10 Hz), 5.50 (s, 1H) and 7.10 to 7.55 (m, 5H), consistant with the structure of 6 (see experimental).

The next aim is to convert cyano group in 3 to aldehyde group; during this conversion it is desirable to retain the benzylidene as well as benzoate blocking groups. In literature methods are known to convert cyano compound into corresponding aldehyde by reductive hydrolysis[23]. Thus reductive hydrolysis reaction of 3 with sodium hypophosphite and Raney nickel in aqueous acetic acid-pyridine in the presence of N,N'-diphenylethylenediamine[24], furnished (±)-4; under these conditions the blocking groups e.g. benzylidene and benzoate, originally present in 3 were left intact and aldehyde group is blocked to give the 1,3-diphenyl imidazolidine derivative 4 in 70% yield. Compound 4 analysed for $C_{33}H_{32}N_2O_4$. IR spectrum shows bands at 1735 cm^{-1} for C=O of benzoate and no band at 2240

cm^{-1} region indicates the absence of -C≡N moiety in 4. PMR spectrum shows signals at δ2.16 (2H, m), 3.58 (5H, m), 4.02 (1H, dt, J = 2 and 10 Hz), 4.41 (1H, dd, J = 5 and 10 Hz) 4.89 (1H, dt, J = 5 and 10 Hz), 5.47 (1H, s), 5.68 (1H, dd, J = 2 and 8 Hz) and 6.72 to 7.95 (20H, m). By the previous knowledge of PMR spectral data and coupling constants for different protons of compounds 2 and 3, the signals at 4.41, 4.89, 5.47 and 6.72 to 7.95 are assigned to equatorial H of $-OC\underline{H}_2-$, H of $-C\underline{H}-OBz$, benzylic H of $\emptyset - CH\begin{matrix}O-\\O-\end{matrix}$ and aromatic H respectively. Further signals at 2.16, 4.02 and 5.68 are assignable to $-CH-C\underline{H}_2-CH\begin{matrix}N-\\N-\end{matrix}$, $-O-C\underline{H}-CH_2-$ and $-CH\begin{matrix}N-\\N-\end{matrix}$, whereas signal at 3.58 is assignable to $-N-C\underline{H}_2-C\underline{H}_2-N-$ and axial H of $-OCH_2-$). Thus assigned structure for compound 4 is in good agreement with the further transformation of 4 into 7.

Literature reports that, 1,3-diphenyl imidazolidine derivatives are stable to alkali. Hence saponification of 4 with sodium hydroxide in aqueous methanol yields hydroxy compound (±)-5 in 93% yield. IR spectrum of compound (±)-5 shows band at 3600 cm^{-1}, indicates the hydroxy group. PMR spectrum exhibits signals at 2.24 (m, 2H), 5.46 (s, 1H), 5.67 (m, 1H) and 7.00 to 7.90 (m, 15H) assignable to $-CH-C\underline{H}_2-CH-$, $\emptyset - C\underline{H}\begin{matrix}O-\\O-\end{matrix}$, $-C\underline{H}\begin{matrix}N-\\N-\end{matrix}$ and aromatic H respectively.

Deblocking of 5 (removal of benzylidene acetal and 1,3-diphenyl imidazolidine moiety) is carried out at room temperature in aqueous acetone by maintaining the pH at 2; work-up after 5 hr furnished (±)-7 (yield 43% based on 5), which was characterised by transorming it into triacetate (8), having IR and PMR identical with those of an authentic sample.

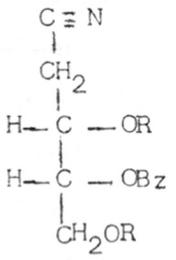
It is of interest to note that in (±)-4 , all the functional groups of 2-deoxy-erythro-pentose (in the open chain form) are blocked; furthermore the two secondary hydroxyl groups are blocked differently. Hence this derivative holds promise as a very useful intermediate for the synthesis of products related to 2-deoxy-erythro-pentose.

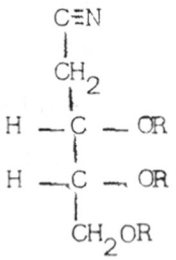
It has been already stated in introduction that 2-deoxy-erythro-penteno-1,4-lactone (9) and 2-deoxy-D-ribitol (11) are important compounds; further lactone (9) is a potential intermediate[7] in the synthesis of 2-deoxy-DL-ribose. Hence we planned to prepare 9 and 11.

Literature reports the acid hydrolysis[25] of -C≡N to -COOH; further deblocking[26] of benzylidene acetal under the same conditions. Hence we chose compound 3 as the starting material for the preparation of 9.

When cyano-compound 3 is treated with 1N HCl at 100° for 3 hr, instead of lactone 9, hydroxy compounds 49 and 51 are obtained. Identities of compound 49 and 51 are established by studying the IR and PMR spectral

data of derived acetates 50 and 52 from 49 and 51 respectively.





49 R = H

50 R = $-COCH_3$

51 R = H

52 R = $-COCH_3$

However, the treatment[27] of 6N HCl with cyano-compound (3) furnished the required lactone 9, which is characterised as diacetate (10). IR spectrum of 10 shows broad band at 1770 to 1742 assignable to C=O of lactone and acetate. PMR spectrum exhibits signals at 2.05 (s, 6H), 3.30 to 4.28 (m, 4H) and 5.15 (m, 2H) which are compatable with the assigned structure of 10 (see experimental, page No. 78).

LAH reduction of 10 in ether afforded 2-deoxy-DL-erythro-pentitol (11) characterised as tetraacetate (12). IR and PMR spectral data of (±)-12 are identical with those of an authentic sample prepared by sodium borohydride reduction of 2-deoxy-D-ribose and acylating the reduced product using a mixture of pyridine and acetic anhydride.

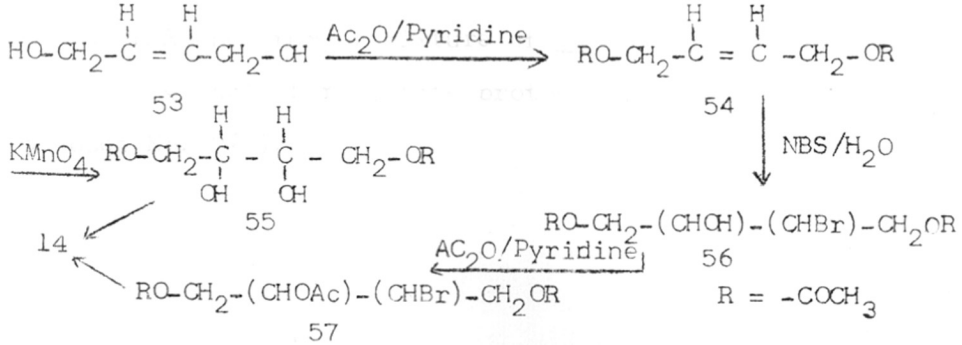
As erythritol (13) was required for the preparation of 2-deoxy-DL ribose (presented as above), we examined different methods of preparation of 13 starting from cis-but-2-ene-1,4-diol-diacetate (54) (prepared by the acylation of cis-but-2-ene-1,4-diol (53) using a mixture of pyridine and acetic anhydride; some of the methods are given below:

(a) Cis-hydroxylation of 54 using $KMnO_4$ in acetone furnished diol (55), which is acylated using pyridine and acetic anhydride to afford 1,2:3,4-tetra-acetyl-erythritol (14).

(b) D-Glucose is treated with lead tetraacetate to furnish erythrose, which is reduced with sodium borohydride to yield erythritol (13), characterised as its tetra-acetate (14).

(c) Action of NBS on diacetate (54) furnished bromohydrin (56). Acylation of 56 using a mixture of aceticanhydride and pyridine afforded triacetate (57), which is treated with sodium acetate in acetic acid to furnish 14.

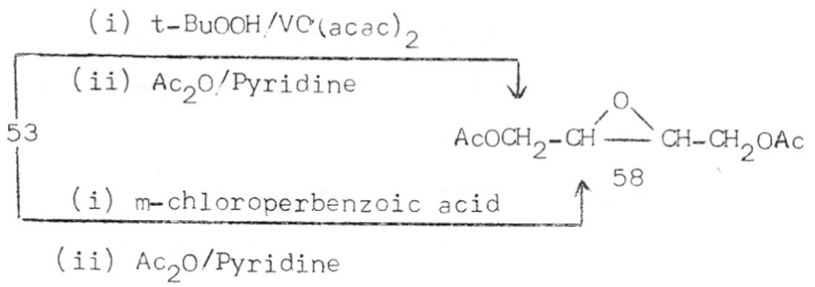
Hydrolysis of 1,2,3,4-tetra-acetyl-erythritol (14) using methanol-ammonia solution furnished erythritol (13)



1,2,3,4-Tetra-acetyl-threitol (16) is prepared by the action of sodium acetate in acetic acid and acetic anhydride on 1,4-di-acetyl-2,3-epoxy-butane (58). Epoxy-compound 58 is prepared by two different routes-

(a) Epoxidation of 53 using m-chloroperbenzoic acid and acylation of the product furnished 58.

(b) Diol 53 is treated with t-butyl hydro peroxide in presence of vanadyl acetyl acetonate in acetonitrile and product after acylation furnished 2:3 mixture of 58 and 53. Pure 58 isobtained by chromatography.



90 MHz PMR spectrum of 14 exhibits two singlets at 2.06 and 2.09 whereas 90 MHz PMR spectrum of 16 shows two singlets at 2.06 and 2.11 for acetate protons. Thus it was anticipated that one can distinguish tetraacetates 14 and 16 by PMR data. In agreement with our anticipation 90 MHz PMR spectrum of mixture of 14 and 16 exhibits three distinct signals for acetate protons (see PMR spectrum on page No. 97).

EXPERIMENTAL

1,3:2,4-Di-O-benzylidene-erythritol (1) was prepared according to literature method,[12] m.p. 201-202° (lit.[18] 201-202).

3-O-benzoyl-2,4-O-benzylidene-1-bromo-1-deoxy-DL-erythritol(2)

A mixture of dibenzylidene derivative 1 (8.94 g, 30 mmol) N-bromosuccinimide (5.34 g, 30 mmol), barium carbonate (1.5 g, 7.6 mmol), benzoyl peroxide (0.3 g, 1.2 mmol) and CCl_4 (250 ml) was heated under reflux with efficient stirring for 1 hr and filtered hot. The cake was washed with hot CCl_4 (100 ml). The filtrates were combined and the solvent removed on steam bath. The residue was extracted with ether (80 ml x 3) to furnish (i) ether extract and (ii) ether insoluble residue. Ether extract (i) after evaporation of solvent furnished 2; yield: 6.20 g (55%). A sample recrystallised from 5:2 mixture of benzene and pet.ether (60°-80°) showed m.p. 128-130°. The insoluble residue (ii) on recrystallisation from 9:1 mixture of benzene and pet.ether furnished recovered starting material 1 (2.4 g). The yield of 2 when corrected for recovered starting material is 75%. TLC (solvent system B); R_f, 0.72; IR (nujol): 1735 (OBz); PMR ($CDCl_3$): 3.58 (2H, d, J = 6 Hz, $C\underline{H}_2$-Br), 3.76 (1H, t, J = 10 Hz, axial H of -OCH_2-), 4.18 (m, 1H, -$OC\underline{H}$-$C\underline{H}_2$-Br),

4.53 (2H, dd, J = 5 and 10 Hz, equatorial H of $-OCH_2-$), 5.14 (1H, dt, J = 5 and 10 Hz, $-CH-OBz$), 5.61 (1H, s, $\phi - CH\begin{matrix}O-\\O-\end{matrix}$), 7.40 - 8.00 (10H, m, aromatic).

(Fround: C, 57.35; H, 4.54. $C_{18}H_{17}BrO_4$ requires C, 57.32; H, 4.51%).

4-O-Benzoyl-3,5-O-benzylidene-2-deoxy-DL-erythro-pentononitrile (3)

A stirred mixture of sodium cyanide (1.8 g, 36.7 mmol) and DMSO (10 ml) was heated to 90°. Bromide 2 (5.6 g, 14.9 mmol) was added to this mixture gradually at such a rate that the temperature of the reaction mixture was below 120°. After completing addition of 2 reaction mixture was stirred at 100-120° for 20 min, cooled to room temperature, diluted with water (100 ml) and extracted with $CHCl_3$ (50 ml x 3). The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on a column of alumina (grade II, 150 g). The column was eluted successively with (i) pet.ether, (ii) 95:5 mixture of pet.ether and ethylacetate and (iii) 90:10 mixture of pet.ether and ethylacetate. The fraction eluted with 90:10 mixture of pet.ether and ethylacetate on solvent removal furnished (±)3; yield: 3.20 g (67%). A sample recrystallized from 1:1 mixture of benzene and pet.ether showed m.p. 130-132°; TLC (R_f, (solvent system B): 0.43;

IR (nujol): 2240 (C≡N), 1735 (OBz); PMR ($CDCl_3$): 2.78 (2H, d, J = 6 Hz, $-C\underline{H}_2-CN$), 3.78 (1H, t, J = 10 Hz, axial H of $-OC\underline{H}_2-$), 4.22 (1H, m, $-OC\underline{H}-CH_2CN$), 4.53 (1H, dd, J = 5 and 10 Hz, equatorial H of $-OC\underline{H}_2-$), 5.04 (1H, dt, J = 5 and 10 Hz, $-C\underline{H}-OBz$), 5.59 (1H, s, Ø - $C\underline{H}\begin{matrix}O-\\O-\end{matrix}$), 7.20 - 8.10 (10 H, m, aromatic). (Found: C, 70.46; H, 5.59 $C_{19}H_{17}NO_4$ requires C, 70.57; H, 5.30%).

(±)3-O-Benzoyl-2,4-O-benzylidene-1-deoxy-1-(1,3-diphenyl-2-imidazolidyl)-erythritol (4)

A mixture of pyridine (50 ml), acetic acid (25 ml), water (25 ml), Raney nickel (18.0 g, 307 mmol), sodium hypophosphite (9.0 g, 83 mmol), N,N'-diphenylethylenediamine (1.2 g, 5.66 mmol) and 3 (1.0 g, 3.09 mmol) was stirred at room temperature for 10 hr and filtered. The precipitate was washed with $CHCl_3$ (100 ml). $CHCl_3$ (300 ml) was added to the combined filtrates. The $CHCl_3$ solution was washed with 10% aqueous sodium carbonate solution (80 ml x 3), saturated copper sulphate solution (50 ml x 3), finally with water and dried (Na_2SO_4). The residue obtained after removal of solvent was chromatographed on a column of alumina (grade II, 50 g). The column was eluted successively with (i) 98:2 mixture of pet.ether and ethylacetate (ii) 96:4 mixture of pet.ether and ethylacetate and (iii) 94:6 mixture of pet.ether and ethylacetate. The fraction eluted with 94:6 mixture of pet.ether and

ethylacetate, after solvent removal and crystallization from1:1 mixture of benzene and pet.ether furnished (±)-4 yield: 1.13 g (70%); m.p.150-152°; TLC (solvent system B) R_f 0.52; IR (Nujol): 1735 (OBz); PMR ($CDCl_3$): 2.16 (2H, m, CH-CH_2-CH), 3.58 (5H, m, -N-CH_2-CH_2-N and axial H of -OCH_2-), 4.02 (1H, dt, J = 2 and 10 Hz, -OCH-CH_2), 4.41 (1H, dd, J = 5 and 10 Hz, equatorial H of -OCH_2-), 4.89 (1H, dt, J = 5 and 10 Hz, -CH-OBz), 5.47 (1H, s, Ø - CH(O-)(O-)), 5.68 (1H, dd, J = 2 and 8 Hz, -CH(N)(N)), 6.72 - 7.95 (20 H, m, aromatic); (Found: C, 76.40; H, 6.49; N, 5.40. $C_{33}H_{32}N_2O_4$ requires C, 76.13; H, 6.20; N, 5.38%).

(±)-2,4-O-Benzylidene-1-deoxy-1-(1,3-diphenyl-2-imidazolidyl)-erythritol (5)

A mixture of sodium hydroxide (0.5 g, 12.5 mmol), water (10 ml), methanol (20 ml) and 4 (0.8 g, 1.54 mmol) was heated under reflux for 8 hr, cooled, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried (Na_2SO_4). The residue obtained after removal of solvent was recrystallized from benzene pet.ether mixture to furnish (±)-5; yield: 0.596 g (93%); m.p.130-132°; TLC (solvent system B): R_f, 0.30; IR(Nujol): 3600 (OH); PMR ($CDCl_3$); 2.24. (2H, m, -CH-CH_2-CH-), 5.46 (1H, s, Ø - CH(O-)(O-)), 5.67 (1H, m, -CH(N-)(N-)), 7.00-7.90 (15H, m, aromatic). (Found: C, 74.95;

H, 7.01; N, 6.79. $C_{26}H_{28}N_2O_3$ requires C, 74.97; H, 6.78; N, 6.73%.

2-Deoxy-DL-erythro-pentose (7)

1% Aqueous HCl was added dropwise to a mixture of 5 (0.3 g, 0.72 mmol), acetone (5 ml) and water (2 ml) till the pH was 2 and stirred at room temperature for 5 hr. The reaction mixture was extracted with $CHCl_3$ (10 ml x 2) and the $CHCl_3$ extract was rejected. The aqueous layer was treated dropwise with 2% aqueous NaOH till the pH was 9, stirred at room temperature for 30 min and extracted with $CHCl_3$ (10 ml x 3). The $CHCl_3$ layer was rejected. The aqueous layer was neutralised with dil. HCl and evaporated to dryness under reduced pressure. The presence of (±) 6 in the residual material was established by acylating it with pyridine (5 ml) and acetic anhydride (5 ml) at room temperature for 15 hr. The acetylation product obtained after usual work up was chromatographed on alumina (grade II, 10 g). The column was eluted successively with (i) 98:2 mixture of pet.ether and ethylacetate and (ii) 95:5 mixture of pet.ether and ethylacetate. The fraction eluted with 95:5 mixture of pet.ether and ethylacetate was composed almost exclusively of triacetate (±)-8; yield: 0.08 g (43%). The identity of triacetate thus obtained was established by comparison (TLC, GLC, IR and NMR) with an authentic sample (prepared by acylation of 2-deoxy-ribose using pyridine and acetic-anhydride).

Action of 1N HCl on 3

A mixture of cyano compound 3 (1.00 gm, 3.09 mmol) and 1N HCl (10 ml) was refluxed for 3 hrs. Reaction mixture was cooled, neutralised with aqueous NaOH solution (10%) and concentrated. Acylation of the residue using acetic anhydride (10 ml) and pyridine (10 ml) furnished a residue (0.84 gm), which was chromatographed over grade II alumina (25 gm). Column was successively eluted with (i) pet.ether (ii) 98:2 mixture of pet.ether + ethylacetate (iii) 96:4 mixture of pet.ether + ethylacetate (iv) 94:6 mixture of pet.ether + ethylacetate. Fraction eluted with 96:4 mixture of pet.ether + ethylacetate furnished 50 (0.43 gm). Yield: 43.8%; TLC (solvent system B): R_f, 0.40; IR: 2240 (-C≡N), 1750 (broad, C=O); PMR: 2.1 (6H, s, -O-CO-CH_3), 2.7 (2H, m, -CH_2-CN), 4.4 (2H, m, -CH_2-OAc), 5.3 (2H, m, CH-OAc, CH-OBz), 7.3 (3H, m, aromatic), 7.9 (2H, m, aromatic H ortho to C=O); (Found: C, 60.30; H, 5.49. $C_{16}H_{17}NO_6$ requires C, 60.18; H, 5.37%).

Fraction eluted with 94:6 mixture of pet.ether + ethylacetate furnished 52 (0.19 gm). Yield: 26.8%; TLC (solvent system B) R_f, 0.35; IR: 2240 (-C≡N), 1750 (C=O); PMR: 2.0 (9H, s, -OCOCH_3); 2.7 (2H, m, CH_2-CN), 4.1 (2H, m, CH_2-OAc), 5.1 (2H, m, CH-OAc); (Found: C, 51.06; H, 5.92. $C_{11}H_{15}NO_5$ requires C, 51.36; H, 5.88%.)

4-O-Acetyl-3,5-O-benzylidene-2-deoxy-DL-erythro-pentononitrile (6)

A mixture of cyano compound (3) (0.30 gm, 0.93 mmole), sodium hydroxide (0.12 gm, 3 mmole), ethanol (5 ml) and water (5 ml) was stirred at room temperature for 6 hrs. Reaction mixture was diluted with water, extracted with chloroform. Chloroform extract was washed with water, dried and concentrated. Residue showed bands at 3545 (OH) and 2240 (-C≡N) but no band at 1735 (C=O), which indicated the complete hydrolysis of benzoate. Hence, the above residue was treated with pyridine (2 ml) and acetic anhydride (2 ml) and kept overnight. Usual work-up of the reaction mixture furnished a residue, which was purified by passing it through grade II alumina column, yield 6 (0.18 gm). Yield: 75.6%; TLC (solvent system B) R_f, 0.42; IR: 2240 (-C≡N), 1745 (C=O); PMR: 2.1 (3H, s, $-OCOCH_3$), 2.78 (2H, d, J = 6 Hz, $-CH_2-CN$), 3.73 (1H, t, J = 10 Hz, axial H of $-OCH_2$), 4.12 (1H, m, $-OCH-CH_2-CN$), 4.48 (1H, dd, J = 5 and 10 Hz, equitorial H of $-OCH_2$), 4.98 (1H, dt, J = 5 and 10 Hz, $-CH-OBz$), 5.50 (1H, s, Ø - $CH\langle^{O-}_{O-}$), 7.10 to 7.55 (5H, m, aromatic).

3,5-Di-O-acetyl-2-deoxy-(±)-erythro-pentanolactone (10)-

A mixture of 3 (0.50 gm, 1.5 mmol), aqueous HCl (6N, 4 ml) and methanol (4 ml) was stirred at room temp. overnight. Reaction mixture was neutralised with aqueous

sodium carbonate (10%) and concentrated to dryness under reduced pressure. Residue was treated with pyridine (5 ml), acetic anhydride (5 ml) and kept overnight. Usual workup of the reaction mixture furnished a residue (0.33 gm), which after purification through column of grade II alumina yielded pure 10 (0.28 gm). Yield: 84%; TLC (solvent system B): R_f, 0.56; IR: 1770 to 1742 (C=O of lactone and acetate), 1227 (acetate); PMR: 2.05 (6H, s, $-OCOCH_3$), 3.30 to 4.28 (4H, m, $-CH_2-COO-$, CH_2-OAc), 5.15 (2H, m, $AcO>CH-CH<^{-OCO-}$);(Found: C, 50.49; H, 5.94 $C_9H_{12}O_6$ requires C, 50.10; H, 5.60%).

1,3,4,5-Tetra-O-acetyl-2-deoxy-(±)-erythropentitol (12)

To a ice-cooled, stirred mixture of LAH (0.25 gm) and ether (20 ml), lactone 9 (0.25 gm, 1.2 mmol) in ether (20 ml) was added dropwise. After complete addition, reaction mixture was stirred at room temperature for 2 hrs and at reflux temperature for 10 hrs. After complete reaction, reaction mixture was cooled and excess of LAH was destroyed by the addition of acetone (10 ml), then with water (5 ml) and filtered off the residue. Residue was washed with water (10 ml). Combined filtrates were concentrated under reduced pressure and residue was acylated using a mixture of acetic anhydride (5 ml) and pyridine (5 ml). Usual work-up furnished crude 11, which was purified by column chromatography on grade II alumina.

Fraction eluted with mixture of 90:10 pet.ether + ethyl-acetate yielded pure tetraacetate (12) (0.15 gm), characterised by comparison (TLC, IR, PMR) with an authentic sample. Yield: 41.5%; IR: 1755 (C=O), 1228 (acetate); PMR; 1.91 (2H, m, $-C\underline{H}_2-CH_2OAc$), 2.05 (12H, broad s, $OCOC\underline{H}_3$), 4.15 (4H, m, $-C\underline{H}_2-OAc$), 5.16 (2H, m, $C\underline{H}-OAc$).

Preparation of authentic sample of 12[11]

A mixture of 2-deoxy-D-ribose (0.25 gm), $NaBH_4$ (0.10 gm) and water (3 ml) was stirred at room temperature overnight. Excess of $NaBH_4$ was destroyed by the addition of acetic acid. Concentrated the reaction mixture under reduced pressure. Usual acylation of the residue using pyridine (2 ml) and acetic anhydride (2 ml) yielded tetraacetate 12 in 80% yield.

2,3-Di-benzoyl-1,4-dibromo-erythritol (48)

A mixture of dibenzylidene compound (1) (1.5 g, 5 mmole), N-bromosuccinimide (1.80 g, 10 mmole), barium carbonate (0.5 g, 2.8 mmole), benzoyl peroxide (0.1 g, 0.4 mmole) and CCl_4 (75 ml) was heated under reflux with efficient stirring for 1 hr and filtered hot. The cake was washed with hot CCl_4 (50 ml). The filterates were combined and the solvent removed on steam bath. The residue was extracted with ether (50 ml x 2) to furnish (i) ether extract and (ii) ether insoluble residue. Ether

extract after evaporation of solvent furnished dibromo-compound (48): yield: 1.72 g (75%). A sample recrystallised from 1:1 mixture of benzene and pet.ether (60-80°) showed m.p.176-78° (lit.[28] 183.5°); IR: 1740 (C=O); PMR ($CDCl_3$); 3.73 (4H, m, $-CH_2-Br$), 5.56 (2H, m, -CH-OBz), 7.43 (10H, m, aromatic).

1,4-Di-acetyl-cis-but-2-ene-1,4-diol (54)

Acylation of cis-but-2-ene-1,4-diol (53) using a mixture of acetic anhydride and pyridine furnished diacetate (54), b.p.105°/0.8 mm (lit.[29] 203°), PMR: 2.0 (6H, s, $-OCOCH_3$), 4.6 (4H, d, J = 6 Hz, $-CH_2-OAc$), 5.6 (2H, t, J = 6 Hz, vinylic H).

1,2,3,4-Tetra-acetyl-erythritol (14)

Method A - To a stirred and ice-cooled mixture of diacetate (54) (5.14 g, 30 mmol), acetone (80 ml) and water (2 ml), $KMnO_4$ (4.74 g, 30 mmol) was added portion by portion, maintaining the temperature of reaction mixture at 0° to 5° After complete addition of $KMnO_4$, reaction mixture was warmed to room temperature and stirred for two hr. Filtered off the residue. Residue was washed with acetone (25 ml x 2). Combined filtrate were concentrated and residue was recrystallised using acetone + pet.ether (5:1). Filtration of the solid furnished diol (55) (3.82 g) yield 61.8%; m.p.93-94° (lit.[30] m.p.93-94°).

Diol (55) was acylated to tetraacetate (14) using pyridine and acetic anhydride in 92% yield, m.p. 89-90° (lit.[16] 89-90°); TLC (solvent system B): R_f, 0.50; IR: 1745 (C=O), 1224 (acetate); PMR: 2.06 (6H, s, $-OCOCH_3$), 2.09 (6H, s, $-OCOCH_3$), 4.22 (4H, m, $-CH_2-OAc$), 5.17 (2H, m, CH-OAc).

Method B - To a stirred mixture[12] of D-glucose (1.5 g, 8 mmol), water (3 ml) and acetic acid (150 ml), lead tetra-acetate (7.7 g, 17 mmol) was added portion by portion. After complete addition of LTA, reaction mixture was stirred for 10 min. more and 1.9 g of oxalic acid was added. After 30 min., filtered off the reaction mixture and filtrate was concentrated. Residue was taken in 20 ml of ethanol and sodium borohydride (0.30 g) was added. Reaction mixture was stirred overnight and concentrated under reduced pressure. Acylation of the residue using pyridine and acetic anhydride furnished tetraacetate (14) (0.87 g), which was purified through column chromatography. Yield: 37%; m.p. 87-88°.

Method C - A mixture of diacetate (54) (3.44 g, 20 mmol), NBS (3.8 g, 21 mmol) and water (50 ml) was stirred overnight at room temperature. Reaction mixture was saturated with sodium chloride and extracted with ether. Ether extract was washed with water, dried. Removal of the solvent furnished threo-bromohydrin (56) (4.96 g). Yield: 90.88%; b.p. 145-50° (bath temp.)/1 mm (lit.[16]

138-140/1 mm); IR: 3550 (OH), 1740 (C=O); PMR: 2.1 (6H, s, $-OCOCH_3$), 3.66 - 4.50 (7H, m, $-CH_2OAc$, -CH(OH), -CHBr).

Bromo-hydrin (56) (2.5 g, 9.2 mmole) was acylated using pyridine (10 ml) and acetic anhydride (10 ml) to furnish bromo-acetate (57) (2.9 g), yield: 98.33%; b.p.140-45° (bath temp.)/1 mm; IR: 1740 (C=O); PMR: 2.1 (9H, s, $-OCOCH_3$), 4.3 (5H, m, $-CH_2-OAc$, CH-Br), 5.2 (1H, m, >CH-OAc).

A mixture of bromo-acetate (57) (8.0 g, 26 mmol), fused sodium acetate (8.0 g), acetic anhydride (20 ml), acetic acid (20 ml) was refluxed for 8 hr, cooled, diluted with water (200 ml) and extracted with ether. Ether extract was washed with sodium carbonate solution (5%), water and dried. Removal of the ether furnished a mixture of tetraacetates (14 and 16) (6.5 g), b.p.140-50° (bath temp.)/1 mm. Above mixture of tetraacetates was seeded with pure 14 and filtered off the solid to furnish tetraacetate (14) (5.6 g), which was recrystalised from benzene + pet.ether (3:1), yield: 75%; m.p.88-9°.

1,4-Di-acetyl-2,3-epoxy-butane 1,4-diol (58)

Method A - A mixture of cis-but-2-ene-1,4-diol (53) (0.6 g, 6.8 mmol), m-chloropebenzoic acid (1.4 g, 8.1 mmol) and acetonitrile (15 ml) was kept at room temperature for 48 hr. To the reaction mixture, acetic anhydride (5 ml) and pyridine (5 ml) were added and kept overnight.

Usual work-up of the reaction mixture furnished crude epoxide (1.0 g), which was chromatographed over grade II alumina (20 g). Fraction eluted with mixture of pet.ether + ethylacetate (94:6) yielded pure epoxide (58) (0.86 g), yield: 67%; m.p.52-4°; IR (Nujol): 1740 (C=O), 1225 (acetate); PMR: 2.1 (6H, s, $-OCOCH_3$), 3.2 (2H, m, oxirane H), 4.2 (4H, m, $-CH_2-OAc$).

Method B - To a stirred mixture of cis-but-2-ene-1,4-diol (53) (2.2 g, 25 mmol), vanadyl acetyl acetonate $[VO(acac)_2]$ (10 mg) and acetonitrile (20 ml), 70% t-butyl hydroperoxide (2.64 g, 29 mmol) in 10 ml of acetonitrile was added drop by dryp. After complete addition of t-BuOOH reaction mixture was stirred at room temperature for 5 hr and at 50° for 5 hr. Reaction mixture was cooled and a mixture of acetic anhydride (10 ml), pyridine (10 ml) was added and kept at room temperature overnight. Usual work-up of the reaction mixture furnished a residue (3.5 g) which was composed of 2:3 mixture of 58 and 54 as revealed by PMR data. Chromatography of the above crude material furnished pure epoxide (58) (1.4 g), yield: 25.35%.

1,2,3,4-Tetraacetyl-threitol (16)

A mixture of epoxide (58) (1.88 g, 10 mmol), sodium acetate (2.5 g, 30 mmol), acetic acid (20 ml) and acetic anhydride (10 ml) was heated under reflux for 3 hr. Reaction mixture was cooled, diluted with water and

extracted with ether. Ether extract was washed with sodium carbonate solution (5%), water, dried and concentrated. Column chromatography of the above residue furnished 16 (2.32 g); yield 80%; m.p.54-55° (lit.[16] 54-55°); TLC (solvent system B): R_f 0.50; IR (Nujol): 1740 (C=O); PMR: 2.06 (6H, s, $-OCOCH_3$), 2.11 (6H, s, $-OCOCH_3$), 4.22 (4H, m, $-CH_2-OAc$), 5.25 (2H, m, CH-OAc).

Preparation of authentic sample of 16[16]

A solution of H_2O_2 (30%, 19 ml) in glacial acetic acid (25 cc) was heated to 85° for 1 hr and cooled. To this solution, diacetate (54) (4.3 g, 25 mmol) was added and mixture was heated to 50° for 15 hr. Removal of the solvent under reduced pressure furnished a viscous oil, which after acylation using pyridine (20 ml) and acetic anhydride (20 ml) yielded crude 16. Purification by column chromatography furnished tetraacetate (16), yield: 53.8%; m.p.54-55° (lit.[16] 54-55°).

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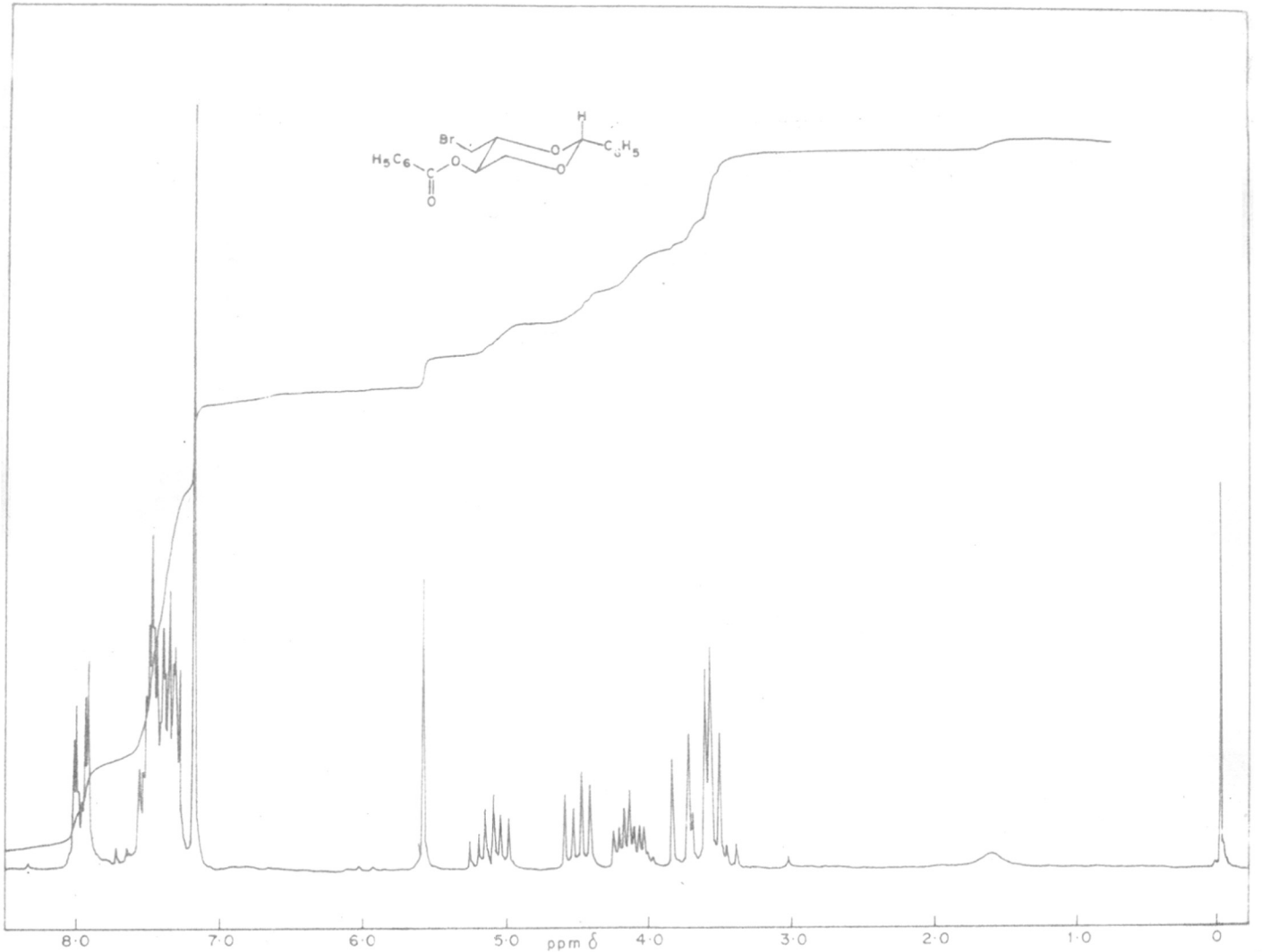

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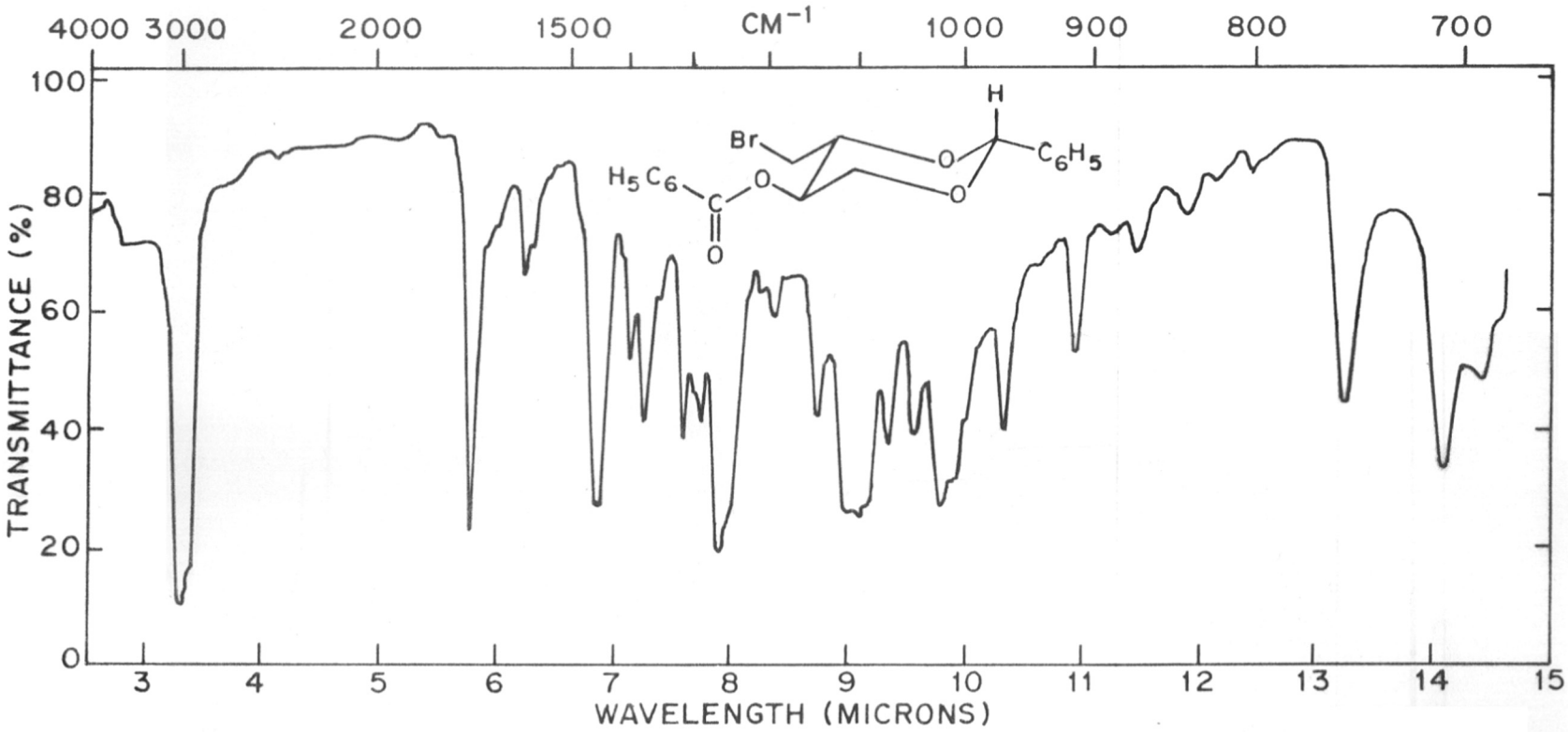

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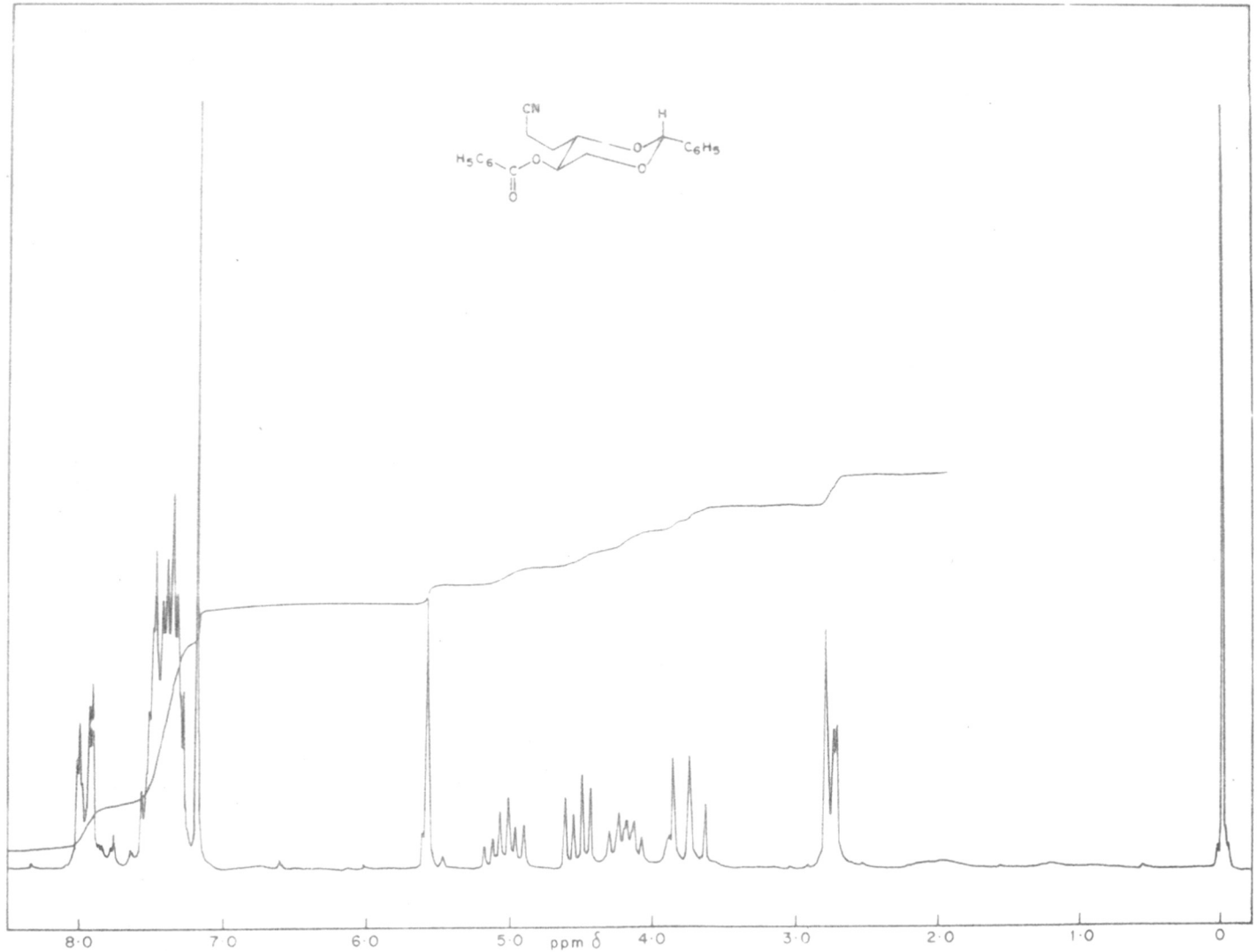

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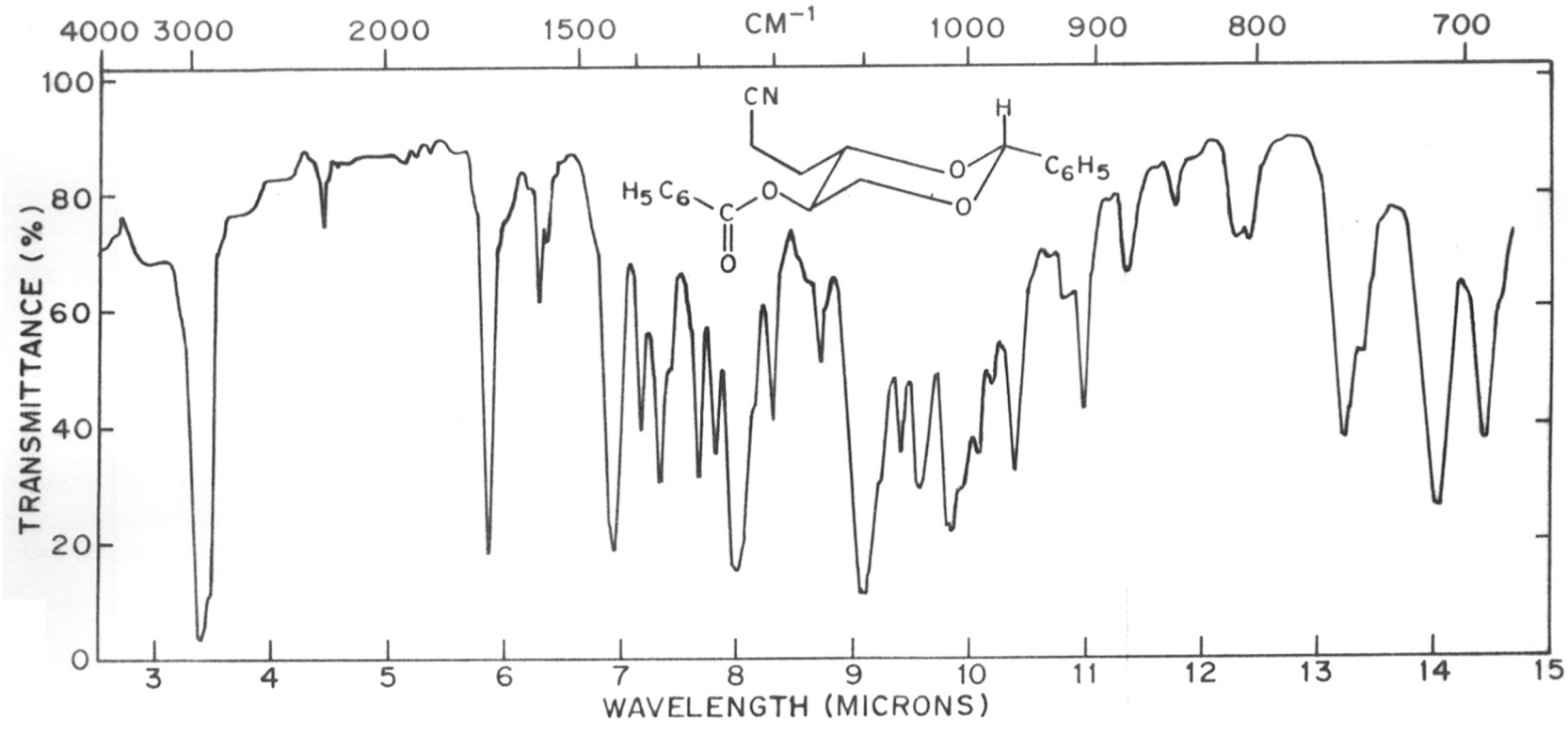

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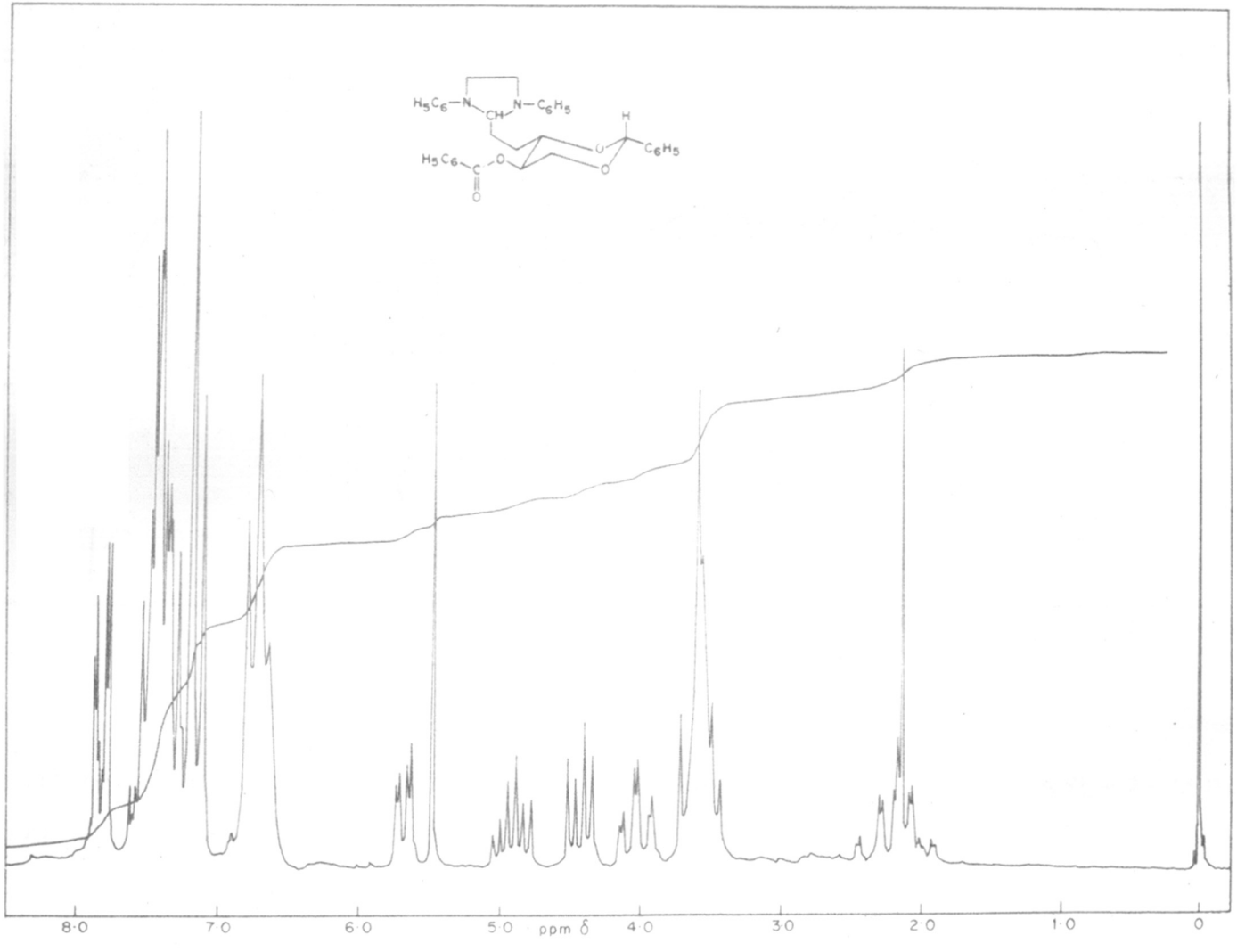
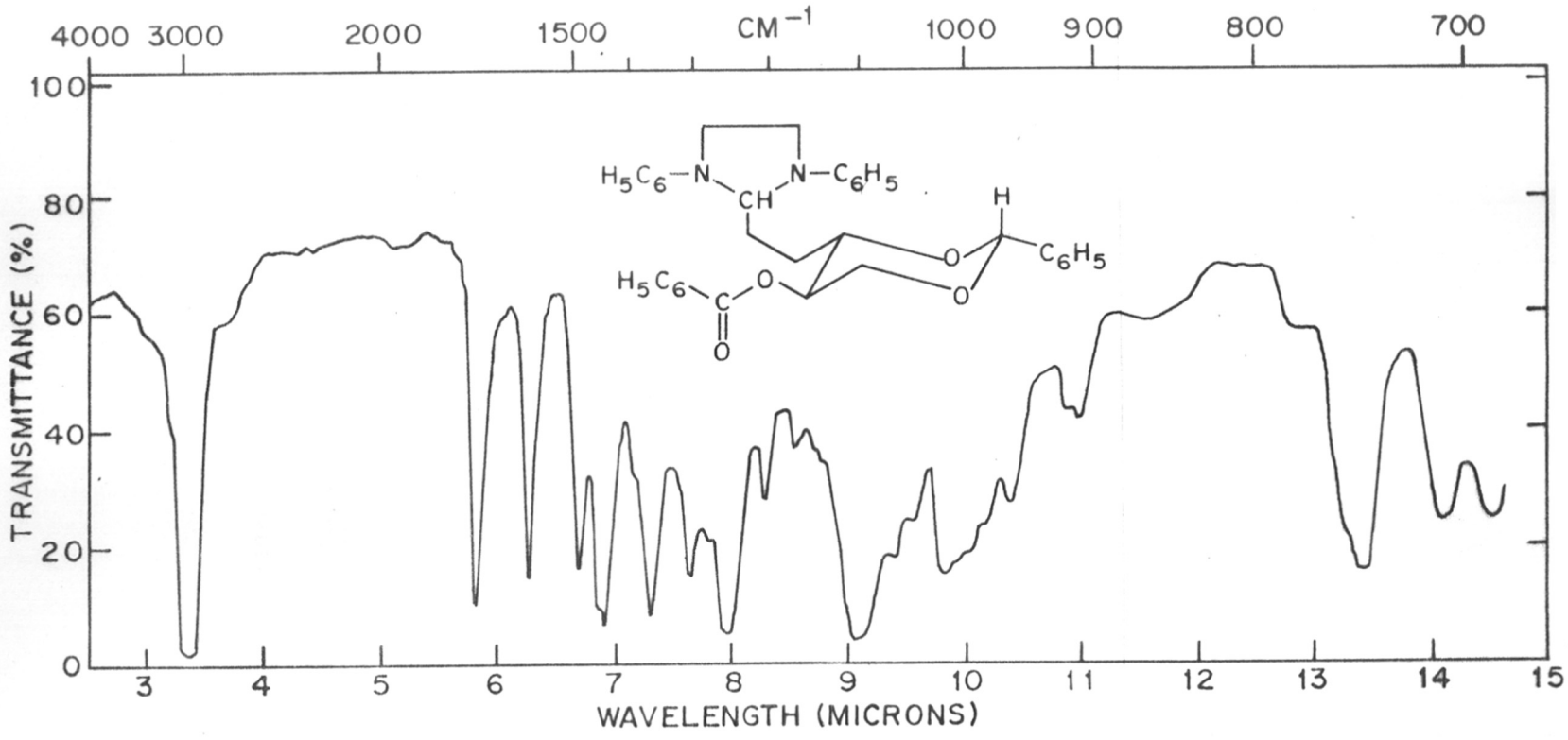
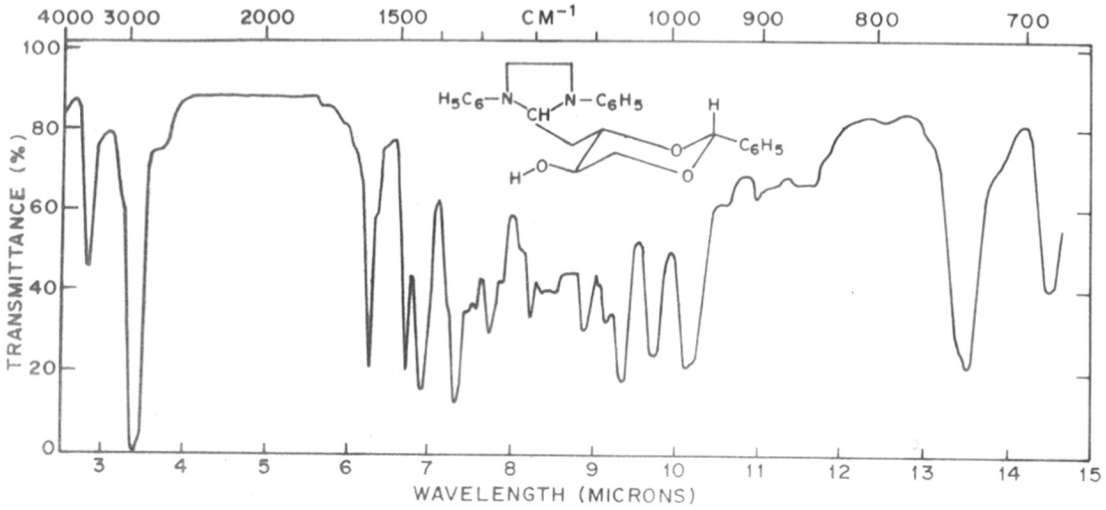
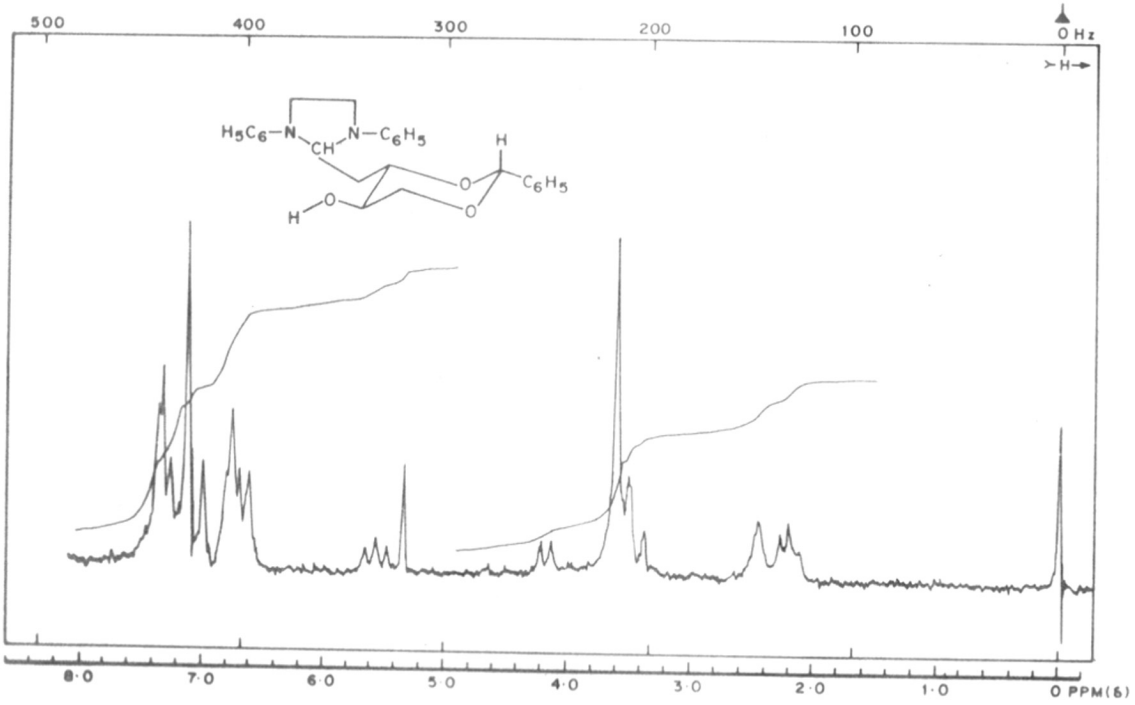


NMR OF (±)-3-BENZOYL-2,4-O-BENZYLIDENE-1-DEOXY-1-(1,3-DIPHENYL-2-IMIDAZOLIDYL) ERYTHRITOL (4)

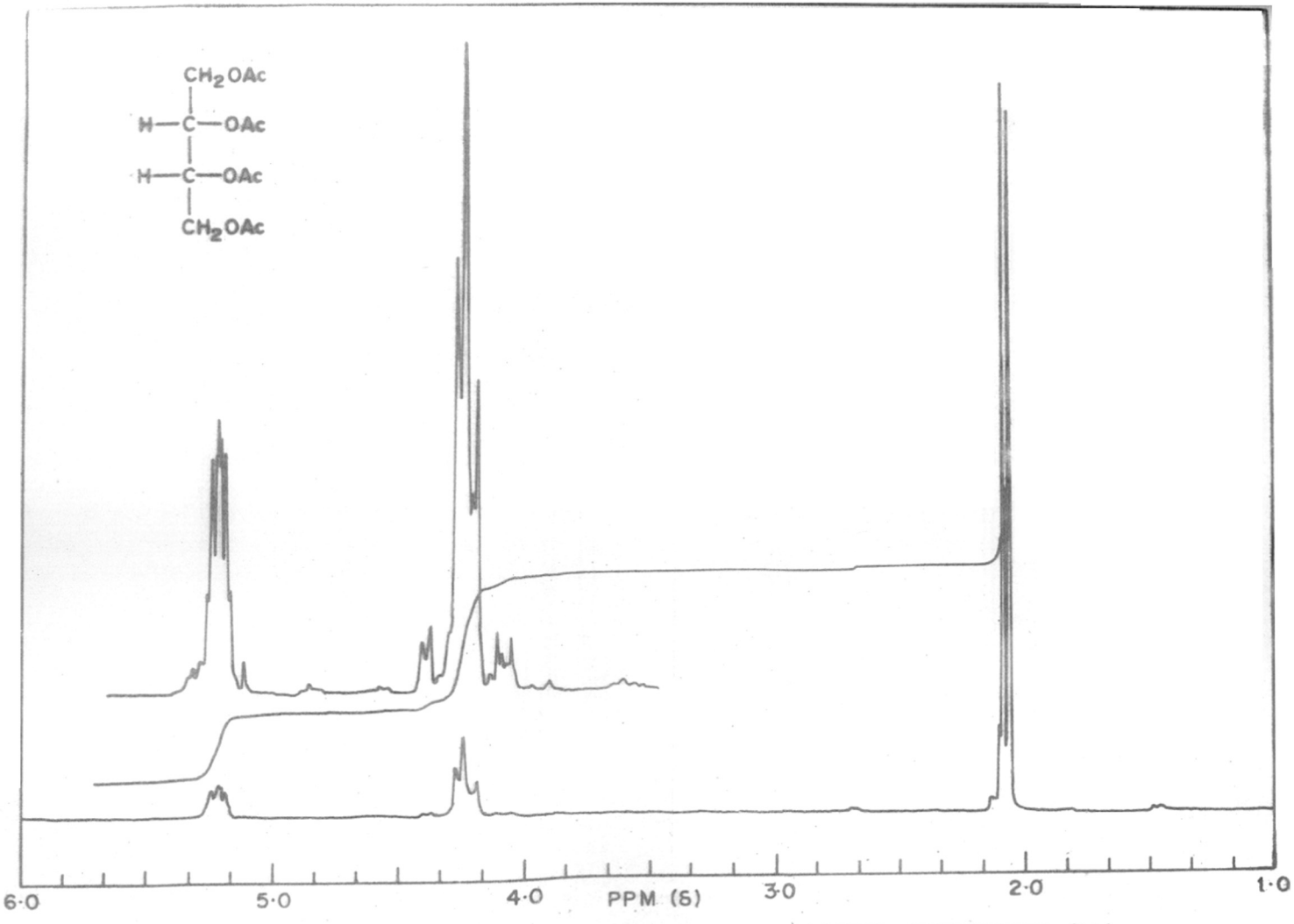


IR OF (±)-3-BENZOYL-2,4-O-BENZYLIDENE-1-DEOXY-1-(1,3-DIPHENYL-2-IMIDAZOLIDYL) ERYTHRITOL (4)

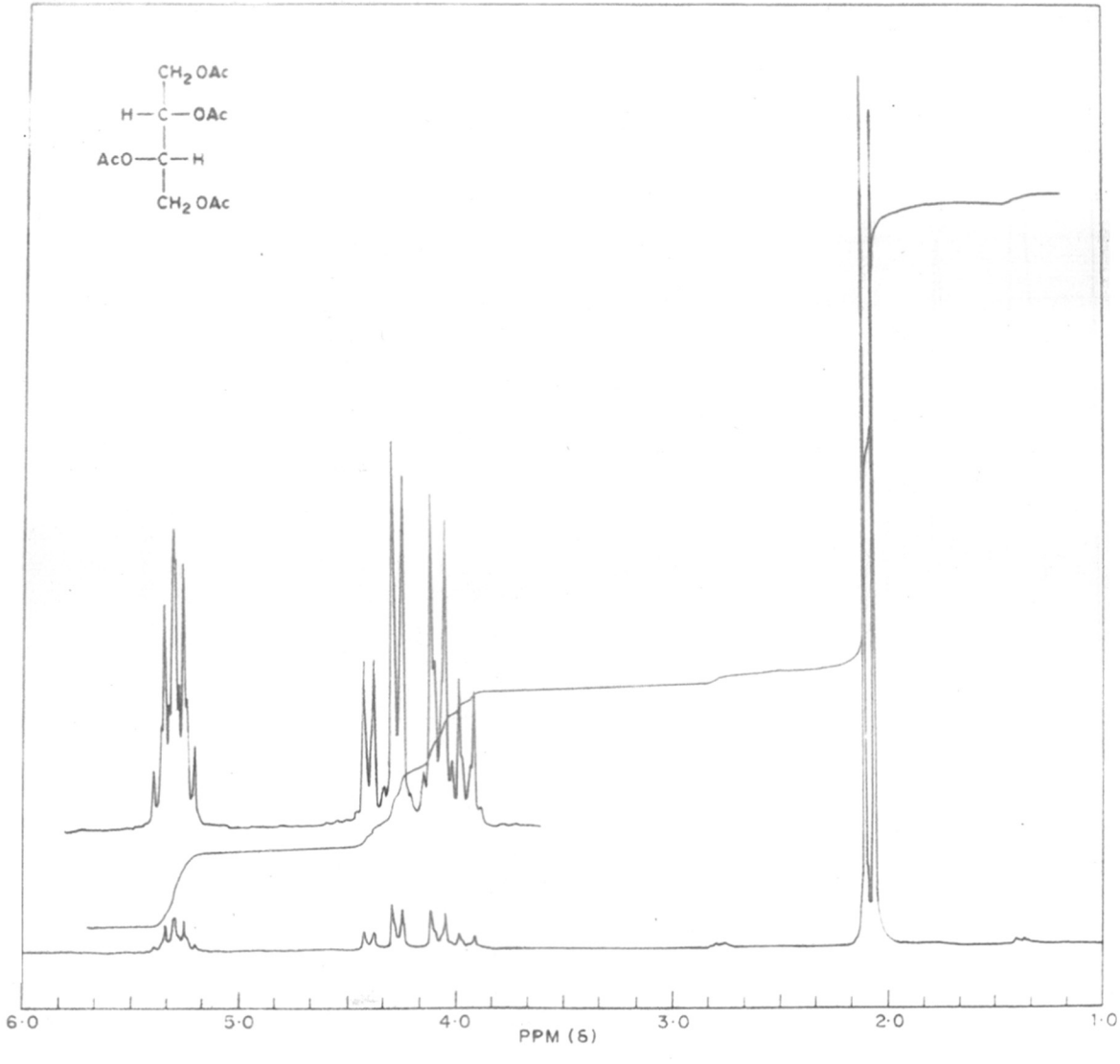




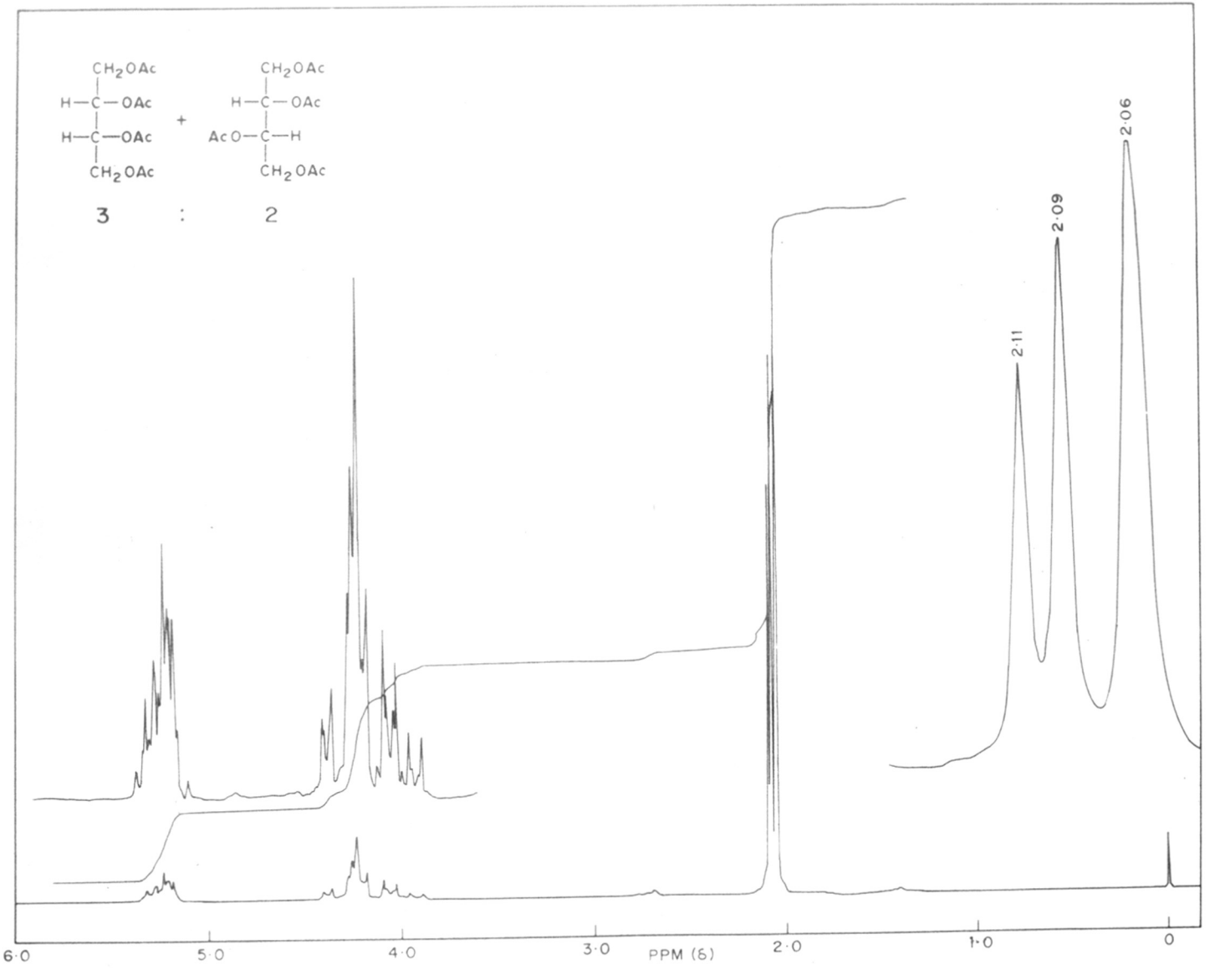
IR & NMR OF (±)-2,4-O-BENZYLIDENE-1-DEOXY-1-(1,3-DIPHENYL-2-IMIDAZOLIDYL)-ERYTHRITOL (5)



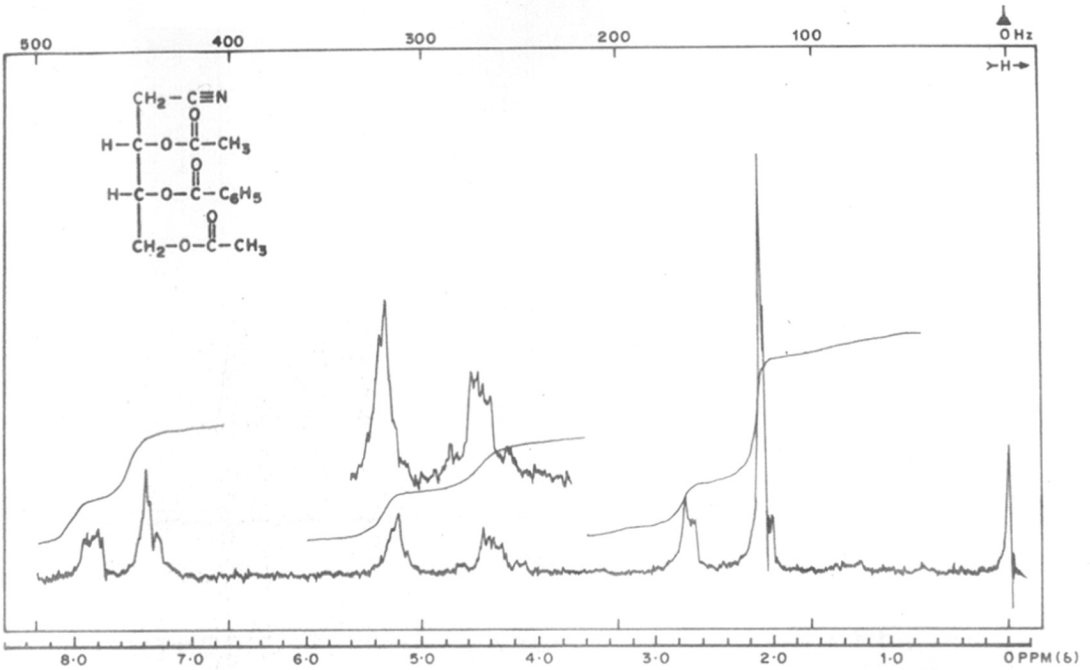
PMR SPECTRUM OF 1,2,3,4-TETRA-O-ACETYL-ERYTHRITOL (14)



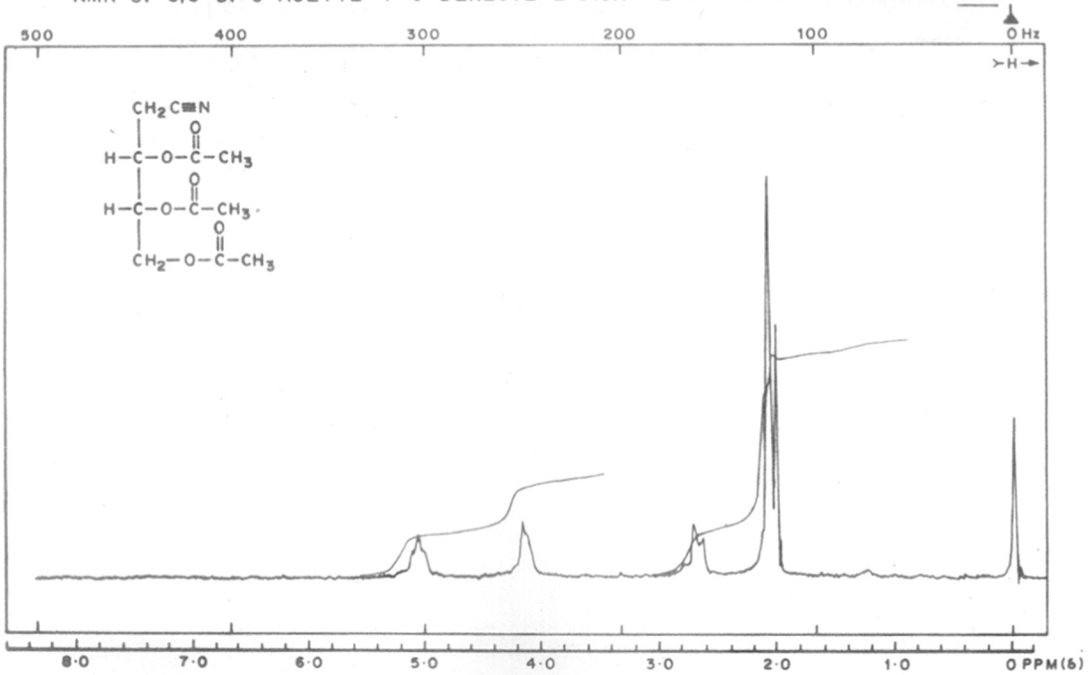
PMR SPECTRUM OF 1, 2, 3, 4-TETRA-O-ACETYL-THREITOL (16)



PMR SPECTRUM OF 3:2 MIXTURE OF 14 AND 16



NMR OF 3,5-DI-O-ACETYL-4-O-BENZOYL-2-DIOXY-ERYTHROPENTANONITRILE (50)



NMR OF 3,4,5-TRI-O-ACETYL-2-DEOXY-ERYTHROPENTANONITRILE (52)

CHAPTER-3

SYNTHESIS OF 5-PHENYL-2(5H)-FURANONE, 5-(2-METHYL-4-METHOXY) PHENYL-2(5H)-FURANONE, AND 5-(2-BENZOYLOXYMETHYL-4-METHOXY) PHENYL -2(5H)-FURANONE

SUMMARY

γ-Phenyl-γ-butyrolactone (1) is transformed to γ-phenyl-α-phenylseleno-γ-butyrolactone (2) employing the method of Sharpless. Oxidation of 2 with m-chloroperbenzoic acid has furnished 5-phenyl-2(5H)-furanone (3). Similarly, using this approach lactones 6 and 13 are prepared from the corresponding saturated lactones (4) and 9 via their seleno-lactones 5 and 10 respectively.

Lactone (4) is prepared from keto-acid (16) by $NaBH_4$ reduction and subsequent acidification.

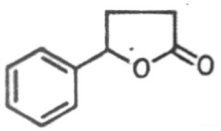
Lactone (9) is prepared from keto-acid (16) through the following sequence of reactions:

(i) Wolff-Kishner reduction, (ii) esterification, (ii) bromination with NBS, (iv) reaction with sodium acetate,, (v) saponification followed by acidification (vi) benzoylation.

The conjugated lactone (3) is transformed to keto-acid (14) on treatment with alkali.

During the Wolff-Kishner reduction of 16 the demethylated product 18 is also observed.

CHART I



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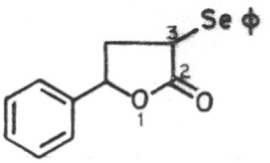

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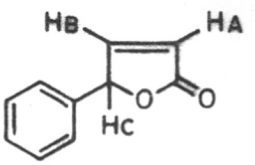

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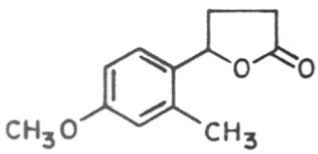

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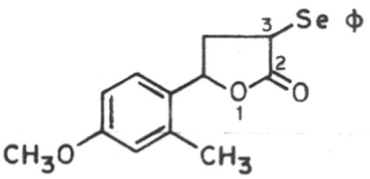

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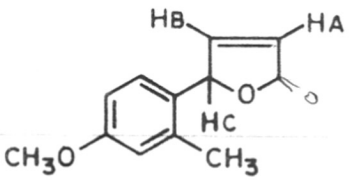

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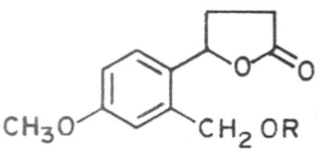
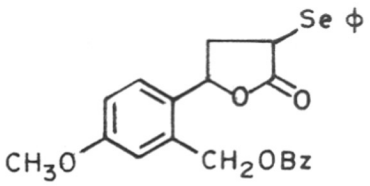


7 R= H

8 R = $COCH_3$

9 R = COC_6H_5



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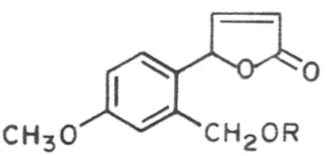
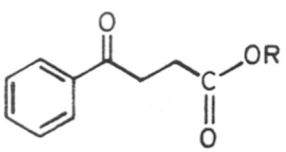


11 R = H

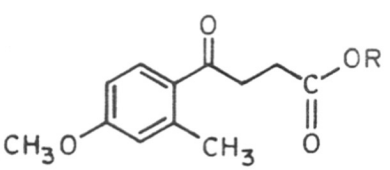
12 R = $COCH_3$

13 R = COC_6H_5



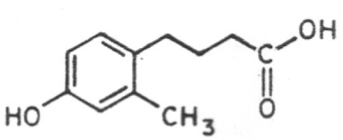
14 R = H

15 R = CH_3



16 R = H

17 R = CH_3

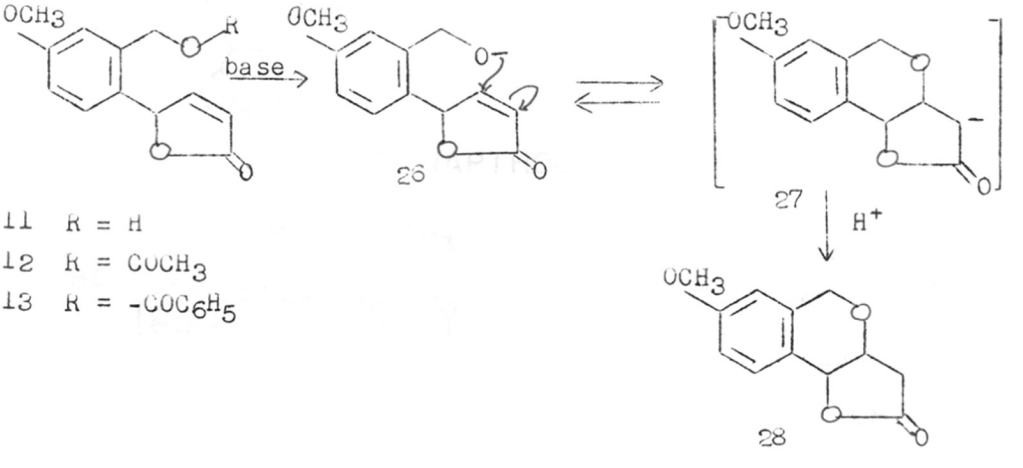


18

INTRODUCTION

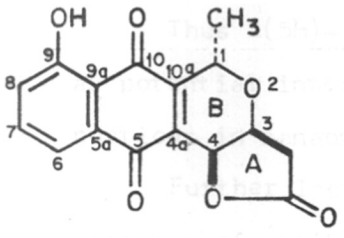
The antibiotics nanaomycin D (19), kalafungin (20), frenolicin B (21), griseusin A (22), naphthocyclinone (23), and granaticin A (24), which have two angularly fused heterocyclic rings, constitute an important series of naturally occurring compounds[1] of the naphthoquinone class of antibiotics. These natural products are potent antimicrobiol agents and nanaomycin D in particular has been shown to be extremely active against mycoplasms. Their rather complex molecular structure with γ-lactone (A) moiety and pyran ring (B) with naphthoquinone may be regarded as "structural turning points" in these antibiotics. Due to the complexity of these molecules many synthetic studies have been reported[2].

The 2(5H)-furanones 11, 12 and 13 can furnish tricyclic system (28) according to the reaction sequence as shown below:

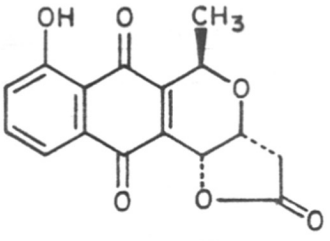


11 R = H
12 R = $COCH_3$
13 R = $-COC_6H_5$

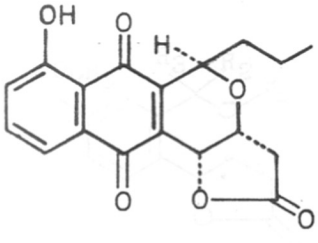
CHART II



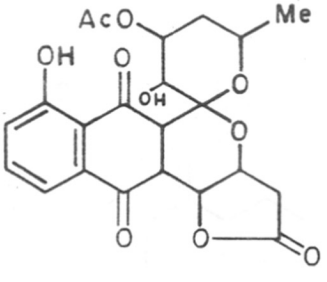
19. NANAOMYCIN D



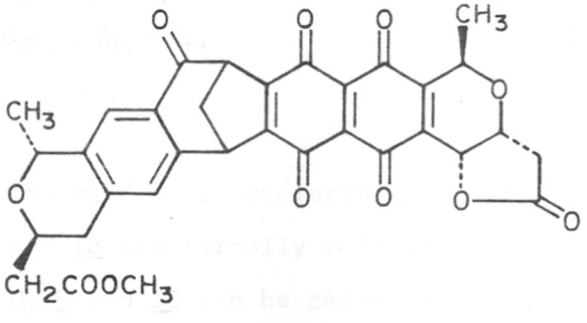
20. KALAFUNGIN



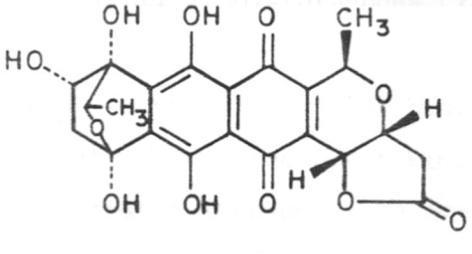
21. FRENOLICIN B



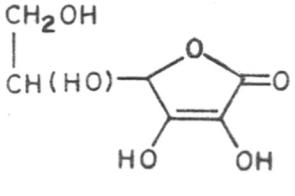
22. GRISEUSIN A



23. NAPTHOCYCLINONE



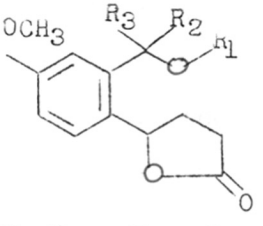
24. GRANATICIN-A



25. VITAMIN C

Thus 2(5H)-furanones 11, 12 and 13 can be considered as potential intermediates for the synthesis of heterocyclic portions in nanaomycin D.

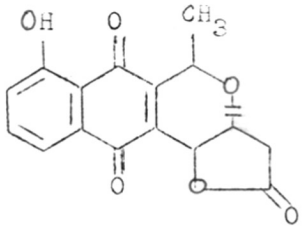
Further lactones 7, 8 and 9 resemble heterocyclic portions of antibiotic nanaomycin D (see Fig. 29, where O_2-C_3 bond has to be connected) as shown below:



7 $R_1 = R_2 = R_3 = H$

8 $R_1 = OCOCH_3$, $R_2 = R_3 = H$

9 $R_1 = -COC_6H_5$, $R_2 = R_3$



29

In turn, as far as heterocyclic portion is concerned lactones 9 and 13 are formally related to the antibiotic nanaomycin D; 9 and 13 can be regarded as 2,3-seco compounds.

Further 2(5H)-furanones (γ-crotonolactones, 2-buten-4-olides, $\Delta^{\alpha,\beta}$-butenolides) occur widely in nature[3] and possess an unusual range of biological activity[4]. They appear throughout the plant kingdom from the simple metabolites of lichens, mold and fungi[5] to the more complex

sesquiterpenes of the family compositae[5] and steriodal glycosides of the families Ranunculaceae, liliaceae, scrophulariaceae and apocyanaceae[7]. Vitamin C (25) is the most physiologically important butenolide. Recently 2(5H) furanone precursors have been used as the intermediates[8] in the synthesis of biologically active compounds like antileukaemic lignans, cerulenin, prostaglandin analogues and avenaciolide. That is why efficient synthesis of 2(5H)-furanones has received much attention during the past several years. A brief review of some of the existing methods for the preparation of 2(5H)-furanones are presented here:

(1) Bromination and dehydrobromination[9] (Scheme A, Chart III)

This method involves bromination and base induced dehydrobromination. For exmple[9], γ-butyrolactone (30) was brominated to bromolactone (31), which after dehydrobromination furnished 2(5H)-furanone (32). But wide diversity of brominating agents and bases attests to the capriciousness of the method. Hence this method may not be useful for the conversion of lactone into corresponding unsaturated lactone having different functionalities.

(2) From acetylenic compounds[10] (Scheme B, Chart III)

Smith et al. used acetylenic compounds as the key intermediates for the synthesis of 2(5H)-furanones. For example, 2(5H)-furanone (32) was prepared starting from

propargyl alcohol (34): Ethyl magnesium bromide was treated with propargyl alcohol (34) to furnish 35, which was treated with CO_2 under pressure to yield 4-hydroxy-2-butynoic acid (37). Compound (37) was hydrogenated in methanol using Pd-$BaSO_4$ at room temperature and product 38 was distilled to yield 2(5H)-furanone (32).

(3) From β,γ-butenolide[11] (Scheme C, Chart III)

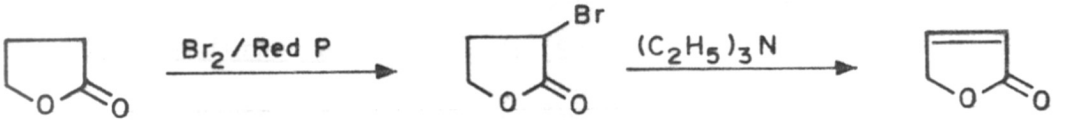
Action of heat, or bases such as triethylamine, piperidine and even benzylamine can isomerise $\Delta^{\beta,\gamma}$-butenolides into corresponding $\Delta^{\alpha,\beta}$-butenolides. Filler et al.[11] isomerised readily available α-benzylidene γ-phen-$\Delta^{\beta,\gamma}$-butenolide (39) to corresponding $\Delta^{\alpha,\beta}$ butenolide (40) using triethylamine or acetic anhydride or benzylamine as shown in Scheme C, Chart III.

(4) By Reformatsky reaction[12] (Scheme D, Chart III)

This is the most common method for the synthesis of $\Delta^{\alpha,\beta}$-butenolides particularly steriodal butenolides. Elderfield et al.[12] synthesised β-(6-methoxy-2-naphthyl)-$\Delta^{\alpha,\beta}$-butenoide (44) from 6-methoxy-2-bromo-naphthalene (41). To a cooled Grignard reagent of 41, methoxy acetonitrile was added to furnish ketone (42). Ethyl β-methoxymethyl-β-(6-methoxy-2-naphthyl)hydracrylate (43) was prepared from 42 using general Reformatsky procedure. Compound 43 with glacial acetic acid (saturated with hydrogen bromide) at 130-140° for 20 minutes furnished 44.

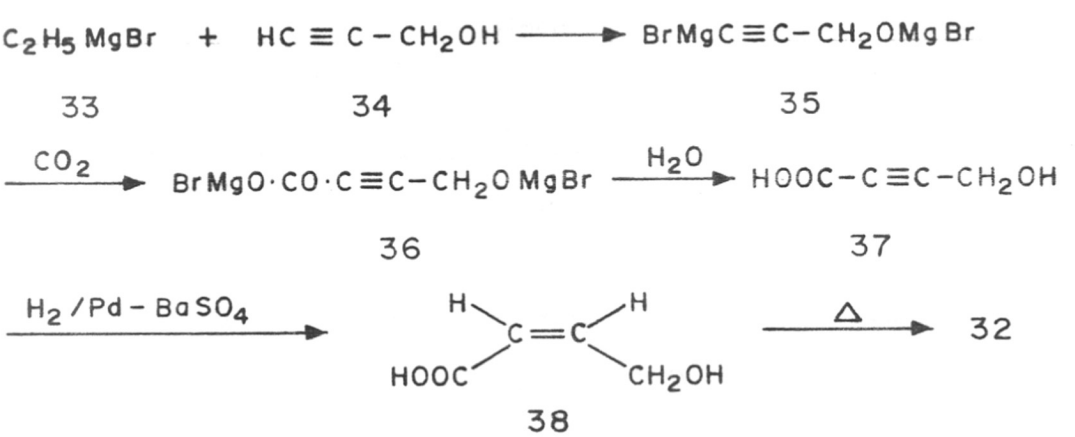
CHART – III

SCHEME A[9]



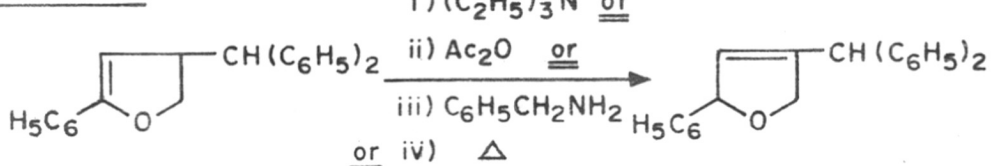
30 31 32

SCHEME B[10]



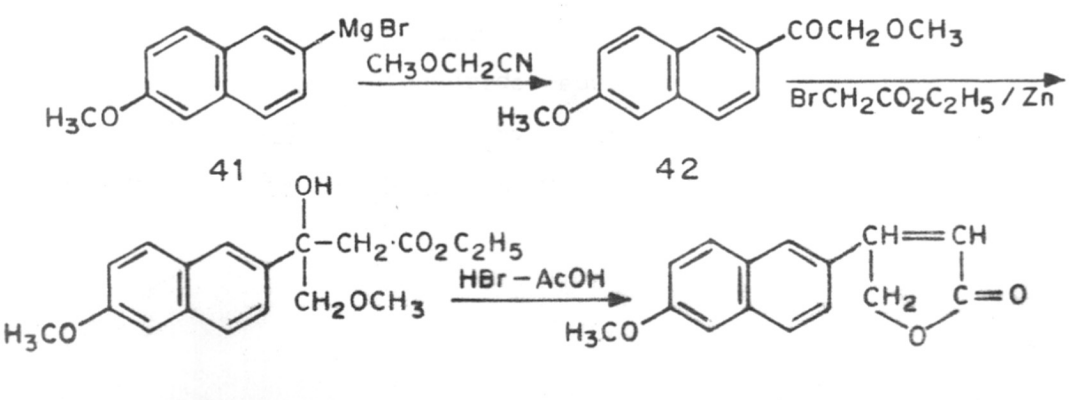
33 34 35 36 37 38 32

SCHEME C[11]



39 40

SCHEME D[12]



41 42 43 44

(5) From furan derivatives[13]: (Scheme E, Chart III)

2-Acetoxy furan (45) was reacted with bromine in CCl_4 at low temperature and furnished γ-bromo $\Delta^{\alpha,\beta}$-butenolide (48). Similarly γ-chloro $\Delta^{\alpha,\beta}$-butenolide (49) was prepared from 45 by the action of chlorine. γ-Acetoxy $\Delta^{\alpha,\beta}$butenolide (50) was obtained by the treatment of lead tetraacetate on 45 as shown in Scheme E, Chart III.

(6) From epoxy compounds[14,15]: (Scheme F, Chart III)

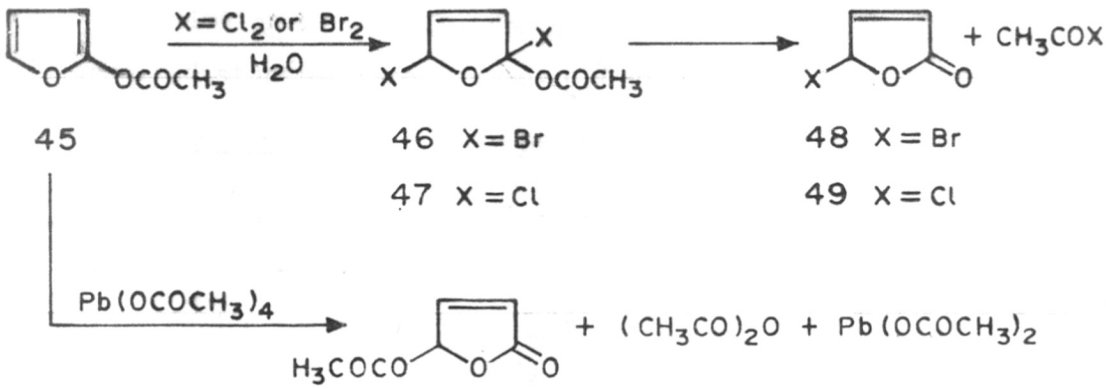
$\Delta^{\alpha,\beta}$-Butenolides are also obtained from epoxy compounds. For example , ethyl 3-cyclohexyl-2,3-epoxy-butyrate (51)(which can be readily formed by the Darzen's reaction) was converted into β-cyclohexyl $\Delta^{\alpha,\beta}$-butenolide (54)[14] and ethyl 3,4-epoxy-butyrate (55) into $\Delta^{\alpha,\beta}$-butenolide (32)[15] in the presence of acid catalyst, as shown by the reaction sequence in Scheme F, Chart III.

(7) Via alkylation of β-keto sulfoxides[16] (Scheme G, Chart III)

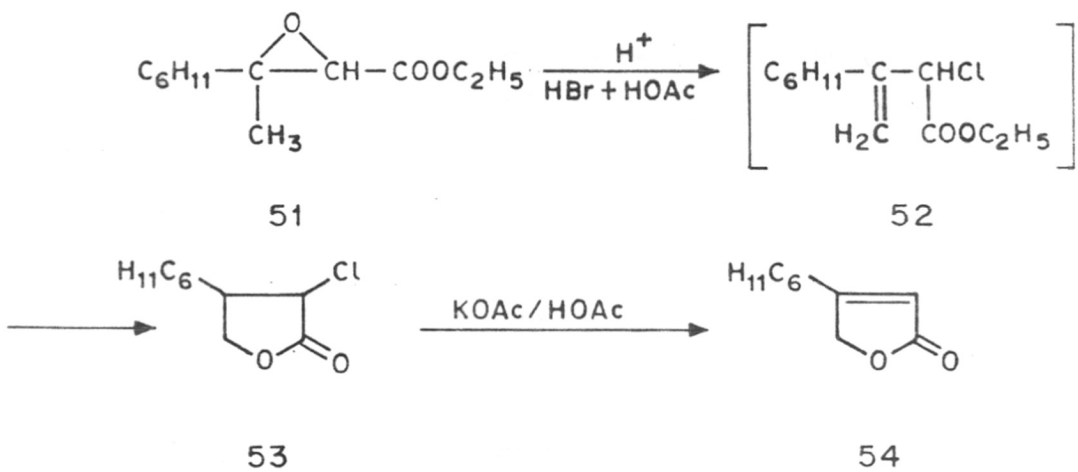
Bartlett et al.[16] prepared 5-cyclohexyl-2(5H)-furanone (59a) from β-keto-sulfoxide (56a) (where R = cyclohexyl): Alkylation of the anion derived from 56a with methyl bromo acetate furnished 57a. 2(5H)-Furanone (59a) was obtained on sodium borohydride reduction of the alkylated intermediate 57a, followed by lactonisation and loss of CH_3SOH, as shown in the Scheme G, Chart III..

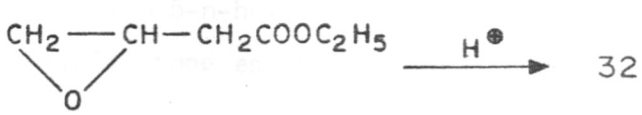
CHART – III (contd.)

SCHEME E[13]



SCHEME F[14]





55

Similarly 2(5H)-furanones 59b, 59c and 59d were prepared starting from β-keto-sulfoxides 56b, 56c and 56d.

(8) By sulfenylation and dehydrosulfenylation

(a) This method involves the direct sulfenylation of saturated lactone to α-thiolactone, which upon oxidation to sulfoxide followed by thermal decomposition furnishes corresponding unsaturated lactone. For example, Trost et al.[17] prepared 5-methyl-2(5H)-furanone (63) from γ-methyl-γ-butyrolactone (60) as shown in Scheme H, Chart III.

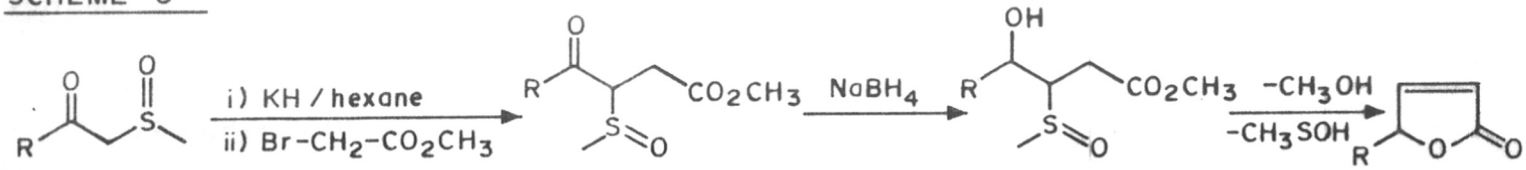
(b) Iwai et al.[18] prepared 5-phenyl-2(5H)-furanone (3) starting from (phenylthio) acetic acid (64). Acid (64) was treated with lithium diisopropylamide and the resulting dianion (65) treated with styrene oxide to give γ-phenyl-α-phenylthio-γ-butyrolactone (66), which was oxidised with m-chloroperbenzoic acid to sulfoxide (67). Pyrolysis of 67 furnished 3 (Scheme I, Chart III).

(9) Via selenylation and dehydroselenation[19] (Scheme J, Chart III)

This method involves selenylation of saturated γ-lactone using phenyl selenyl anion to phenyl seleno lactone, which on oxidation furnishes good yield of α,β-butenolide. Sharpless et al.[19] prepared 5-n-hexyl-2(5H)-furanone (71) from γ-n-hexyl-γ-butyrolactone as shown in Scheme J, Chart III.

CHART– III (contd.)

SCHEME G[16]



56 57 58 59

R =

a. METHYL

b. CYCLOHEXYL

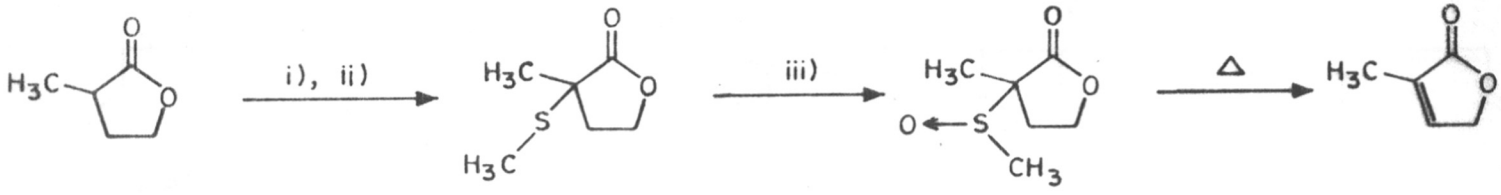
c. 10-ACETOXYDECYL

R =

d. p-METHOXY PHENYL

e. p-BROMO PHENYL

SCHEME H[17]



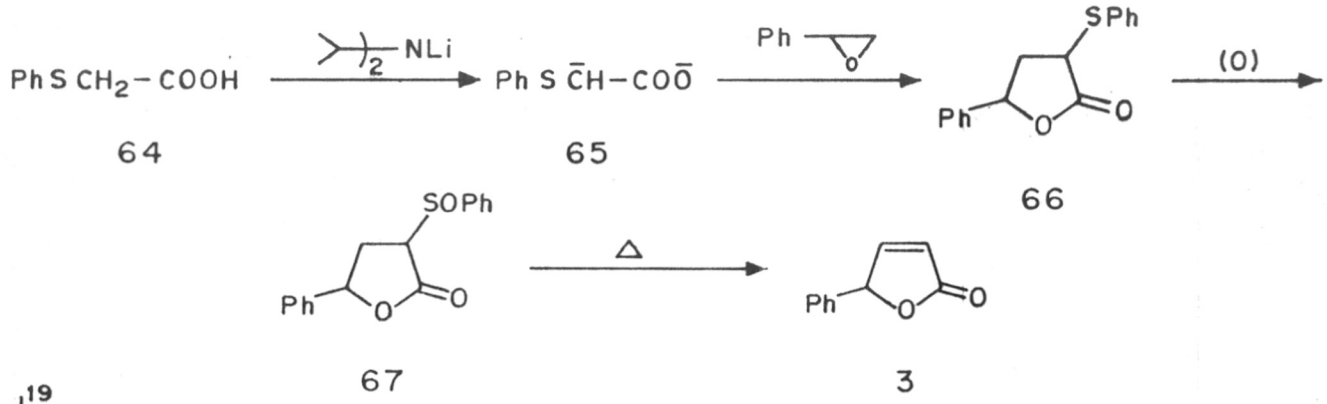
60 61 62 63

i) LITHIUM N-CYCLOHEXYL-N-ISOPROPYL AMIDE, –78°, THF ii) DIMETHYL DISULFIDE

iii) SODIUM META PERIODATE / CH_3OH

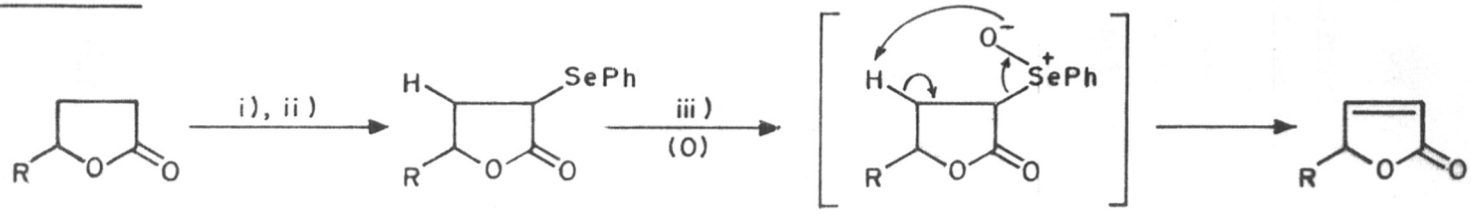
CHART – III (contd.)

SCHEME I[18]



64 65 66 67 3

SCHEME J[19]

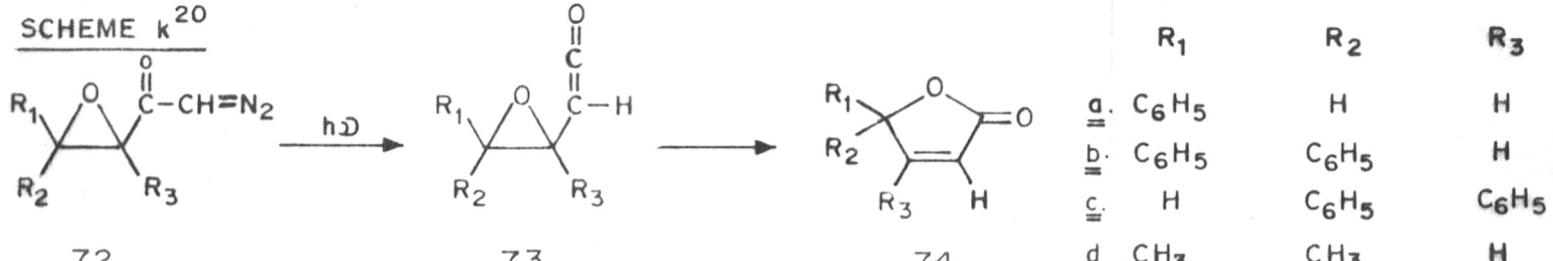


68 69 70 71

R = n-hexyl

i) LITHIUM DIISOPROPYL AMIDE, THF, –78° ii) PhSeBr iii) $NaIO_4$

SCHEME k[20]



72 73 74

	R_1	R_2	R_3
a.	C_6H_5	H	H
b.	C_6H_5	C_6H_5	H
c.	H	C_6H_5	C_6H_5
d	CH_3	CH_3	H

(10) By photochemical rearrangement of α,β-epoxy diazomethyl ketones[20] (Scheme K, Chart III)

B. Zwanenburg et al. prepared 5-phenyl-2(5H)-furanone (74a) in 80% yield, by the irradiation of β-phenyl-α,β -epoxydiazomethyl ketone (72a) in benzene solution for 1.5 to 2 hr via intramolecular cyclisation of initially formed ketene intermediate 73a. Reaction sequence is as shown in Scheme, K, Chart III.

Similarly, 2(5H)-furanones 74b, 74c and 74d were prepared by the irradiation of epoxy diazomethyl ketones 72b, 72c and 72d respectively.

(11) By reaction of lithium β-lithioacrylates with carbonyl compounds[21]: (Scheme L, Chart III)

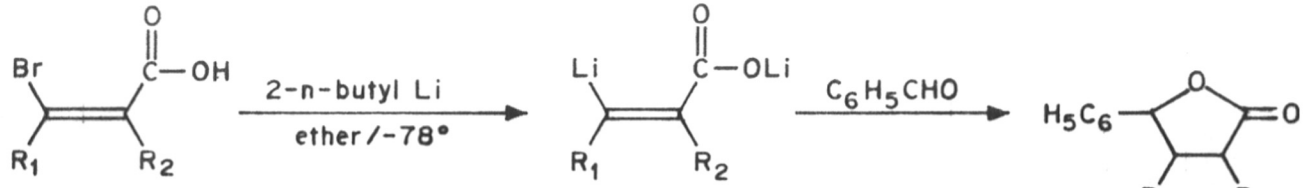
Lithium β-lithioacrylate (76a) prepared from z-β-bromoacrylic acid (75a)(by treatment with 2 moles equivalent of n-butyl lithium in ether at -78°) was condensed with benzaldehyde to furnish 5-phenyl-2(5H)-furanone (77a) in moderate yield. Similarly, 2(5H)-furanones 77b and 77c were prepared from 75b and 75c respectively.

(12) From furfural[22]: (Scheme M, Chart III)

4-Hydroxy-2-butenolide 80 (easily prepared from furfural (78) by photochemical oxidation) was used for the preparation of substituted $\Delta^{\alpha,\beta}$-butenolides. For example,

CHART – III (contd.)

SCHEME L[21]



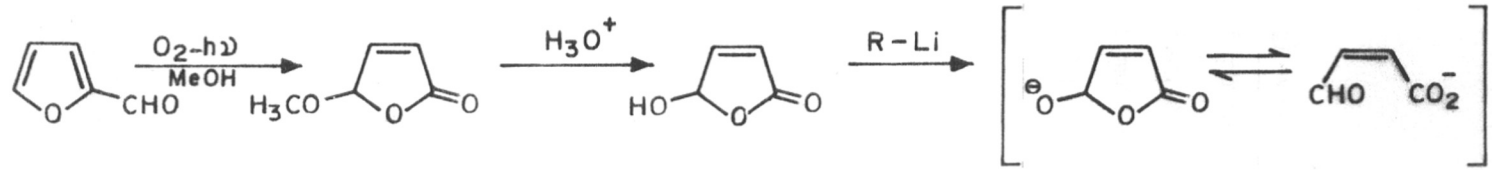
75 76 77

a. $R_1=R_2=H$

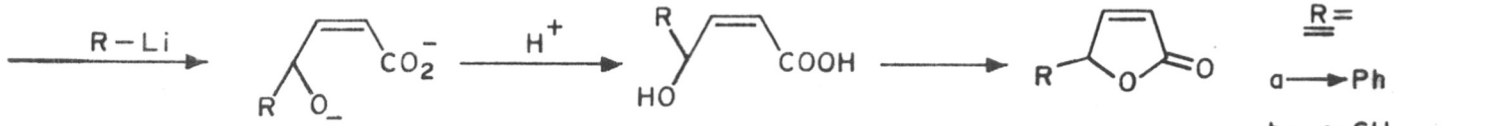
b. $R_1=H$, $R_2=CH_3$

c $R_1=CH_3$, $R_2=H$

SCHEME M[22]



78 79 80 81 82



83 84 85

R=

a → Ph

b → CH_3

c → VINYL

d → n-BUTYL

e → t-BUTYL

5-phenyl-2(5H)-furanone (85a) was prepared by the actionof two molecular equivalents of phenyllithium on 80. Similarly, 2(5H) furanones 85b, 85c, 85d and 85e were prepared by the treatment of methyllithium, vinyllithium, n-butyllithium and t-butyllithium on 80.

PRESENT WORK

Preparation of 2(5H)-furanones 3, 6 and 13 starting from 1, 4 and 9 are presented in this chapter. A convenient route to lactone 9 is also described.

As the lactones 9 and 13 can be regarded as seco-compounds of the heterocyclic portions of antibiotic nanaomycin D (see introduction, page No.101&103), we decided to prepare 9 and 13.

Literature revealed that, lactone (1) can be obtained[23] easily from keto-acid (14) (which can be prepared[84] by Friedel-Crafts acylation of benzene using succinic anhydride in presence of anhydrous aluminium chloride) by reduction of ketonic function and subsequent dehydration. Moreover methods are known to convert saturated lactones into the corresponding unsaturated lactones[17,19]. Hence we planned to use lactone 4 as the starting compound for the preparation of 9 which can be further used for the preparation of 13. Compound 13 may be expected to be reactive[25] due to the presence of butenolide ring; hence the step wherein the double bond is introduced to furnish compound 13 should involve mild experimental conditions. Since the method of Sharpless[19] for the preparation of α,β-unsaturated ketones and lactones through use of organoselenium reagent has proved useful[26] for the synthesis of a number of sensitive conjugated lactones, we chose this approach for the

preparation of 13 from 9.

Before actually preparing 13 from 9 using Sharpless approach we planned to prepare some 2(5H)-furanones e.g. 3 and 6 as model compounds.

Preparation of 5-phenyl-2(5H)-furanone (3)

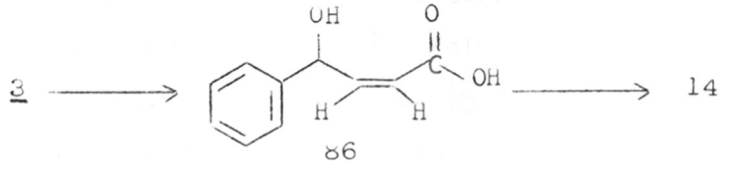
Keto-acid (14) is prepared[24] by the Friedel-Crafts acylation of benzene using succinic anhydride in presence of anhydrous aluminium chloride. Sodium borohydride reduction of 14 in presence of sodium carbonate and subsequent acidification furnished lactone (1) in good yield.

Enolate of 1 is obtained by treating 1 with lithium diisopropylamide (LDA prepared from n-butyllithium and diisopropylamine) at -78°; the resulting enolate is reacted with diphenyl diselenide ($\emptyset_2Se_2$) in hexamethylphosphoramide [$(Me_2N)_3PO$, HMPA] and worked out to furnish selenolactone (2); beside selenolactone (2), lactone (1) and $\emptyset_2Se_2$ having wide range of R_f values are also obtained. Pure selenolactone (2) is obtained in 89% yield [after correcting for the recovery of unreacted lactone (1)] by column chromatography over silica gel. Selenolactone (2) is characterised by PMR and mass spectral data: Mass spectrum shows M^+ (318) (100%) along with other peaks 316, 314, 320, 315 and 312 arranged according to decreasing order of their intensities, which

is in good agreement with the relative abundance of Se isotopes; relative abundance of Se isotopes are ^{80}, ^{78}, ^{76}, ^{82}, ^{77} and ^{74} in the decreasing order. This indicates the presence of selenium metal in 2. PMR spectrum shows a characteristic 1H doublet of doublets at δ 4.07 assignable to proton at C_3 in 2.

Oxidation of selenolactone (2) with H_2O_2 in acetic acid[26] was tried, but reaction mixture after workup did not show the presence of conjugated lactone (3), by PMR spectrum study. However, oxidation of 2 with m-chloroperbenzoic acid furnished conjugated lactone (3) in good yield. Pure lactone 3 is obtained by column chromatography over silica-gel and has been characterised by mass, IR and PMR spectral data. Mass spectrum shows the M^+ (106); IR spectrum shows bands at 1785 and 1760 cm^{-1} assignable[20] to C=O of conjugated lactone; PMR spectrum shows signals at δ 5.83 (1H, t, J = 2 Hz), 6.10 (1H, dd, J = 6 Hz and 2 Hz), 7.25 (5H, m) and 7 50 (1H, dd, J = 6 Hz and 2 Hz). A triplet at 5.83 having small coupling constant (J = 2 Hz) is assignable to H_6, whereas two doublet of doublets at 6.10 and 7.50 with coupling constants (J = 6 Hz and 2 Hz) can be assigned to H_A and H_B of the butenolide system in 3; these assignments are in good agreement with the one reported in literature[18].

Further, the action of alkali on 3 may be expected to open the conjugated lactone ring[3] to furnish the γ-hydroxy acid (86); since γ-hydroxy-α,β-unsaturated acids are known to isomerise to γ-keto-acids on treatment.



86

with alkali[27] (see Chapter I, page No. 19), it was anticipated that the butenolide 3 would furnish the keto-acid (14) on heating with alkali. In agreement with our expectation 3 is transformed to 14 upon heating with alcoholic alkali in good yield. γ-Keto-acid (14) thus obtained is characterised by converting it into its methyl ester (15) by diazomethane and by comparing the spectral data with the authentic sample. Thus identity of 3 is confirmed.

Preparation of 5-(2-methyl-4-methoxy)phenyl-2(5H)-furanone(6)

Keto-acid (16) is prepared[28] by the Friedel-Crafts acylation of m-cresol methyl ether using succinic anhydride in nitrobenzene as solvent. $NaBH_4$ reduction of keto-acid (16) in presence of sodium carbonate and subsequent acidification furnished lactone (4) in good yield.

Enolate of 4 is prepared by treating 4 with LDA at -78°; the reaction of the enolate with ϕ_2Se_2 in HMPA. furnished selenolactone (5). Pure selenelactone (5) is obtained in 89% yield (after correcting for the recovery of unreacted lactone (4) by column chromatography over silica-gel. Seleno-lactone (5) is characterised by PMR spectrum, which shows a characteristic 1H doublet of doublets at 4.13 assignable to proton at C_3.

Oxidation of 5 with m-chlorperbenzoic acid furnished conjugated lactone (6) in good yield, characterised through mass, IR and PMR spectral data: Mass spectrum shows M^+ (204); IR spectrum shows bands at 1788, 1770 and 1724 cm^{-1} assignable to C=O of conjugated lactone; PMR spectrum shows signals at 2.33 (3H, s), 3.77 (3H, s), 6.03 (2H, m), 6.70 (3H, m), and 7.46 (1H, dd, J = 5 Hz and 2 Hz); a doublet of doublets at 7.46 and two singlets at 2.33 and 3.77 are compatable with olefinic H_B, aromatic CH_3 and aromatic OCH_3 whereas 2H multiplet at 6.03 is assignable to H_A and H_C of butenolide (6).

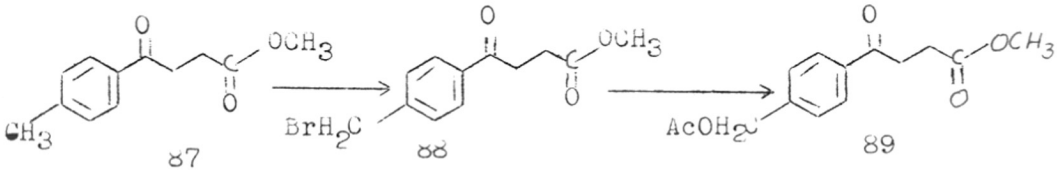
Further, the identity of 6 is confirmed by transforming it into keto-acid (16) upon treatment with alcoholic alkali as in the case of lactone (3).

Preparation of lactones 7,8 and 9

Literature reports[29] that NBS can be used to functionalise aromatic methyl into $-CH_2Br$, which can be

easily transformed to $-CH_2-OAC$ by heating with sodium acetate in acetic acid. But we could not functionalise the aromatic methyl group in 4 by heating with NBS and catalytic amount of benzoylperoxide in CCl_4 at reflux temperature; considerable amount tarry material was formed under these experimental conditions. That is why we planned to use keto-ester (17) easily prepared by esterification of keto-acid (16) as the starting material to get the required lactones 7, 8 and 9 on the basis of our model experiments as discussed below:

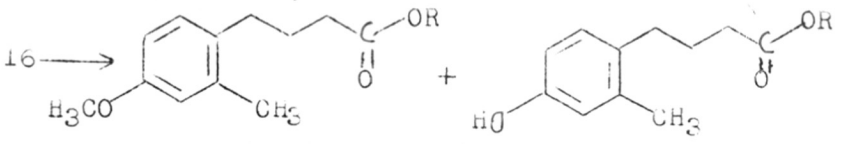
Bromo-compound (88) is obtained in 100% yield when keto-ester 87 is treated with NBS and catalytic amount



of benzoyl peroxide in CCl_4 at reflux temperature. Bromo-compound (88) is characterised by its PMR spectrum, which shows 2H singlet at δ 4.36 assignable to $-CH_2Br$. Identity of bromo compound (88) is further confirmed by transforming it into 89; PMR spectrum of 89 shows singlets at δ 2.03 (3H) and 5.03 (2H), assignable to $-OCOCH_3$ and $-CH_2-OAC$ respectively.

On the basis of these observations, we expected the functionalisation of aromatic methyl in 17 by NBS; but we could not achieve it, as approximately 50% of starting compound (17) was obtained back along with tarry material, when 17 was treateed with NBS and catalytic amount of benzoyl peroxide in CCl_4. Hence functionalisation of benzylic methyl in 17 is achieved through an alternate route as described below:

(a) Wolff-Kishner reduction of keto-acid (16) furnished a mixture of acids 90 and 18 in 1:1 proportion; identities of 90 and 18 are established by studying the mass, IR and PMR spectra of the derived methyl esters 91 and 92, which are isolated in pure form by column chromatography.

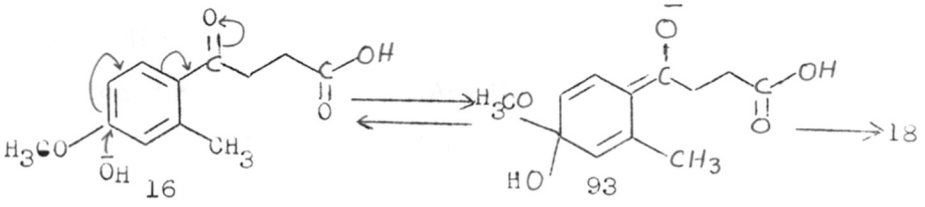


90 R = H
91 R = CH_3

18 R = H
92 R = CH_3

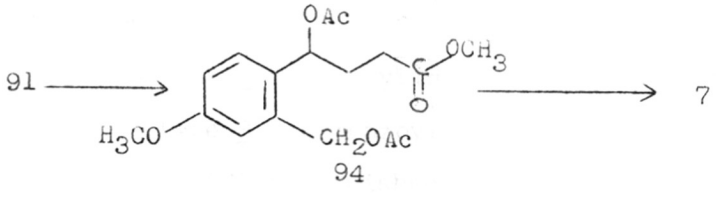
The acid 18 is probably formed through demethylation. It is suggested that 93 may be an intermediate during the demethylation of 16. There are precedents in literature

for demethylation of related compounds during Wolff-Kishner reduction[30].



Hence the product obtained after Wolff-Kishner reduction is methylated using dimethylsulfate-alkali and subsequently esterified to furnish high yield of 91.

(b) Ester 91 is treated with two moles of NBS in CCl_4 and the crude bromo-compound thus obtained is heated with sodium acetate in acetic acid to furnish the diacetate (94), characterised by analytical data:



Elemental analysis and mass spectral data fix the molecular formula, $C_{17}H_{22}O_7$; IR spectrum shows bands at 1730 (carbonyl) and 1225 cm^{-1} (acetate); PMR spectrum

exhibits signals at δ1.96 (6H, s), 2.26 (4H, m), 3.60 (3H, s), 3.83 (3H, s), 5.16 (2H, s), 5.83 (1H, m), 6.79 (2H, m), 7.23 (1H, d). 6H Singlet at 1.96 assignable to acetate CH_3 indicates the presence of two acetate moieties whereas 2H singlet and 1H multiplet at 5.16 and 5.83 can be assigned to $-CH_2-OAC$ and $Ar-CH(OAC)-$. Other signals are compatable with the assigned structure of 94 (see experimental, page No. 137).

(c) Diacetate (94) is saponified by alcoholic alkali and subsequently acidified to furnish the hydroxy lactone (7), characterised by mass, IR and PMR spectral data: Mass spectrum shows M^+ (222); IR spectrum exhibits bands at 3540 and 1779 cm^{-1} assignable to OH and C=O of γ-lactone; PMR spectrum shows signals at 2.50 (4H, m), 3.03 (1H, s), 3.80 (3H, s), 4.66 (2H, s), 5.80 (1H, t, J = 7 Hz), 6.90 (2H, m), 7.26 (1H, d, J = 8 Hz), which are consistant with the assigned structure of lactone 7 (see experimental, page No. 138).

Acylation of 7 using pyridine and acetic anhydride furnished acetate 8 and benzoylation of 7 using benzoyl-chloride and pyridine furnished benzoate 9 in good yield.

Introduction of conjugation in lactone moiety

Lactone 7 is not a good candidate to introduce double bond in lactone ring by Sharpless method, as it contains hydroxy group, which can react with LDA. Hence we

chose acetate (8) and benzoate (9) as the candidates for the introduction of conjugation.

Acetate (8) is reacted with LDA at -78°, the resulting anion is treated with ϕ_2Se_2 in HMPA. The product thus obtained is apparently a complex mixture, since TLC showed several spots; the PMR spectrum of the product did not exhibit a singlet at 2.03 for $-OCOCH_3$, suggesting that probably a proton has been abstracted from the CH_3CO-O- group. This suggestion is supported by the appearance of a signal at 4.46 (2H, s), which may be due to $-O-CO-CH_2-Se\phi$. Obviously the acetate 8 is also not a convenient starting material for introducing conjugation in the lactone ring employing the method of Sharpless. Hence benzoate (9) is used, as there are no acidic protons in the acyl moeity.

Benzoate 9 is treated with LDA and resulting enolate of 9 is reacted with ϕ_2Se_2 in HMPA to give selenolactone (10), characterised by its IR and PMR spectral data. (see experimental, page No. 140).

Oxidation of 10 with m-chloroperbenzoic acid furnished conjugated lactone 13. IR spectrum of 13 exhibit bands at 1780, 1757, 1724 and 1701 cm^{-1} indicating the presence of carbonyl (IR spectral data is not much useful due to the presence of benzoate group and conjugated lactone moiety in 13, leading to complex pattern in carbonyl region). PMR spectrum shows signals at δ 3.82

(3H, s), 5.40 (2H, s), 6.24 (1H, dd, J = 5 Hz and 2 Hz), 6.42 (1H, t, J = 2 Hz) 7.00 (2H, m), 7.51 (5H, m), 8.04 (2H, m), compatable with the structure of unsaturated lactone lactone (13) (see experimental, page No. 140).

EXPERIMENTAL

Diphenyl diselenide (ϕ_2Se_2)

Diphenyl diselenide was prepared from seleno-phenol (PhSeH) (prepared from phenylmagnesium bromide and selenium metal according to literature[31] method) by air-oxidation in very good yield[32].

Phenyl-γ-butyrolactone (1)

To a stirred solution of keto-acid (14)[24] (5.34 g, 30 mmol), sodium carbonate (3.5 g, 33 mmol), methanol (30 ml) and water (30 ml), $NaBH_4$ (1.13 g, 30 mmol) was added in portions. After complete addition of $NaBH_4$, reaction mixture was stirred overnight, diluted with water, acidified and heated to 60° for 15 min. Reaction mixture was cooled and extracted with ethylacetate (3 x 50 ml). Combined ethylacetate extracts were washed with sodium carbonate solution (10%), water and dried. Removal of ethylacetate furnished lactone (1) (4.20 g), purified through distillation. Yield: 89%, b.p. 150-55°(bath temp.)/1 mm (lit.[23] b.p. 178-79°/18 mm); TLC (solvent system B): R_f 0.65; IR: 1785 (C=O of γ-lactone); PMR: 2.43 (4H, m, $-C\underline{H}_2-C\underline{H}_2-$), 5.33 (1H, m, $\phi-C\underline{H}<$), 7.29 (5H, s, aromatic H).

Y-Phenyl-α-phenylseleno-Y-butyrolactone (2)

To a dry THF solution of lithium diisopropylamide (LDA. prepared from 2.96 M butyllithium (1.5 ml, 5.2 mmol) in hexane, dry THF (3 ml) and diisopropylamine (0.8 ml, 5.7 mmole) under nitrogen at -78°, lactone (1) (0.40 g, 2.5 mmol) in dry THF was added dropwise over a period of 45 min. After the reaction mixture was stirred at -78° for 1 hr., diphenyl diselenide (1.60 g, 5.1 mmol) in dry THF (4 ml) and hexamethyl-phosphoramide (HMPA) (0.9 ml, 5.2 mmol) was added dropwise at -78°. The mixture was stirred at -78° for 30 min then at -40° for 2 hr and subsequently quenched with 0.5 N HCl. The mixture was extractedwith ether (3 x 50 ml). Ether extracts were washed with water, dried and concentrated. Residue (1.76 g) was chromatographed on silica-gel (35 g). The column was eluted with (i) pet.ether, (ii) pet.ether + ethylacetate (98:2), (iii) pet.ether + ethylacetate (96:4), (iv) pet.ether + ethylacetate (94:6), (v)pet.ether + ethylacetate (92:8), (vi) pet.ether + ethylacetate (90:10). Fraction (ii) was composed of unreacted ϕ_2Se_2; fraction (vi) furnished unreacted lactone (1) (0.09 g); fraction (iv) yielded selenolactone (2) (0.53 g); yield 89% (after correcting for the recovery of unreacted lactone (1); m.p.76-78°; TLC (solvent system B): R_f, 0.71;

IR: 1788 (γ-lactone C=O); PMR: 2.23 (1H, m, Ø-C$\underset{1}{H}$-C$\underline{H}_2$-), 3.00 (1H, m, Ø-C$\underset{1}{H}$-C$\underline{H}_2$-), 4.07 (1H, dd, J = 11 Hz and 9 Hz, >CHSeØ), 5.30 (1H, dd, J = 9 Hz and 7 Hz, Ø-C$\underline{H}$-CH$_2$-), 7.23 (8H, m, aromatic H), 7.70 (2H, m, aromatic H ortho to Se); MS: m/z 318 (M^+).

5-Phenyl-2(5H)-furanone (3)

To a stirred solution of seleno-lactone (2) (0.32 g, 1 mmol) in dry THF (5 ml) at 0°, m-chloroperbenzoic acid (0.52 g, 3 mmol) was added. After 15 min, the reaction mixture was allowed to warm to 25° and maintained at 25° for 2 hr and then poured into cold saturated sodium-bicarbonate solution and extracted with ether (3 x 25 ml). Combined ether extracts were washed with water and dried. Removal of ether furnished crude 2(5H)-furanone (3), which was purified through column chromatography over silica-gel. Fraction eluted with pet.ether + ethylacetate (94:6) yielded pure 3 (0.15 g), yield: 93%; TLC (solvent system B): R_f, 0.64; IR: 1786, 1751, 1718; PMR: 5.83 (1H, t, J = 2 Hz, Ø-C$\underline{H}$<), 6.10 (1H, dd, J = 6 Hz amd 2 Hz, vinylic H to C=O), 7.25 (5H, m, aromatic H), 7.50 (1H, dd, J = 6 Hz and 2 Hz, vinylic H β to C=O); MS: m/z 160 (M^+).

Action of alkali on 3

A mixture of 3 (45 mg, 28 mmol), sodiumhydroxide (90 mg, 2.8 mmol), methanol (5 ml) and water (5 ml) was

heated under reflux for 2 hr, diluted with water, acidified and extracted with ether. Ether extract was washed with aqueous sodium carbonate (10%), water and dried. Removal of the ether furnished practically no residue. Sodium carbonate extract was acidified with and extracteed with ether. Ether extract was washed/water, dried and concentrated. Residue after esterification using diazomethane furnished ester (15) (38 mg), yield:70%; identity of 11 was established through TLC, IR and PMR comparison with an authentic sample.

4-Oxo-4-(2-methyl-4-methoxyphenyl)butanoic acid (16)

Keto-acid (16) was prepared using methyl ether of m-cresol and succinic anhydride in presence of anhydrous aluminium chloride and nitrobenzene as solvent, according to literature method[33], m.p.136-38° (lit.[33] 138-40°).

Methyl 4-oxo-4-(2-methyl-4-methoxyphenyl)butanoate (17)

A mixture of keto-acid (16) (5 g, 22 mmol), methanol (100 ml) and conc. H_2SO_4 (2 ml) was refluxed on water bath for 5 hr. Removed the excess of methanol under suction and residue was extracted with ether. Ether extract was washed with aq.sodium carbonate (10%), water and dried. Evaporation of ether furnished ester (17) (4.66 g); m.p.45-46°; b.p.165-170 (bath temp.)/0.5 mm; yield: 87%; (solvent system B): R_f, 0.64; IR: 1751 (ester carbonyl), 1681 (benzylic carbonyl); PMR: 2.46 (3H, s,

Ar-C$\underline{H}_3$), 2.60 (2H, t, J = 6 Hz, -C$\underline{H}_2$-COOCH$_3$), 3.10 (2H, t, J = 6 Hz, Ar-CO-C$\underline{H}_2$-), 3.63 (3H, s, -COOC$\underline{H}_3$), 3.80 (3H, s, Ar-OC$\underline{H}_3$), 6.70 (2H, m, aromatic H), 7.73 (1H, d, J = 10 Hz, aromatic H).

Y-(2-Methyl-4-methoxy)phenyl-Y-butyrolactone (4)

To a stirred solution of keto-acid[33] (16) (4.44 g, 20 mmol), sodium carbonate (2.50 g, 24 mmol), methanol (30 ml) and water (30 ml, $NaBH_4$ (0.75 g, 20 mmol) was added in portions. After complete addition of $NaBH_4$, reaction mixture was stirred overnight, diluted with water, acidified and heated at 60° for 15 min. Reaction mixture was cooled and extracted with ethylacetate (3 x 75 ml). Combined ethylacetate extracts were washed with sodium carbonate solution (10%), water and dried. Removal of ethylacetate furnished lactone (4) (3.73 g), purified through column chromatography over silica-gel (50 g, yield: 90%; m.p.49-50°; TLC (solvent system B): R_f, 0.61; IR: 1786 (Y-lactone C=O); PMR: 2.30 (3H, s, Ar-C$\underline{H}_3$), 2.44 (4H, m, -C$\underline{H}_2$-C$\underline{H}_2$-), 3.80 (3H, s, Ar-OC$\underline{H}_3$), 5.57 (1H, t, J = 7 Hz, Ar-C$\underline{H}$), 6.73 (2H, m, aromatic H), 7.30 (1H, d, J = 10 Hz, aromatic H); (Found: C, 69.63; H, 6.87. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%).

Y-(2-Methyl-4-methoxy) phenyl-α-phenylseleno-Y-butyrolactone (5)

To a dry THF solution of LDA (prepared from 2.96 M butyllithium (3.7 ml, 10 mmol) in hexane, dry THF (4 ml)

and diisopropylamine (1.4 ml, 10 mmol)under N_2 at -78°, lactone (4) (1.03 g, 5 mmol) in dry THF (4 ml) was added dropwise over a period of 1 hr. After the reaction mixture was stirred at -78° for 1.5 hr, ϕ_2Se_2 (3.12 g, 10 mmol) in dry THF (5 ml) and HMPA (1.8 ml, 10 mmol) mixture was added dropwise at -78°. The mixture was stirred at -78° for 30 min. then at -40° for 2 hr. and subsequently quenched with 0.5 NHCl. The mixture was extracted with ether (4 x 50 ml). Ether extracts were washed with water, dried and concentrated. Residue was subjected to column chromatography on silica-gel (75 gm). The column was eluted with (i) pet.ether, (ii) pet.ether + ethylacetate (96:4), (iii) pet.ether + ethylacetate (92:8), (iv)pet.ether + ethylacetate (90:10). Fraction eluted with pet.ether furnished ϕ_2Se_2 (1.80 g); fraction eluted with pet.ether + ethylacetate (90:10) yielded unreacted lactone (4) (0.31 g); fraction eluted with pet.ether + ethylacetate (92:8) was composed of pure selenolactone (5)(1.06 g); yield 89% (after correcting for the recovery of unreacted lactone (4); TLC (solvent system B): R_f, 0.66; IR: 1779 (lactone C=O); PMR: 2.20 (3H, s, Ar-C$\underline{H}_3$), 2.25 to 3.1 (2H, m, Ar-C$\underline{H}$-C$\underline{H}_2$); 3.80 (3H, s, Ar-OC$\underline{H}_3$), 4.13 (1H, dd, J = 10 Hz and 2 Hz, >C$\underline{H}$-Se-ϕ), 5.46 (1H, dd, J = 9 Hz and 7 Hz, Ar-C$\underline{H}$<), 6.60 to 7.70 (m, aromatic H), 7.80 (2H, m, aromatic H ortho to Se).

5-(2-Methyl-4-methoxy) phenyl-2(5H)-furanone (6)

To a stirred solution of selenolactone (5) (0.40 g, 1.1 mmol) in dry THF (4 ml) at 0°, m-chloroperbenzoic acid (0.60 g, 3.4 mmol) was added. After 20 min, the reaction mixture was allowed to warm to 25° and maintained at 25° for 2 hr. Poured into ice-cold sodium-dicarbonate solution (10%, 40 ml) and extrcted with ether. Ether extract was washed with water, dried and concentrated. Residue was chromatographed using silica gel (5 gm). Fraction eluted with pet.ether + ethylacetate (91:9) yielded pure conjugated lactone (6) (0.20 g) yield: 89%; TLC (solvent system B): R_f, 0.60; IR: 1788, 1770, 1724; PMR: 2.33 (3H, s, Ar-CH_3), 3.77 (3H, s, Ar-OCH_3), 6.03 (2H, m, Ar-CH_3), 6.03 (2H, m, Ar-CH and vinylic H α to C=O), 6.70 (3H, m, aromatic H), 7 46 (1H, dd, J = 5 Hz and 2 Hz; vinylic Hβ to C=O); MS: M/z 204 (M^+).

Action of alcoholic alkali on 6

A mixture of 6 (0.05 g, 0.25 mmol), sodium hydroxide (0.10 g, 2.5 mmol), methanol (5 ml) and water (5 ml) was heated under reflux for 2 hr, diluted, acidified and extracted with ether. Ether extract was washed with water and dried. Removal of the ether furnished a residue, which after esterification using diazomethane yielded ester (17) (0.04 g), yield 73.63%; the identity of 17 was established through comparison of IR and PMR spectra with an

authentic sample.

Methyl 4-oxo-4-(4'-bromomethylphenyl)butanoate (88)

A mixture of keto-ester (87) (see Chapter I, Page No.) (2.06 g, 10 mmol), NBS (1.96 g, 11 mmol), benzoyl peroxide (100 mg) and CCl_4 was refluxed for 1 hr. During reflux, reaction mixture was irradiated with 250 W IR lamp. Filtered hot. Residue was washed with hot CCl_4. Filtrates and washings were combined and concentrated to furnish 88 (2.80 g). Recrystalised by pet.ether + ethylacetate (9:1); yield: 100%; m.p.81-82°; IR: 1739 (ester C=O), 1684 (benzylic C=O); PMR: 2.63 (2H, t, J = 6 Hz, $-CH_2-COOCH_3$), 3.13 (2H, t, J = 6 Hz, $Ar-CO-CH_2-$), 3.60 (3H, s, $-COOCH_3$), 4.36 (2H, s, $-CH_2-Br$), 7.26 (2H, d, J = 8 Hz, aromatic H), 7.76 (2H, d, J = 8 Hz, aromatic H);

(Found: C, 50.56; H, 4.59. $C_{12}H_{13}BrO_3$ requires C, 50.22; H, 4.63%).

Methyl 4-oxo-4-(4'-acetoxymethylphenyl)butanoate (89)

A mixture of bromo-compound (88) (1.42 g, 5 mmol), sodium acetate (0.82 g, 10 mmol), acetic acid (10 ml) and acetic anhydride (5 ml) was heated at 115-120° for 1.5 hr. Reaction mixture was cooled, diluted with water (100 ml) and extracted with ether. Ether extract was washed with sodium carbonate solution (10%), water and dried. Evaporation of the ether furnished 89 (1.22 g, yield: 92%

IR: 1742 (broad, acetate and ester C=O), 1684 (benzylic C=O), 1220 (acetate); PMR: 2.03 (3H, s, $-OCOCH_3$), 2.60 (2H, t, J = 6 Hz, $-CH_2-COOCH_3$), 3.13 (2H, t, J = 6 Hz, $Ar-CO-CH_2-$), 3.66 (3H, s, $-COOCH_3$), 5.03 (2H, d, $-CH_2-OAc$), 7.33 (2H, d, J = 8 Hz) aromatic H), 7.86 (2H, d, J = 8 Hz, aromatic H to C=O) (Found: C, 63.40; H, 6.26. $C_{14}H_{16}O_5$ requires C, 63.62; H, 6.10%).

Wolff-Kishner reduction of 16

A mixture of keto-acid (16) (5 g, 22.5 mmol), potassium hydroxide (3.5 g, 62 mmol), hydrazine hydrate (3 ml) and diethylene glycol (30 ml) was heated under reflux for 1.5 hr. Water and excess of hydrazine hydrate were distilled out. Then reaction mixture was heated under reflux for 3 hr, cooled, diluted with water (200 ml), acidified (10% HCl) and extracted with ether (3 x 100 ml). Ether extracts were washed with water, dried and concentrated. Residue (4.64 g) thus obtained was esterified using methanol (50 ml) and conc. H_2SO_4 (1 ml). Crude ester (4.90 g) was chromatographed using grade II alumina (100 gm). Column was eluted with (i) pet.ether, (ii) pet.ether + ethylacetate (97:3), (iii) pet.ether + ethylacetate (94:6), (iv) pet.ether + ethylacetate (91:9), (v) pet.ether + ethylacetate (88:12). Fraction (ii) furnished (91) (2.32 g); yield 46%; b.p.135/1 mm; TLC (solvent system B): R_f 0.75; IR: 1733 (C=O);

PMR: 1.93 (2H, m, $-CH_2-\underline{CH_2}-CH_2-$), 2.33 (3H, s, Ar-$\underline{CH_3}$), 2.46 (4H, m, $-\underline{CH_2}-CH_2-\underline{CH_2}$), 3.66 (3H, s, $-COO\underline{CH_3}$), 3.80 (3H, s, Ar-$O\underline{CH_3}$), 6.66 (2H, m, aromatic H), 7.03 (1H, d, J = 10 Hz, aromatic H); MS: m/z 222 (M^+); (Found: C, 70.51; H, 8.32. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.11%).

Fraction (V) was composed of ester methyl 4-(2-methyl-4-hydroxy) phenyl-butanoate (92) (2.12 g), yield 45%; m.p.68°; TLC (solvent system B); R_f 0.59; IR: 3550 (OH), 1724 (C=O); PMR: 1.83 (2H, m, $-CH_2-CH_2-$), 2.13 (3H, s, Ar-$\underline{CH_3}$); 2.33 (4H, m, $-\underline{CH_2}-CH_2-\underline{CH_2}-$), 3.60 (3H, s, $-COO\underline{CH_3}$), 6.43 (3H, m, aromatic H and OH), 6.73 (1H, d, J = 10 Hz, aromatic H); MS: m/z 208 (M^+); Found: C, 69.53; H, 8.04. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%).

4-(2-Methyl-4-methoxy)phenyl-butanoic acid (90)

A mixture of keto-acid (16) (6.00 g, 27 mmol), hydrazine hydrate (5 ml), potassium hydroxide (4.50 g, 80 mmol) and diethylene glycol (40 ml) was heated under reflux for 1.5 hr. Water and excess of hydrazine hydrate was distilled off and reaction mixture was heated under reflux for 3 hr, cooled, diluted with water, acidified (10% HCl) and extracted with ether (4 x 75 ml). Ether extracts were washed with water, dried and concentrated. Residue (mixture of acids 90 and 18) was heated at 100° with continuous stirring with dimethylsulfate (10 ml), sodium hydroxide (7 g) and water (100 ml) for 2 hr.

Reaction mixture was cooled, acidified (10% HCl) and extracted with ether. Ether extract was washed with water, dried and concentrated. Residue after recrystalisation using ethylacetate + pet.ether (1:1) furnished 90 (5.22 g); yield 93%; m.p.76 78°; IR: 3490 (OH), 1720 (C=O); (Found: C, 68.85; H, 7.75. $C_{12}H_{14}O_3$ requires C, 69.21; H, 7.74%).

Methyl 4-(2-methyl-4-methoxy)phenyl-butanoate (91)

To the mixture of acid (90) (6.24 g, 30 mmol), methanol (100 ml), concentrated H_2SO_2 (2 ml) was added and reaction mixture was refluxed on water bath for 5 hr. Excess of methanol was removed under reduced pressure and residue was extracted with ethylacetate. Organic extract was washed with aqueous sodium carbonate (10%), water and dried. Solvent was distilled off and residue was distilled under vacuum to furnish 91 (6.31 g); yield, 95%; b.p.134-5°/1 mm; IR and PMR data were identical with the sample prepared as described above.

Methyl 4-(2-acetoxymethyl-4-methoxy)phenyl-4-acetoxy-butanoate (94)

A mixture of (91) (4.44 g, 20 mmol), NBS (7.85 g, 44 mmol), benzoylperoxide (0.10 g) and CCl_4 (100 ml) was heated under reflux for 1 hr under irradiation with 250W IR lamp and filtered hot. Filtrate was washed with water, dried and concentrated. Residue (7.42 g) was heated at

115-120° for 1.5 hr with a mixture of sodium acetate (3.3 g), acetic acid (30 ml) and acetic anhydride (15 ml), cooled, diluted with water (100 ml) and extracted with ether. Ether extract was washed with sodium carbonate solution (10%), water and dried. Evaporation of the ether furnished crude 94 (5.60 g), which was purified by column chromatography over grade II alumina (110 g). Fraction eluted with pet.ether + ethylacetate (92:8) furnished pure diacetate (94), (4.21 g); yield 62%; TLC (solvent system B): R_f, 0.60; IR: 1730 (C=O); PMR: 1.96 (6H, s, $-OCOCH_3$), 2.26 (4H, m, $-CH_2-CH_2-$), 3.60 (3H, s, $-COOCH_3$), 3.83 (3H, s, $Ar-OCH_3$), 5.16 (2H, s, $-CH_2-OAc$), 5.83 (1H, m, $Ar>CH-OAc$), 6.79 (2H, m, aromatic H), 7.23 (1H, d, J = 10 Hz, aromatic H); MS: m/z 338 (M^+); (Found: C, 60.26; H, 6.48. $C_{17}H_{22}O_7$ requires C, 60.34; H, 6.55%).

Y-(2-Oxymethyl-4-methoxy)phenyl-Y-butyrolactone (7)

A mixture of 94 (2.00 g, 5.9 mmol), sodium hydroxide (2.00 g, 50 mmol), ethanol (20 ml) and water (20 ml) was stirred at 30° for 20 hr. Reaction mixture was diluted with water, acidified (10% HCl) and extracted with ether. Ether extract was washed with sodium carbonate solution (10%), water, dried and concentrated. Residue was chromatographed over silica-gel (25 g). Fraction eluted with pet.ether + ethylacetate (55:45) yielded pure lactone (7) (0.42 g), yield 32%; TLC (solvent

system B): R_f, 0.18; IR: 3540 (OH), 1779 (lactone C=O); PMR: 2.50 (4H, m, $-CH_2-CH_2-$), 3.03 (1H, broad s, exchanges with D_2O, $-CH$), 3.80 (3H, s, $Ar-OCH_3$), 4.66 (2H, s, $-CH_2-OH$), 5.80 (1H, t, J = 7 Hz, $Ar-CH<$), 6.90 (2H, m, aromatic H), 7.26 (1H, d, J = 8 Hz aromatic H); MS: m/z 222 (M^+); (Found: C, 65.07; H, 6.25. $C_{12}H_{14}O_4$ requires C, 64.84; H, 6.35%).

Y-(2-Acetoxymethyl-4-methoxy)phenyl- -butyrolactone (8)

A mixture of 7 (0.50 g, 2.3 mmol), pyridine (4 ml) and acetic anhydride (5 ml) was kept overnight. Diluted with water, extracted with ether. Ether extract was washed with aqueous sodium carbonate solution, dil.HCl, water and dried. Evaporation of ether furnished 8 (0.52 g), yield 87%; TLC (solvent system B): R_f 0.52; IR: 1779 (lactone C=O), 1739 (acetate C=O); PMR: 2.03 (3H, s, $-COOCH_3$), 2.50 (4H, m, $-CH_2-CH_2$), 3.76 (3H, s, $Ar-OCH_3$), 5.03 (2H, s, $-CH_2-OAc$), 5.56 (1H, t, J = 7 Hz, Ar-CH), 6.80 (2H, m, aromatic H), 7.30 (1H, d, J = 10 Hz, aromatic H); MS: m/z 264 (M^+); (Found: C, 63.34; H, 6.36. $C_{14}H_{16}O_5$ requires C, 63.62; H, 6.10%).

Y-(2-Benzoyloxymethyl-4-methoxy)phenyl-Y-butyrolactone (9)

A mixture of 7 (0.40 g, 1.8 mmol), pyridine (5 ml) and benzoylchloride (2 ml) was kept overnight. Reaction mixture was diluted with water and heated at 60° for 1 hr, cooled and extracted with ether. Ether extract was washed

with sodium carbonate solution (10%), dil. HCl (10%), water, dried and concentrated. Residue was chromatographed on grade II alumina (15 g). Fraction eluted with pet.ether + ethyl acetate (90:10) yielded 9 (0.44 g), yield 74.5%; TLC (solvent system B): R_f 0.45; IR: 1788 (lactone C=O), 1730 (benzoyl C=O); PMR: 2.45 (4H, m, $-C\underline{H}_2-C\underline{H}_2-$), 3.76 (3H, s, $Ar-OC\underline{H}_3$), 5.26 (2H, s, $Ar-C\underline{H}_2-$), 5.66 (1H, t, J = 7 Hz, $Ar-C\underline{H}$), 6.83 (2H, m, aromatic H), 7.33 (4H, m, aromatic H), 7.90 (2H, m, aromatic H ortho to C=O); (Found: C, 69.88; H, 5.27. $C_{19}H_{18}O_5$ requires C, 69.92; H, 5.56%).

Y-(2-Benzoyloxymethyl-4-methoxy) phenyl-α-phenylseleno-Y butyrolactone (10)

To a dry THF solution of LDA (prepared from 2.96 M butyllithium (0.85 ml, 2.5 mmol) in hexane, dry THF (1.5 ml) and diisopropylamine (0.4 ml, 2.6 mmol) under N_2 at -78° 7, lactone 9 (0.40 g, 1.2 mmol) in dry THF (2 ml) was added over a period of 1 hr. After the reaction mixture was stirred at -78° for 1 hr, $Ø_2Se_2$ (0.78 g, 2.5 mmol) in dry THF (2 ml) and HMPA (0.45 g, 2.5 mmol) mixture was added dropwise at -78° for 30 min, then at -40° for 2.5 hr and subsequently quenched with 0.5 N HCl. The mixture was extracted with ether (3 x 50 ml). Ether extracts were washed with water, dried and concentrated . Residue was subjected to column chromatography on silica gel (20 g). Fraction eluted

with pet.ether + ethyl acetate (92:8) furnished seleno-lactone (10) (0.32 g), yield 53%; TLC(solvent system B): R_f, 0.48; IR: 1786 (lactone C=O), 1724 (benzoyl C=O); PMR: 2.20 to 3.00 (2H, m, Ar-CH-CH_2-), 3.75 (3H, s, Ar-OCH_3), 4.05 (1H, m, >CH-Se-Ø), 5.35 (3H, m, Ar-CH_2-OBz and Ar-CH<), 6.60 to 7.58 (m, aromatic H), 7.76 (2H, m, aromatic H ortho to Se).

5-(2-Benzoyloxymethyl-4-methoxy)phenyl-2(5H)-furanone (13)

To a stirred solution of 10 (0.30 g, 0.6 mmol) in dry THF (3 ml) at 0°, m-chloroperbenzoic acid (0.25 g, 1.4 mmol) was added. After 30 min the reaction mixture was allowed to warm to 25° and maintained at 25° for 2 hr. Reaction mixture was poured into cold sodium bicarbonate solution (10%, 20 ml) and extracted with ether. Ether extract was washed with water, dried and concentrated to furnish 13, which was purified through column chromatography over silica gel (8 g). Fraction eluted with pet.ether + ethylacetate (88:12) yielded pure 13 (65 mg), yield 32%; TLC(solvent system B): R_f, 0.45; IR: 1780, 1757, 1724, 1701 (C=O); PMR: 3.82 (3H, s, Ar-OCH_3), 5.40 (2H, s, Ar-CH_2-OBz), 6.24 (1H, dd, J = 5 Hz and 2 Hz, vinylic H α to C=O), 6.42 (1H, t, J = 2 Hz, benzylic H), 7.00 (2H, m, aromatic H), 7.51 (5H, m, aromatic H and vinylic H β to C=O), 8.04 (2H, m, aromatic H ortho to benzylic C=O).

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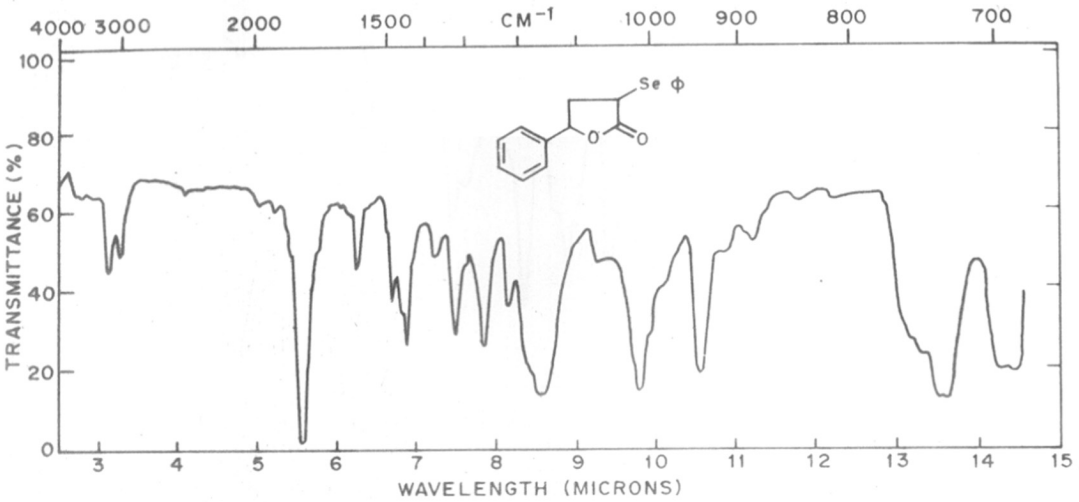
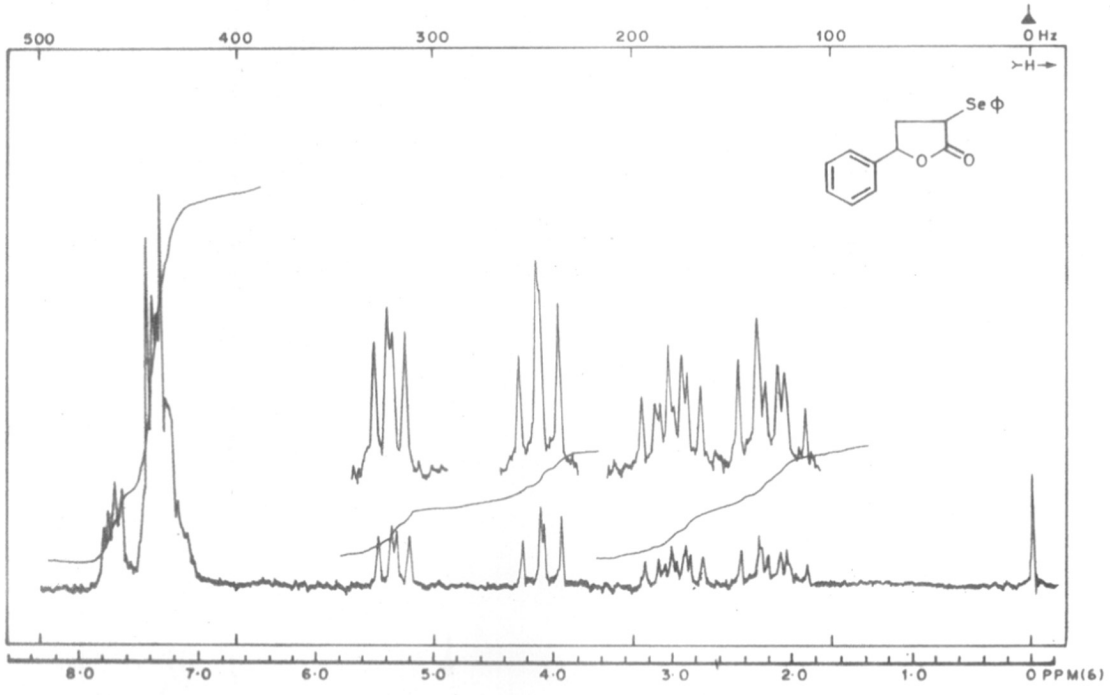
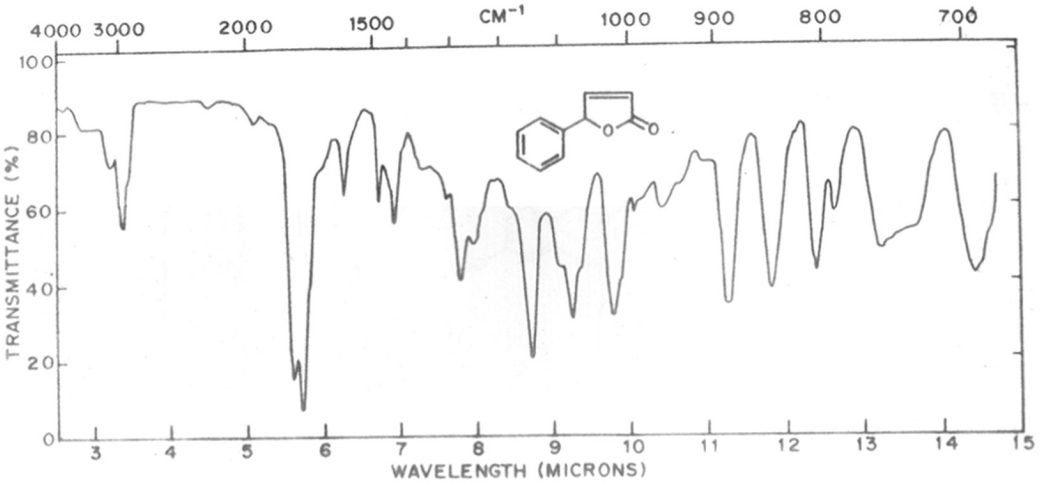
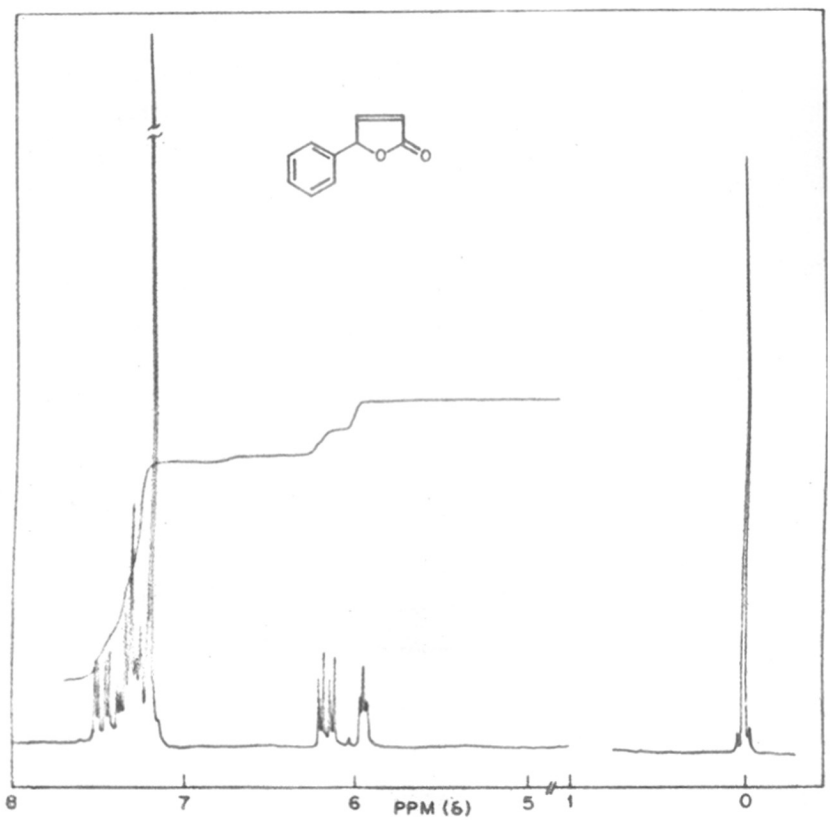


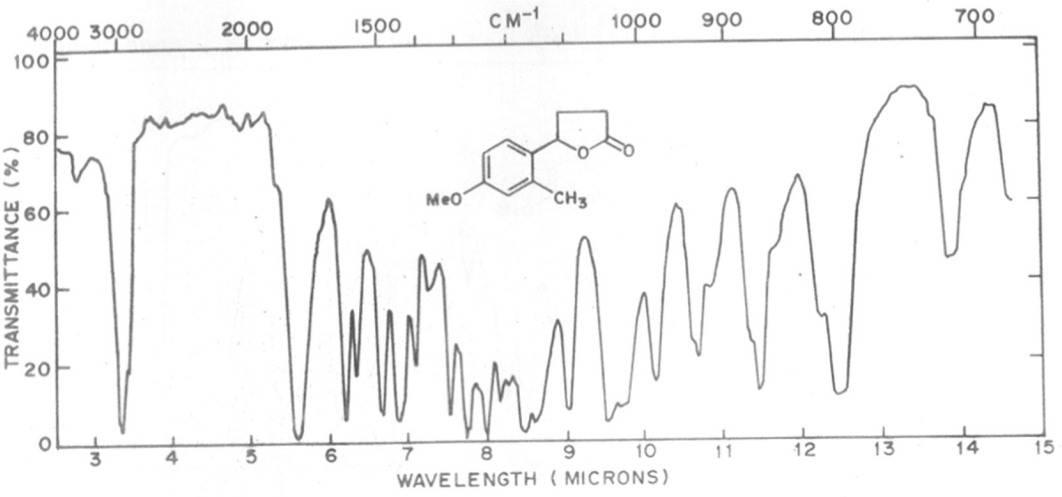


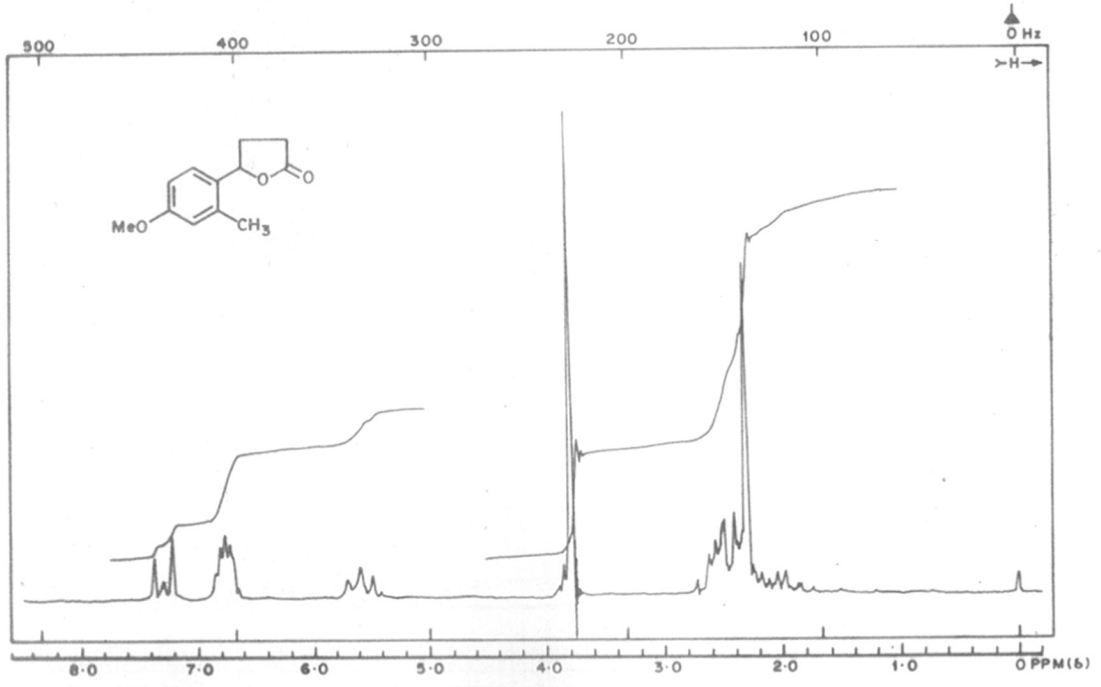
IR & NMR OF γ-PHENYL-α-PHENYLSELENO-γ-BUTYROLACTONE **(2)**



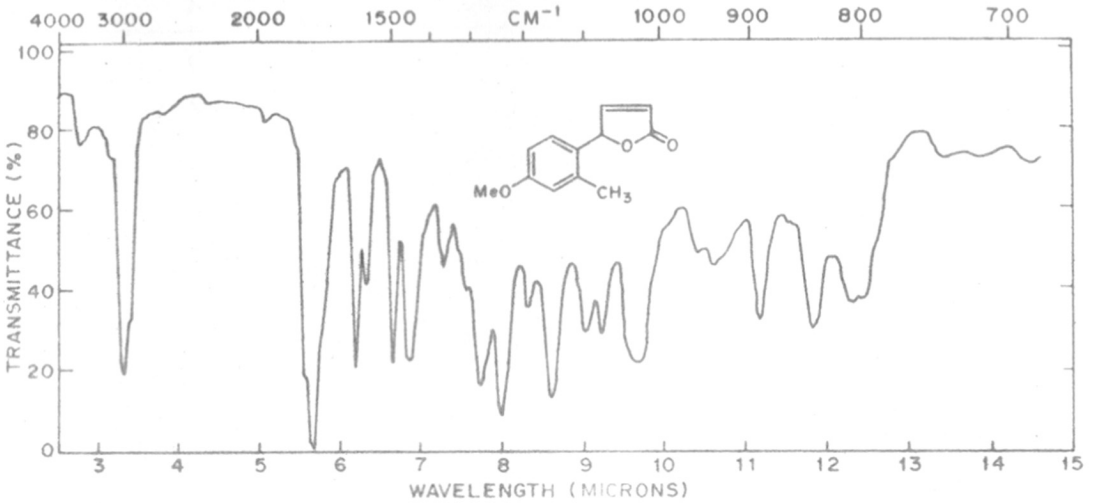


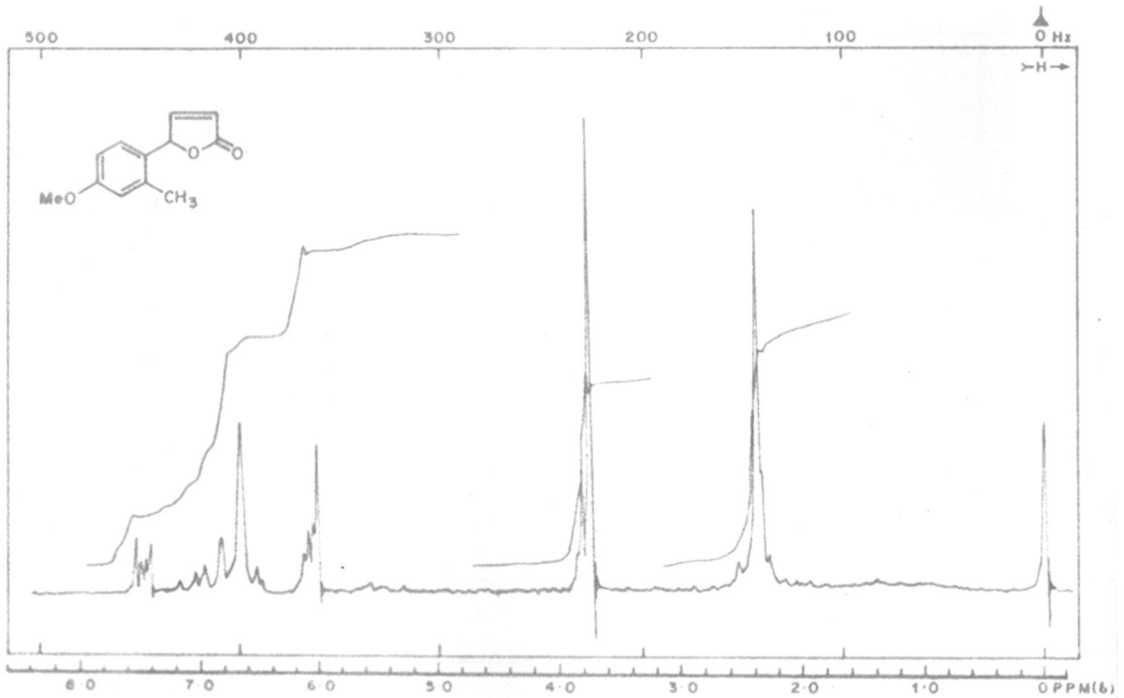
IR & NMR OF 5-PHENYL-2(5H)-FURANONE (3)



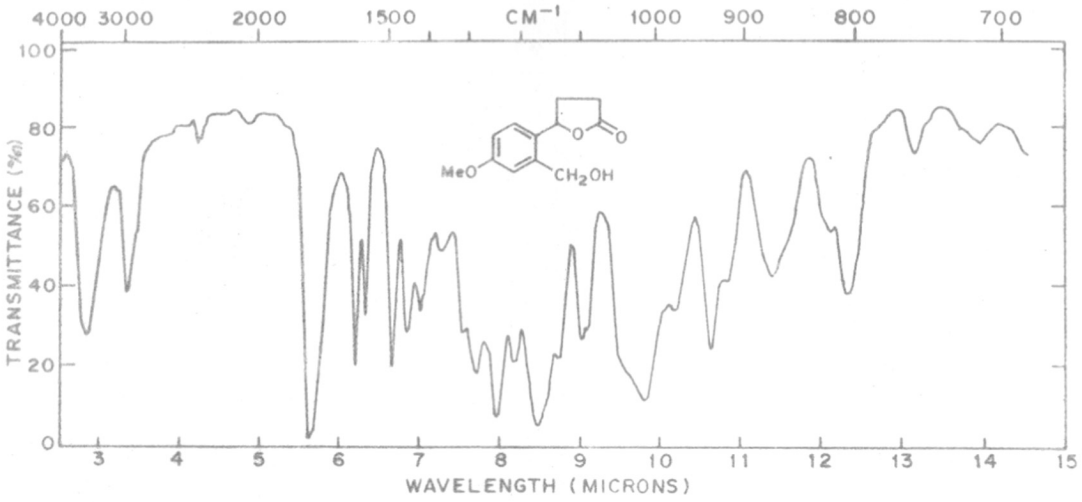


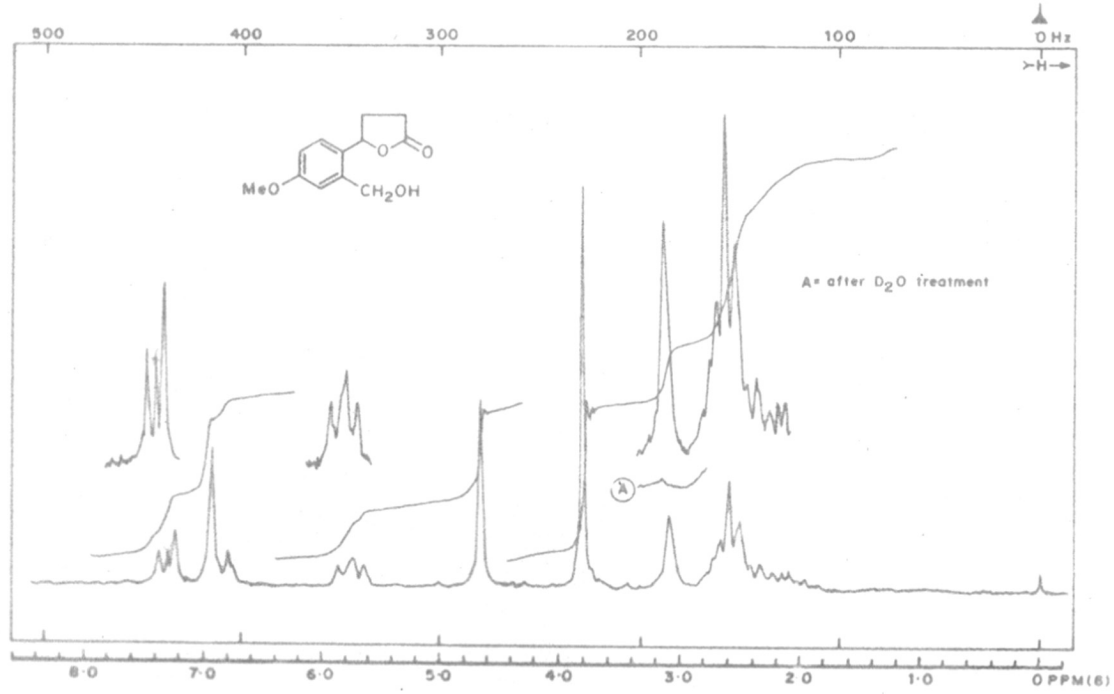
IR & NMR OF γ-(2-METHYL-4-METHOXY) PHENYL-γ-BUTYROLACTONE (4)



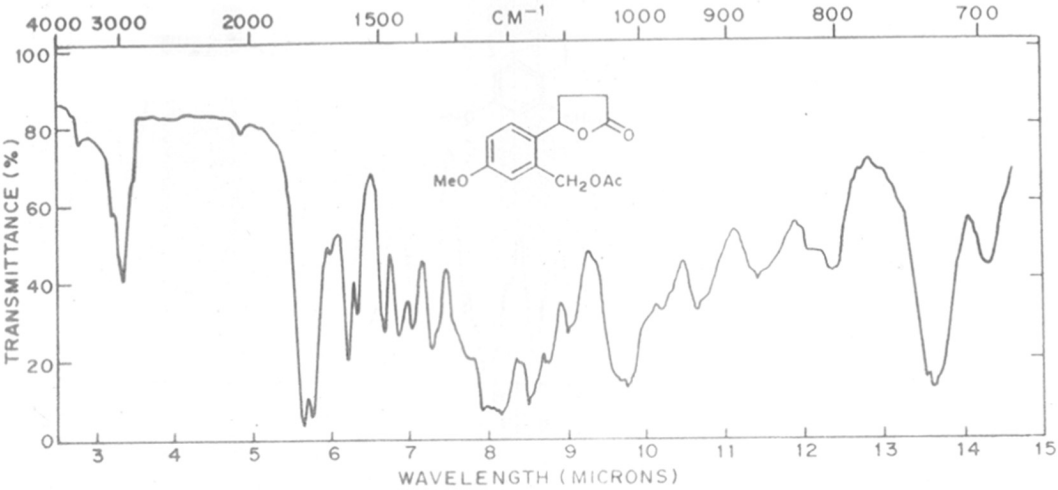


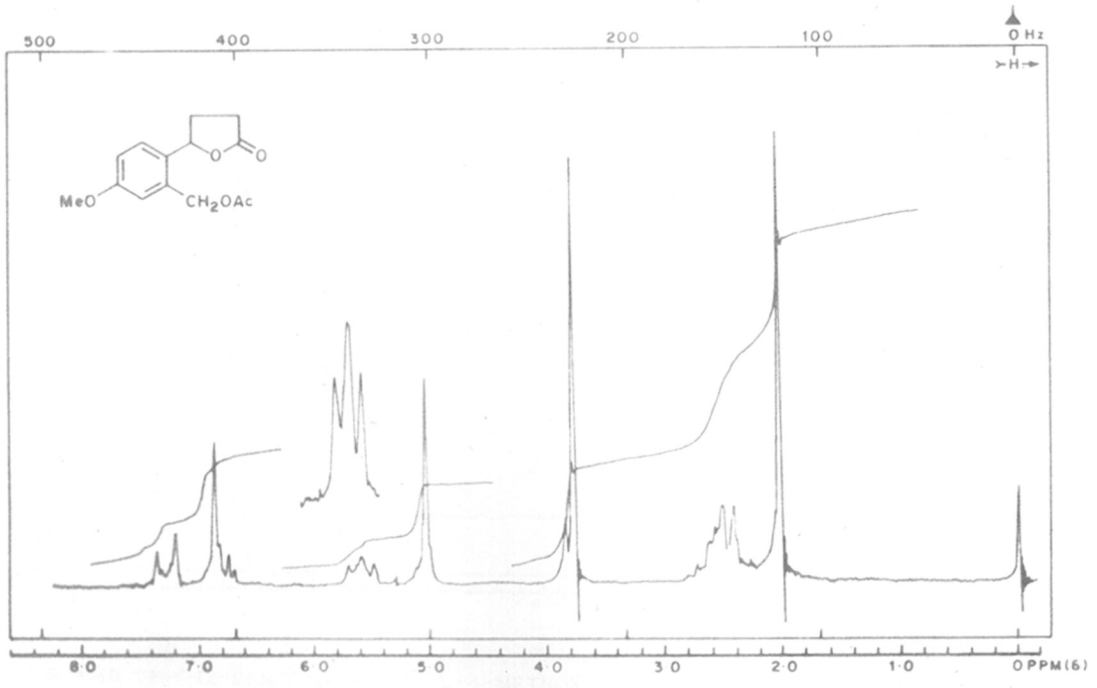
IR & NMR OF 5-(2-METHYL-4-METHOXY) PHENYL-2(5H)-FURANONE (6)



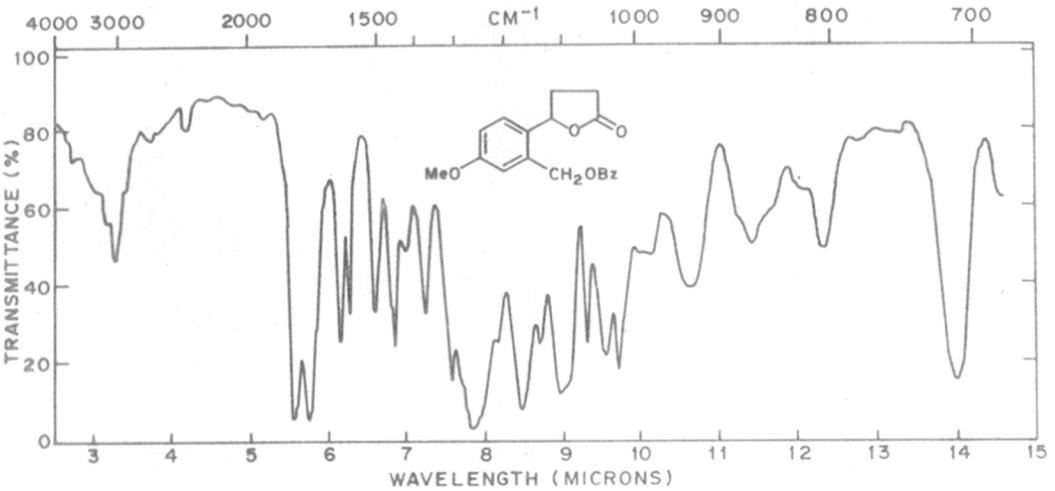


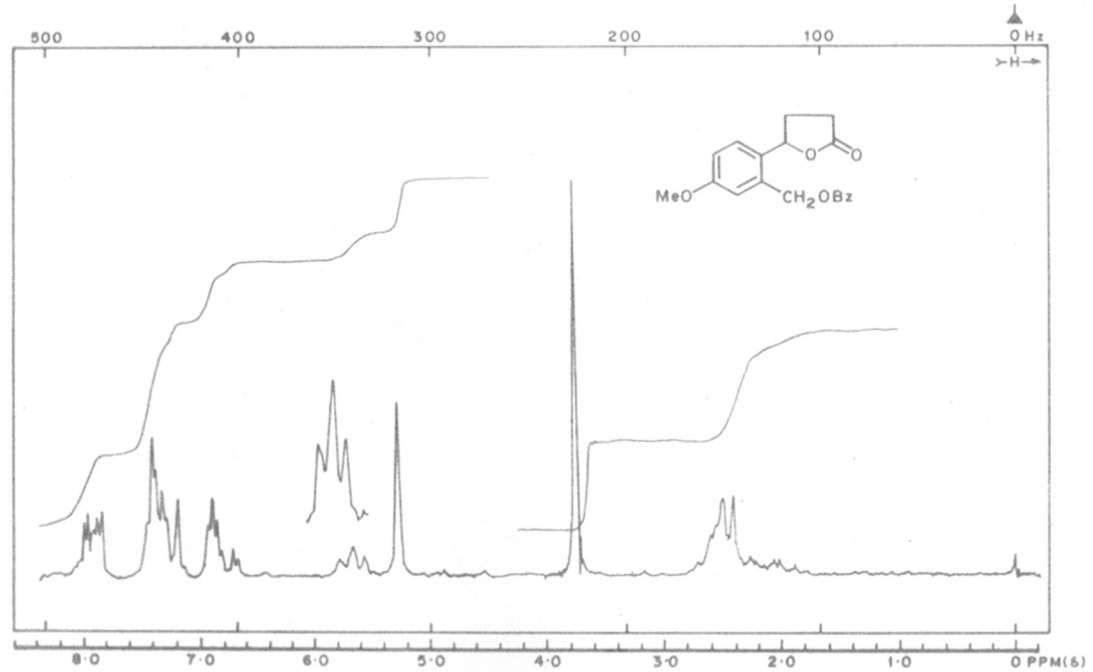
IR & NMR OF γ-(2-OXYMETHYL-4-METHOXY) PHENYL-γ-BUTYROLACTONE (7)



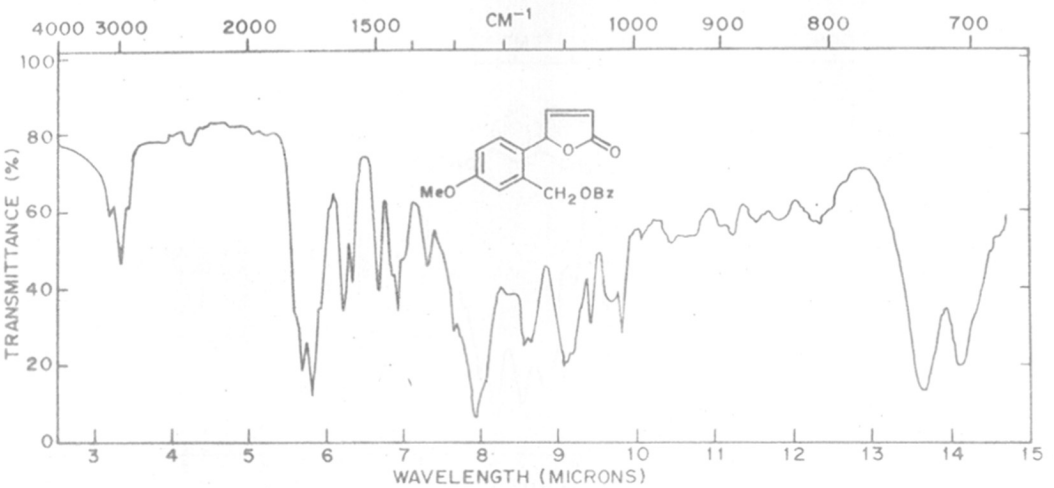


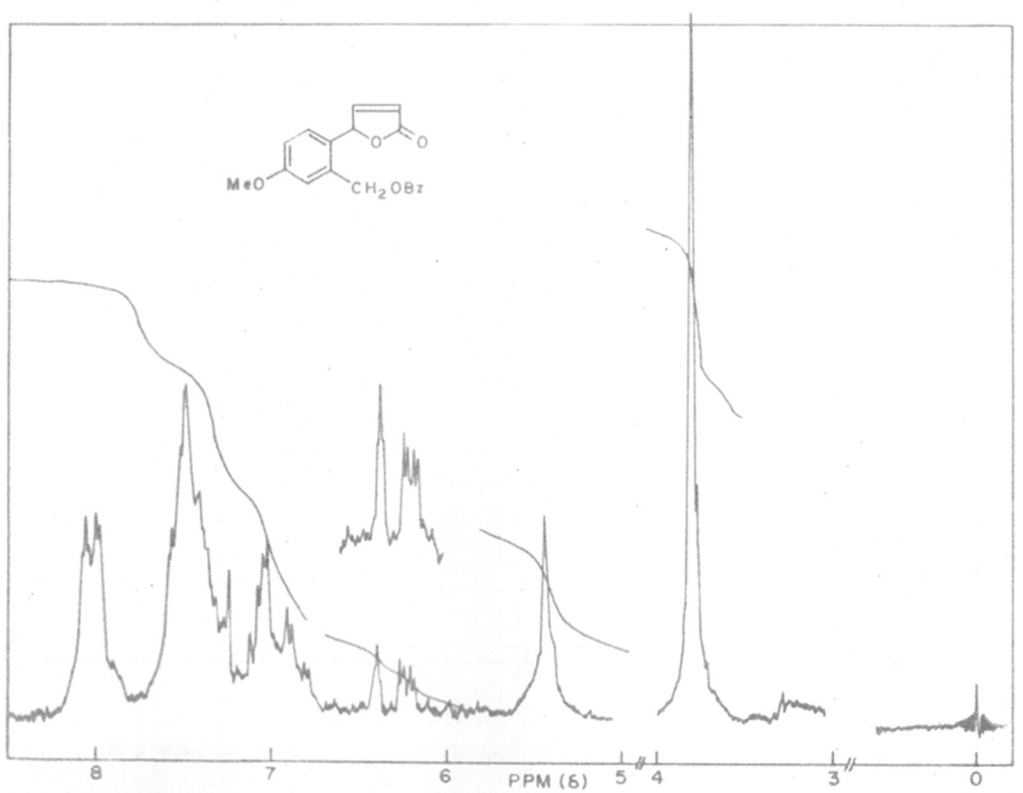
IR & NMR OF γ-(2-ACETOXYMETHYL-4-METHOXY) PHENYL-γ-BUTYROLACTONE (8)



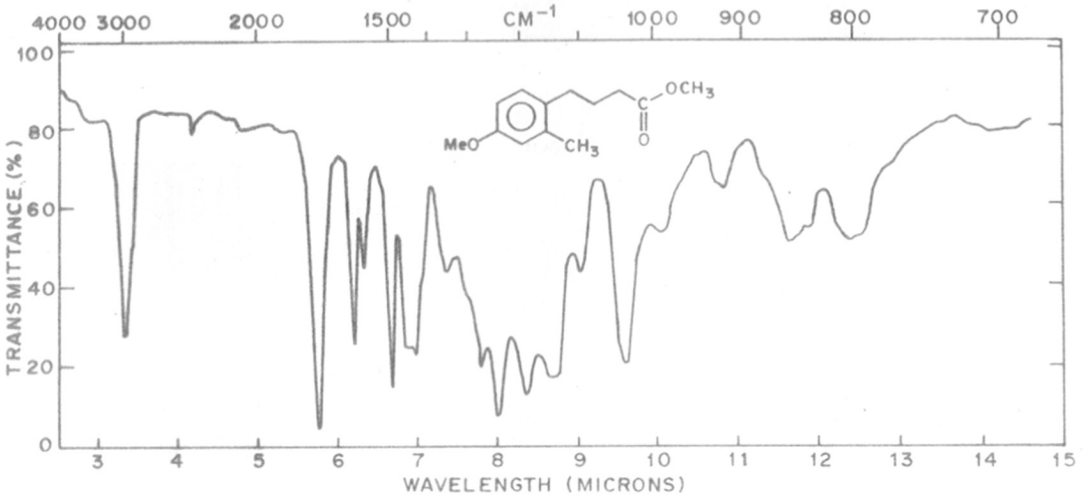


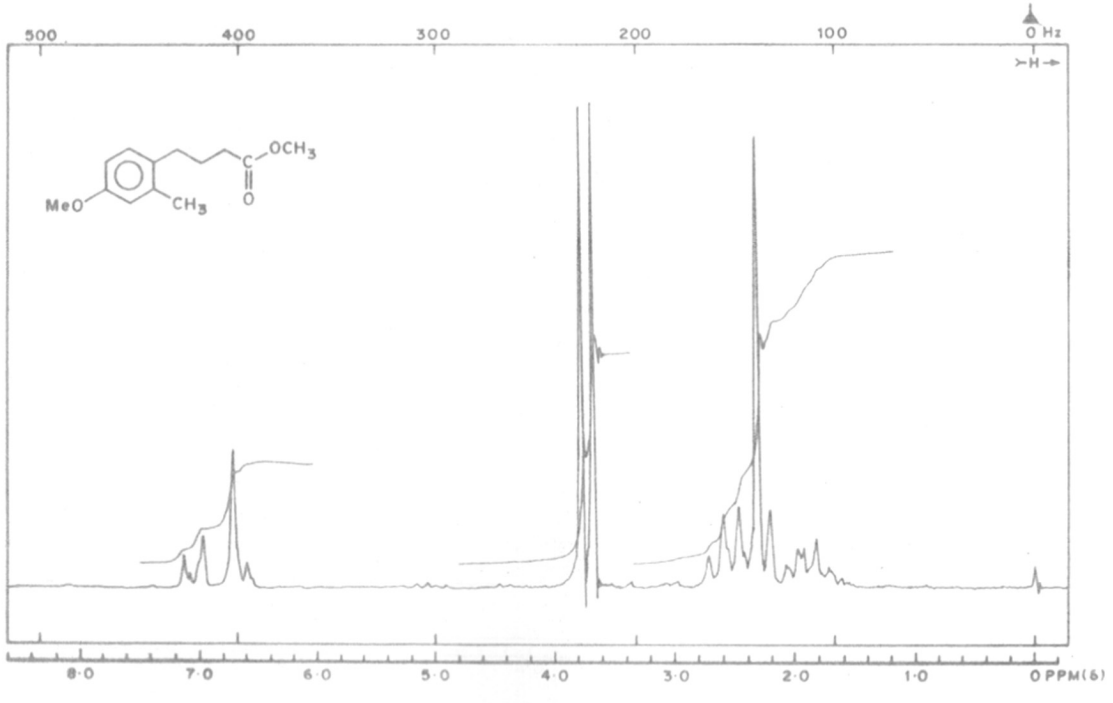
IR & NMR OF γ-(2-BENZOYLOXYMETHYL-4-METHOXY) PHENYL-γ-BUTYROLACTONE (9)



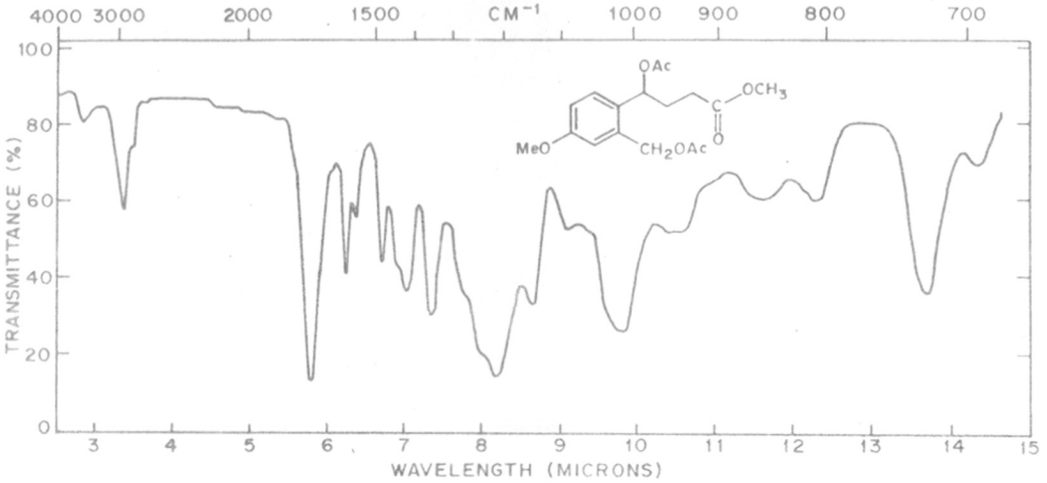


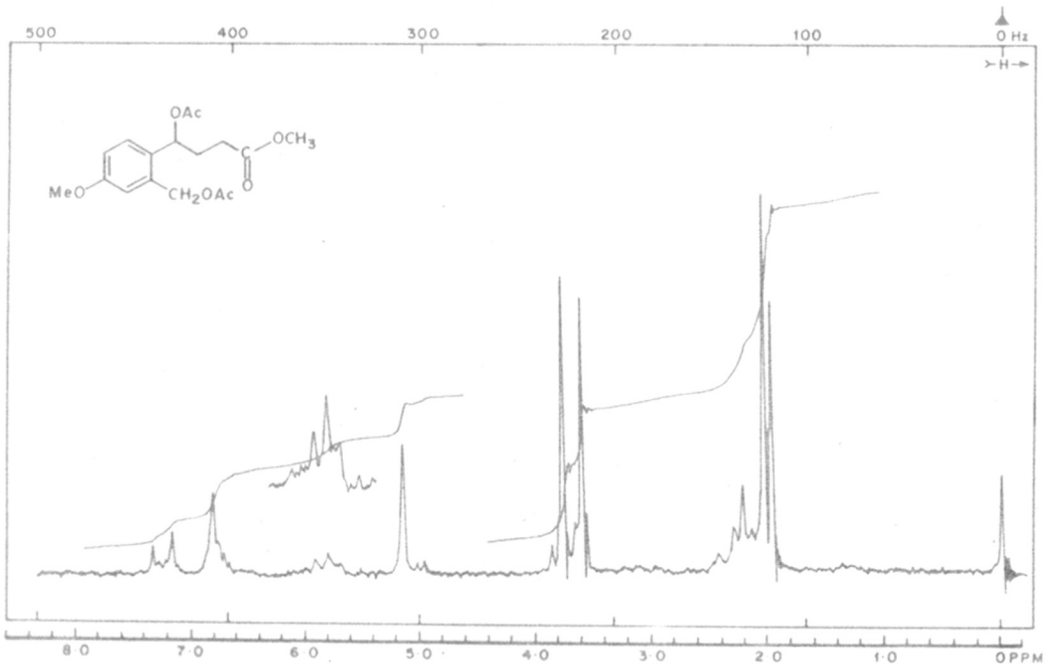
IR & NMR OF 5-(2-BENZOYLOXYMETHYL-4-METHOXY) PHENYL-2(5H)-FURANONE (13)





IR & NMR OF METHYL 4-(2-METHYL-4-METHOXY) PHENYL-BUTANOATE (91)





IR & NMR OF METHYL 4-(2-ACETOXYMETHYL-4-METHOXY) PHENYL-4-ACETOXY-BUTANOATE (94)

CHAPTER-4

A CONVENIENT ROUTE TO URACILS AND DIHYDROURACILS

SUMMARY

Uracil (5) has been prepared by two different methods:

(i) action of $Pb(OAc)_4$ on succinamide (1) furnished dihydrouracil (3); bromination of 3 yielded 5-bromo-dihydrouracil (4), which on dehydrobromination afforded uracil (5).

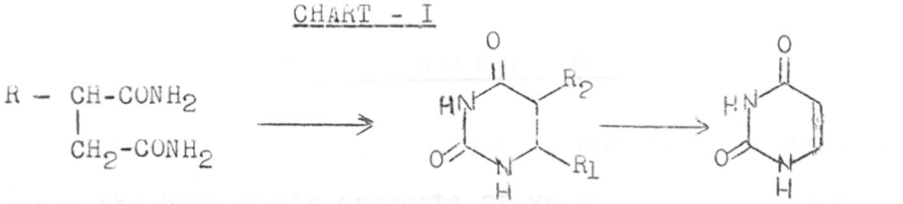
(ii) action of $Pb(OAc)_4$ on acetoxysuccinamide (2) furnished uracil (5).

Bromination of 6-methyldihydrouracil (7) [which is obtained by the action of $Pb(OAc)_4$ on methylsuccinamide (6)] furnished 5-bromo-6-methyldihydrouracil (7a); dehydrobromination of 7a afforded 6-methyluracil (8).

Sodium borohydride reduction of keto-ester (9) (obtained by the condensation of methyl propionate and dimethyl oxalate) furnished hydroxy-ester (12) as a mixture of *erythro* and *threo* isomers; 12 is then converted into acetoxy-amide (15) by the action of methanolic ammonia and subsequent acylation of resulting amide. 15 on treatment with $Pb(OAc)_4$ furnished 5-acetoxy-6-methyldihydrouracil (18) as a mixture of *cis* and *trans* isomers.

Similarly, 5-acetoxy-6-ethyldihydrouracil (19) and 5-acetoxy-6-phenyldihydrouracil (20) are prepared from keto-esters (10) and (11).

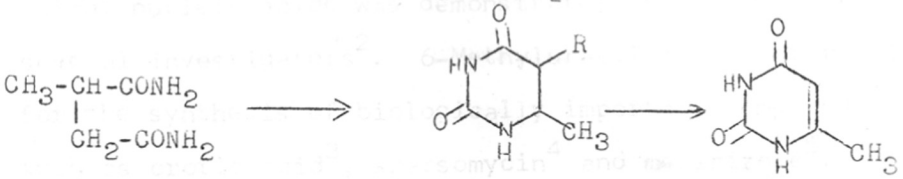
CHART - I



1. R = H
2. R = OAc

3. R_1 = H, R_2 = H
4. R_1 = H, R_2 = Br

5

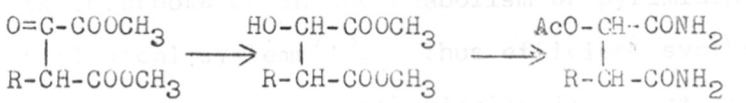


6

7 R = H

7a R = Br

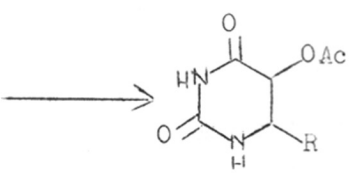
8



9. R = CH_3
10. R = C_2H_5
11. R = C_6H_3

12. R = CH_3
13. R = C_2H_5
14. R = C_6H_5

15. R = CH_3
16. R = C_2H_5
17. R = C_6H_5



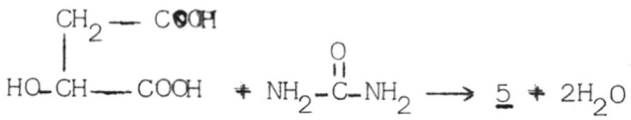
18. R = CH_3
19. R = C_2H_5
20. R = C_6H_5

INTRODUCTION

Uracil a pyrimidine class of compound was isolated from the hydrolytic products of yeast nucleic acid by Ascoli[1] in 1900. Its wide distribution in plant and animal nucleic acids was demonstrated by the work of several investigators[2]. 6-Methyluracil is an intermediate for the synthesis of biologically important compounds such as orotic acid[3], sparsomycin[4] and mepirizole[5]. Further, recent reports have indicated that dihydrouracil is incorporated in the anabolism of pyrimidines by certain biological systems[7,8]. Thus efficient synthesis of these compounds is synthetically important and has received much attention during the past several decades.

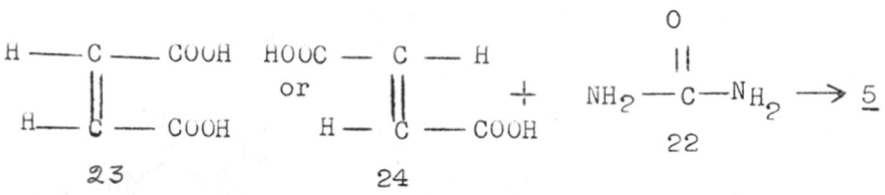
Several methods are available for the synthesis of uracil, 6-methyluracil and dihydrouracils. A brief review of some of these methods is attempted here:

1. Davidson et al.[9] prepared uracil (5) in 50-55% yield by reacting urea (22) and malic acid (21) in presence of fuming sulfuric acid (15% of SO_3).



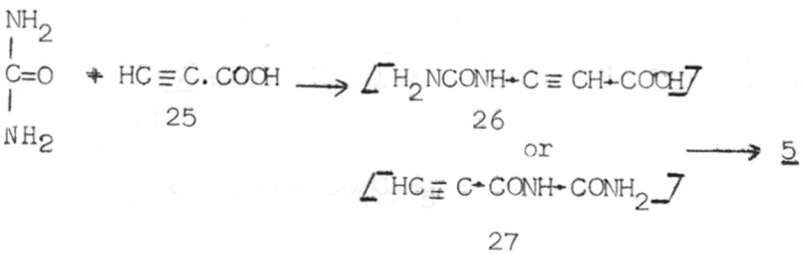
21 22

2. Takemoto et al.[10] found that, condensation of urea with maleic acid (23) in PPA at 160° furnishes uracil (5) in 20% yield, whereas fumaric acid (24) furnishes 5% yield of uracil(5).

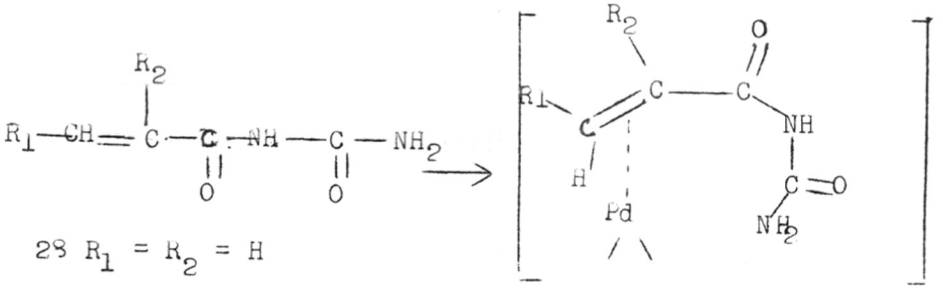


3. Reaction between malic acid (21) and urea (22) in presence of polyphosphoric acid furnished uracil (5) in very low yield[11].

4. J. Ralph et al.[12] reported the preparation of uracil (5) by condensing urea (22) and propiolic acid (25) under acid catalyst in and refluxing benzene.

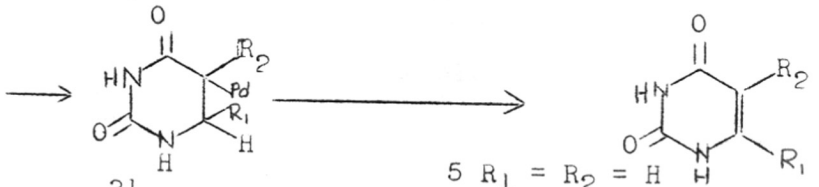


5. In the presence of sodium carbonate, the solution of acryloylurea (28) in water was treated with lithium chloropalladite at 60°, to furnish uracil (5) in 42% yield[13].



28 $R_1 = R_2 = H$

29 $R_1 = Me$, $R_2 = H$



31

5 $R_1 = R_2 = H$

8 $R_1 = Me$, $R_2 = H$

Similarly crotonoylurea (29) afforded 6-methyluracil (8) in 46% yield.

6. Urea, ethylacetoacetate (32) in absolute alcohol and a few drops of concentrated hydrochloric acid furnished β-uraminocrotonic ester (33), which was stirred with sodium hydroxide to obtain sodium salt (34); clear solution of 34 was carefully acidified to furnish 6-methyluracil (8)[14].

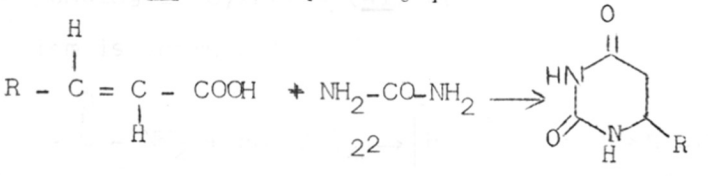
$$\underset{22}{NH_2CONH_2} + \underset{32}{CH_3COCH_2CO_2C_2H_5} \longrightarrow \underset{33}{CH_3C(NHCONH_2) = CHCO_2C_2H_5} + H_2O$$

$$33 + NaOH \longrightarrow \underset{34}{CH_3C(NHCONH_2) = CHCO_2Na} + C_2H_5OH$$

$$34 + HCl \longrightarrow 8 + H_2O + NaCl$$

7. Dihydrouracils

(a) Dihydrouracils are usually synthesised directly by the reaction of urea with an α,β-unsaturated carbonyl compounds[15]. For example, condensation of urea and crotonic acid (35) in ethylene glycol furnished 45% yield of 6-methyldihydrouracil (7). Similarly dihydrouracil (8) was obtained in 24% yield by condensation of urea and acrylic acid (36) in ethylene glycol.

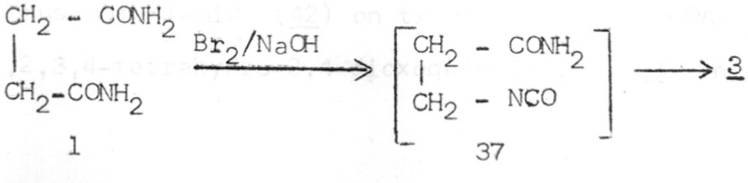


35 R = CH_3 7. R = CH_3

36 R = H 8. R = H

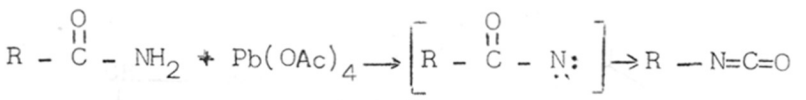
(b) The catalytic hydrogenation of uracils were reported[15] to yield 5,6-dihydrouracils. The value of this route is limited in that the yields are usually low, the reactions are difficult to control, and the structures of the products are quite often, uncertain.

(c) Hofmann degradation of succinamide derivatives are reported[16] to form dihydrouracils, presumably through the intermediacy of a monoisocyanate as shown below.



For example succinamide (1) on treatment with Br_2/NaOH furnished dihydrouracil (3)[17].

(d) H.E. Baumgarten[18] showed that oxidative rearrangement of simple amides using $Pb(OAc)_4$ yields products similar to those obtained from the Hofmann rearrangement. Thus, under suitable reaction conditions a number of aliphatic and aromatic amides could be quickly converted into the corresponding isocyanates (41) or their derivatives; mechanism is shown below.



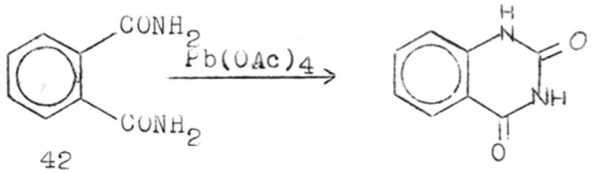
38 39 40 41

Reaction is presumably proceeding through a nitrene intermediate (40).

Later on, R.J. Hickman et al.[19] studied the application of the amide - $Pb(OAc)_4$ reaction to substrates containing a carboxy or second carbamyl function in close juxtaposition to the reactive centre, and so disposed as to allow intramolecular reaction with the initially formed isocyanata group to give six-membered heterocyclic systems.

Thus phthalamide (42) on treatment with $Pb(OAc)_4$ gave 1,2,3,4-tetrahydro-2,4-dioxoquinazoline (43) in

good yield.



42 43

Similarly, treatment of succinamide (1) and 2-phenylsuccinamide (44) with $Pb(OAc)_4$ afforded dihydrouracil (3) and 6-phenyldihydrouracil (45) respectively.

1 R = H 3 R = H

44 R = Ph 45 R = Ph

PRESENT WORK

Preparation of uracil, 6-methyluracil, 5-acetoxy-6-methyldihydrouracil, 5-acetoxy-6-ethyldihydrouracil and 5-acetoxy-6-phenyldihydrouracil are described in this chapter.

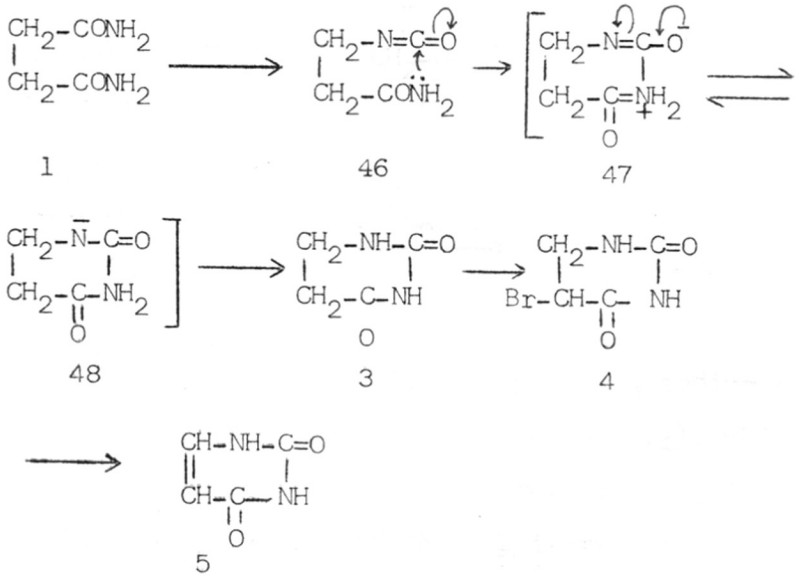
Work of R.J. Hickman et al.[19] (conversion of succinamide into dihydrouracil using $Pb(OAc)_4$ in high yield) and also the earlier work of C.C. Cheng[15] that dihydrouracil can be converted to uracil via bromination and dehydrobromination, encouraged us to carry out a systematic study of $Pb(OAc)_4$ oxidation of some substituted succinamides to dihydrouracils and conversion of dihydrouracils to uracils**. Our results of this investigation are presented below.

For the general synthesis of dihydrouracil skeletons, we envisioned approaches which consisted of the intramolecular cyclization of suitably substituted succinamides using $Pb(OAc)_4$ in dimethylformamide. Further, bromination of dihydrouracils and subsequent dehydrobromination of resulting bromodihydrouracils to uracils were planned.

** Uracils, the heterocyclic portion of nucleosides, were needed for some laboratory project.

Preparation of uracil

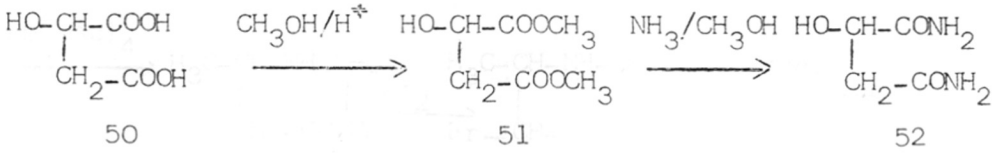
Method (A): Reaction of $Pb(OAc)_4$ with succinamide (1) in dimethylformamide furnished dihydrouracil (3) in 94%.



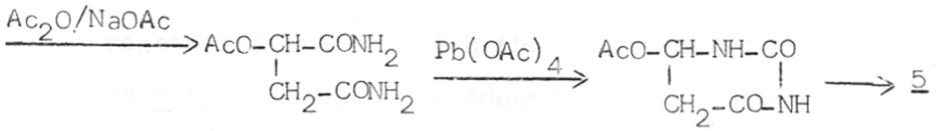
1 46 47 48 3 4 5

yield[5]. Bromination of 3 using bromine in acetic acid furnished the known 5-bromodihydrouracil 4 in 94% yield. Dehydrobromination of 4 using sodium acetate-acetic acid -acetic anhydride at reflux temperature furnished uracil (5) in 72% yield. Uracil thus obtained is identical in all respects with an authentic sample. Reaction sequence 1 → 3 → 5 constitutes a good method for the preparation of uracil.

Method B: Dimethyl malate (51) [prepared by the esterification of malic acid (50) using methanol and sulphuric acid] is treated with methanolic ammonia to



50 51 52

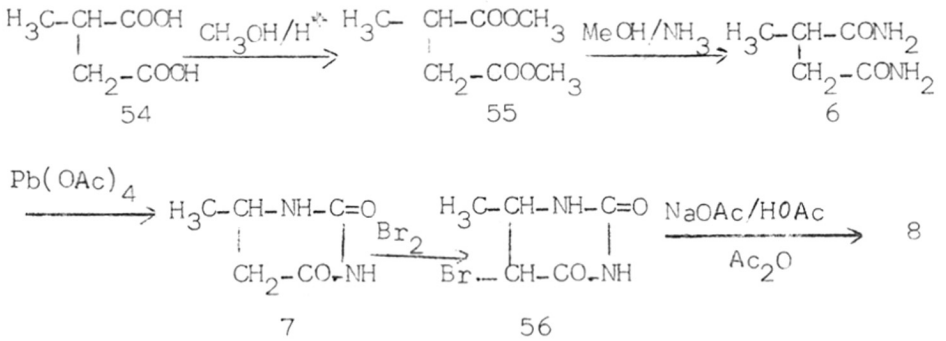


2 53

furnish malamide (52); acylation of 52 using sodium acetate in acetic anhydride furnished acetoxy-amide (2), which on treatment with $Pb(OAc)_4$ in DMF afforded uracil 5 in 71% yield. Probably the oxidation of 2 is regioselective involving attack on the amide nearer to OAc to furnish the acetate (53), which may be expected to undergo facile β-elimination to uracil under the reaction conditions. Reaction sequence 52 → 2 → 5 constitutes an alternate route for the preparation of uracil.

6-Methyluracil

Methylsuccinamide (6) is obtained by treating ester (55) [which is prepared by esterification of methylsuccinic acid (54)] with methanolic ammonia solution. Action of $Pb(OAc)_4$ on 6 in DMF furnished 6-methyldihydrouracil (7) (90% yield), suggesting that the amide nearer to



C-CH_3 reacts selectively with the oxidising agent. Compound 7 thus prepared is identical in all respects with an authentic sample prepared by condensation of crotonic acid and urea in ethylene glycol[15].

Bromination of 7 in acetic acid furnished in 85% yield, 5-bromo-6-methyldihydouracil (56), which on heating with sodium acetate-acetic anhydride-acetic acid, furnished 6-methyluracil (8) in 87% yield. The compound 8 thus prepared is characterised through m.mp., IR and PMR spectral data with an authentic sample. Yields in all the steps, during the transformation of 6 → 7 → 56 → 8 are high and above described reaction sequence constitutes a convenient method for the preparation of 6-methyl-uracil (8).

Preparation of acetoxy-amides 15, 16, and 17

Keto-ester (9) is prepared by the Claisen condensation of dimethyl oxalate (60) and methyl propionate (57) according to the procedure of F.B. Fox[20].

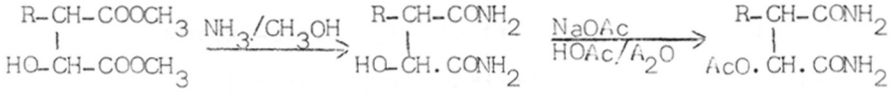
Sodium borohydride reduction of 9 furnished hydroxy ester (12), characterised through IR and PMR spectral data. IR spectrum shows bands at 3610 and 1748 cm^{-1}.

Scheme

57 R = CH_3
58 R = C_2H_5
59 R = C_6H_5

60

9 R = CH_3
10 R = C_2H_5
11 R = C_6H_5



12 R = CH_3
13 R = C_2H_5
14 R = C_6H_5

61 R = CH_3
62 R = C_2H_5
63 R = C_6H_5

15 R = CH_3
16 R = C_2H_5
17 R = C_6H_5

assignable to OH and C=O; PMR spectrum exhibits signals at 1.23 (3H, d, J = 8 Hz), 2.93 (1H, m), 3.40 (1H, broad s, exchangable with D_2O), 3.66 (3H, s), 3.80 (3H, s) and 4.23 (1H, m). 3H doublet at 1.23 and singlets at 3.66 and 3.80 are assigned to C<u>H</u>-CH_3, COOC<u>H</u>$_3$, -COOC<u>H</u>$_3$, whereas multiplets at 2.93 and 4.23 are assignable to C<u>H</u>-CH_3 and C<u>H</u>-OH.

Acetate (<u>64</u>) (derived from hydroxy-ester (<u>12</u>) using pyridine and acetic anhydride) is a mixture of <u>erythro</u> and <u>three</u> isomers. Hence PMR spectrum of <u>64</u> shows two

two doublets (5:1) at 5.10 (J = 6 Hz) and 5.36 (4 Hz) for CH-OAc.

$$\begin{array}{l} R - CH - COOCH_3 \\ AcO- CH - COOCH_3 \end{array}$$

64 R = CH_3

65 R = C_2H_5

66 R = C_6H_5

Thus, the parent hydroxy-ester (12) (from which acetate (64) has been prepared) must also be a mixture of erythro and threo isomers.

Hydroxy-ester (12) is treated with methanolic ammonia to furnish hydroxy-diamide (61), which is heated with NaOAc- acetic acid- acetic anhydride to afford acetoxy-amide (15), characterised through elemental analysis, IR and PMR spectral data. PMR spectrum of 15 (once recrystalised) shows two singlets (6:1) at 2.02 and 2.08 (together 3H, $-OCOCH_3$), and two doublets (6:1) at 4.89 (J = 10 Hz) and 5.23 (J = 6 Hz) (together 1H, for CH-OAc). Two singlets for $-OCOCH_3$ and two doublets for CH-OAc indicates acetoxy-amide (15) is a mixture of erythro and threo isomers.

Keto-ester (10) is prepared by the Claisen condensation of methyl butyrate (58) and dimethyl oxalate (60) using sodium methoxide as a base.

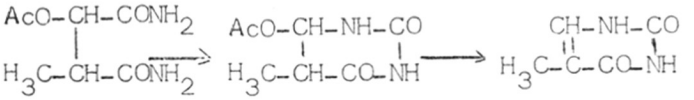
Sodium borohydride reduction of 10 furnished hydroxy-ester (13), as a mixture of erythro and threo isomers, as evident by the PMR spectrum study of the acetate 65 derived from 13.

Hydroxy-ester (13) on treatment with methanolic ammonia furnished hydroxy-amide (62), which on heating with NaOAc-acetic acid-acetic anhydride afforded acetoxy-amide (16), characterised through elemental analysis, IR and PMR spectral data. PMR spectrum of 16 shows two singlets (7:4) at 2.02 and 2.08 (together 3H, $-OCOCH_3$) and two doublets (7:4) at 4.88 (J = 10 Hz) and 5.15 (J = 6 Hz) (together 1H, >CH-OAc), indicating the acetoxy-amide (16) is a mixture of erythro and threo isomers.

Similarly acetoxy-amide (17) (a mixture of erythro and threo isomers) is prepared from hydroxy-ester (14) (prepared by sodium borohydride reduction of keto-ester (11), which is obtained by claisen condensation of methyl phenyl acetate (59) and dimethyl oxalate (60)7 via hydroxy-amide(63).

Action of $Pb(OAc)_4$ on 15, 16 and 17

In view of facile elimination of acetic acid from the intermediate 53, during the conversion of acetoxy-amide (2) into uracil (5) (see page No. 165), we expected that, acetoxy-amide (15) would furnish 5-methyl-uracil (thymine) (68).



15 67 68

But, action of $Pb(OAc)_4$ on acetoxy-amide (15) in DMF furnished 5-acetoxy-6-methyldihydrouracil (18), characterised through elemental analysis, IR and PMR spectral data. PMR spectrum of 18 exhibits two doublets (1:11) at 4.88 (J = 10 Hz) and 5.25 (J = 6 Hz) together 1H, assignable to CH-OAc, indicating 18 is a mixture of cis and trans isomers. On the basis of literature reports[21], coupling constant 10 Hz is assigned to trans coupling, whereas coupling constant 6 Hz is assigned to cis coupling.

Similarly, acetoxy-amides (16) and (17) furnished 5-acetoxy-6-ethyldihydrouracil (19) and 5-acetoxy-6-phenyldihydrouracil (20) (as a mixture of cis and trans isomers), on treatment with $Pb(OAc)_4$ in DMF; 19 and 20 are characterised through elemental analysis, IR and PMR spectral data.

Thus above conversion of acetoxy-amides (15, 16 and 17) to dihydrouracils (18, 19 and 20) using $Pb(OAc)_4$ indicates that, oxidising agent $[Pb(OAc)_4]$ reacts selectively with the amide nearer to C-alkyl or C-aryl in acetoxy amides (15, 16 and 17).

EXPERIMENTAL

I. URACIL [2,4(1H, 3H)-pyrimidinedione] (5)

(a) Method A

Dihydro-2,4-(1H,3H)-pyrimidinedione (3) -

3 was prepared according to literature method[19] using succinamide (1) and $Pb(OAc)_4$ in DMF as a solvent, yield: 94%; m.p.276-77° (lit.[15] 276-78°); IR: 3344, 3195, 1770, 1709 cm^{-1}.

5-Bromo-dihydro-2,4-(1H, 3H)-pyrimidinedione (4) -

4 was prepared according to literature method[15], by the bromination of 3 using bromine in acetic acid; yield:94% m.p.195-200°(lit.[15] 207-208°); IR: 3344, 3125, 1724 to 1639.

2,4(1H, 3H)-Pyrimidinedione (5)

A mixture of bromo-compound (4) (1.00 g, 5.2 mmol), acetic anhydride (6 ml), acetic acid (8 ml) and sodium acetate (0.60 g) was heated under reflux for 6 hr. Removed all acetic acid and acetic anhydride under reduced pressure. Residue was heated with 10 ml of water on water-bath and cooled. Filtration of the solid furnished 5 (0.42 g), yield: 72%; analytically pure sample was obtained by sublimation m.p. above 300°(d); IR: 3205, 1733, 1667, 1235, 1002 and 990;(Obs: C, 42.68; H, 4.00. $C_4H_4N_2O_2$ requires C, 42.86; H, 3.60%).

(b) Method B

Dimethyl malate (51) - Conventional method of esterification of malic acid (50) using methanol and conc. H_2SO_4 furnished 51 in 94% yield; b.p.:122°/12 mm [lit.[22] 122°/12 mm ; IR: 3590(OH), 1727 (ester C=O).

Malamide (52) - A mixture of dimethyl malate (16.2 g, 0.1 mole) and methanol (100 ml), was s turated with ammonia at 0-5° and kept at that temperature for 28 hr. Concentrated to half of the volume under reduced pressure and filtered off the solid to furnish 52 (12.00 g), yield: 91%; m.p.163-64° (lit.[23] 163-64°); IR: 3495, 3279, 1669 to 1616.

O-Acetyl malamide (2) - A mixture of malamide (52)(6.6 g, 50 mmol), acetic anhydride (40 ml) and sodium acetate (0.2 g) was refluxed for 30 min. Removed excess of acetic anhydride under reduced pressure. Dissolved the residue in chloroform (20 ml) and solid was filtered off to furnish 2 (8.3 g), yield: 95%, m.p.168-70°(d); IR: 3395, 3226, 1742, 1672, 1626; (Obs: C, 41.70; H, 6.05. $C_6H_{10}N_2O_4$ requires C, 41.38; H, 5.79%).

2,4(1H, 3H)- Pyrimidinedione (5) - To a mixture of 2 (2.00 g, 11 mmol) and DMF (20 ml), $Pb(OAc)_4$ (6.5 g, 14 mmol) was added and reaction mixture was stirred at 50-60°(bath temperature) for 1 hr. DMF was removed under reduced pressure and residue was heated with 20 ml of water, on

water-bath and cooled. Filtered off the solid to furnish 5 (0.91 g), yield: 71%. The compound 5 thus prepared is identical in all respects with the sample prepared above.

II. 6-Methyluracil [6-methyl-2,4(1H,3H)-pyrimidinedione 7 (8)

Methylsuccinamide (6) - A solution of dimethyl methylsuccinate (55) (4.0 g) [prepared by esterification of methylsuccinic acid (54)][24] in methanol (25 ml) was saturated with ammonia at 0-5° and kept at that temperature for 30 hr. Solution was concentrated under reduced pressure to dryness and residue was treated with 10 ml of chloroform. Filtered off the solid to furnish 6 (2.9 g), yield: 90%; m.p.225° (lit.[25] 225°): IR: 3500, 3279, 1739, 1681.

6-Methyl-dihydro-2,4 (1H, 3H)-pyrimidinedione (7)

A mixture of methylsuccinamide (0.55 g, 4.2 mmol), DMF (10 ml) and $Pb(OAc)_4$ (3.0 g, 6.7 mmol) was stirred at 50-60° (bath temperature) for 40 min. DMF was removed under reduced pressure and residue was heated with 10 ml of water for 10 min at 100° and cooled. Filtered off the solid to furnish 7 (0.49 g); yield: 90.5%; recrystalised from ethanol, m.p.216-218°(lit.[15] 217-18°) IR: 3279, 3155, 1739, 1698; PMR (DMSO-d_6): 1.16 (3H, d, J = 7 Hz, $CH-C\underline{H}_3$), 2.36 [2H, dd, J = 7 Hz and 8 Hz, $-C\underline{H}_2-C\underline{H}(CH_3)$], 3.63

(1H, m, >C<u>H</u>-CH_3), 7.60 (1 H, broad s, exchangable with D_2O, -N<u>H</u>), 10.06 (1H, broad s, exchangable with D_2O, -N<u>H</u>).

<u>5-Bromo-6-methyl-dihydro-2,4(1H, 3H)-Pyrimidinedione</u> (<u>56</u>)-

It was prepared from <u>7</u> using bromine in acetic acid, according to literature method[15], yield 85%; m.p.312-15°(d) [lit.[15] 313-15°(d)]; recrystalised from ethanol, IR: 3333, 3106, 1724 to 1667; PMR: 1.30 (3H, d, J = 7 Hz, >CH-C<u>H</u>$_3$), 3.73 (1H, m, >C<u>H</u>-CH_3), 4.53 (1H, d, >C<u>H</u>-Br), 7.91 (1H, broad s, N<u>H</u>), 10.38 (1H, broad s, N<u>H</u>).

<u>6-Methyl-2,4(1H, 3H)-pyrimidinedione</u> (<u>8</u>) -

A mixture of <u>56</u> (2.00 g, 9.6 mmol), sodium acetate (1.00 g), acetic acid (15 ml), acetic anhydride (8 ml) was heated under reflux for 5 hr. Removed all acetic acid and acetic anhydride under reduced pressure. Residue was heated on water bath with 10 ml of water and cooled. Filtered off the solid to furnish <u>8</u> (1.06 g), yield: 87%; m.p.318-20° (lit.[13] 320°); analytically pure sample was obtained by sublimation. IR: 3205, 1730, 1692 (broad); PMR(DMSO-d_6):2.33 (3H, s, >C=C(C<u>H</u>$_3$)-), 6.00 (1H, s, >C=C(-<u>H</u>)-) (Obs: C, 47.16; H, 4.37. $C_5H_6N_2O_2$ requires C, 47.52; H, 4.70%).

III. 5-Acetoxy-6-methyl-dihydro-2,4(1H, 3H)-pyrimidinedione (5-Acetoxy-6-methyl-dihydrouracil) (18)

Methyl methyl-oxaloacetate (9)- To a stirred solution of sodium methoxide [prepared from sodium (12.6 g, 0.55 mol) and methanol (20 ml)] in ether (100 ml), mixture of methyl propionate (44 g, 0.5 mol) and dimethyl oxalate (59 g, 0.5 mol) was added drop-by-drop, controlling the temperature at 5-10°. After complete addition, reaction mixture was stirred at room temperature for 4 hr. Removed the ether and excess of methanol under reduced pressure (bath temp. 55°) and kept overnight. Decomposed the sodium salt by aqueous HCl solution (10%) and extracted with ether. Ether extract was washed with aqueous sodium carbonate (10%) water, dried and concentrated to furnish 9 (78.00 g), yield: 90%; b.p. 100-105°/10 mm. (lit.[20] 114-116°/10 mm for ethyl ester); IR: 1739 (ester C=O), 1667 (C=O); PMR: 1.43 (3H, d, J = 8 Hz, >CH-CH_3), 3.93 (3H, s, -COOCH_3), 4.10 (3H, s, -COOCH_3), 4.27 (1H, q, J = 8 Hz, CH_3-CH<).

Dimethyl α-hydroxy-β-methyl-succinate (12) -

To a stirred solution of 9 (8.8 g, 50 mmol) in methanol (30 ml), $NaBH_4$ (1.00 g, 26 mmol) was added at the interval of 10 min. keeping the reaction mixture at 5-10°. After complete addition of $NaBH_4$, reaction mixture was stirred at room temperature for 1 hr., diluted with water, saturated with sodium chloride and extracted with ether.

Ether extract was washed with water, dried and concentrated to furnish 12 (8.5 g), yield: 95%; b.p. 140-145°(bath temp.)/12 mm [lit.[26] 121-24°/10 mm (for ethyl ester)]7; IR: 3610 (OH), 1748 (ester C=O); PMR: 1.23 (3H, d, J = 8 Hz, $C\underline{H}_3$-CH<), 2.93 (1H, m, >C<u>H</u>-CH_3), 3.40 (1H, broad s, exchangable with D_2O, OH), 3.66 (3H, s, -COO$C\underline{H}_3$), 3.80 (3H, s, -COO$C\underline{H}_3$), 4,23 (1H, m, >C<u>H</u>-OH).

<u>Dimethyl α-acetoxy-β-methyl-succinate</u> (<u>64</u>) - <u>13</u> (1 g) was acylated using pyridine (2 ml) and acetic anhydride (2 ml) to furnish (<u>64</u>) (1.2 g), yield: 97%; b.p. 135-40 (bath temp.)/5 mm; IR: 1746 (C=O); PMR: 1.3 (3H, d, J = 8 Hz, >CH-$C\underline{H}_3$), 2.18 (3H, s, -OCO$C\underline{H}_3$), 3.1 (1H, m, >C<u>H</u>-CH_3), 3.65 (3H, s, -COO$C\underline{H}_3$), 3.78 (3H, s, -COOCH_3) [doublets (5:1) at 5.10 (J = 6 Hz) and 5.36 (4 Hz), together 1H, C<u>H</u>-OAc]7.

<u>α-Hydroxy-β-methyl-succinamide</u> (<u>61</u>) - Reaction of <u>13</u> (5.00 g, 28 mmol) with methanolic ammonia (as in the case of <u>52</u>) furnished <u>61</u> (3.3 g), yield: 80%, m.p. 155-58° (lit.[27] m.p. 159-60°), recrystalised from methanol); IR: 3350, 3226 and 1695 to 1613 (broad).

<u>α-Acetoxy-β-methyl-succinamide</u> (<u>15</u>)- A mixture of <u>61</u> (2.00 g, 13 mmol), acetic anhydride (10 ml), acetic acid (5 ml) and sodium acetate (0.1 g) was stirred at 100° for 30 min. Removed acetic anhydride and acetic acid under reduced pressure and residue was treated with pet.ether-acetone (1:1) (10 ml) and filtered off the solid

to furnish 15 (2.35 g), yield: 91% ; m.p.180-82 (d); recrystalised by water + acetone (1:5), m.p.182-83°(d); IR: 3300, 3247, 1757, 1681, 1653 and 1232; PMR (DMSO-d_6): 1.05 (3H, d, J = 7 Hz, >CH-CH_3), singlets (6:1) at 2.02 and 2.08, together 3H, -OCOCH_3, 2.73 (1H, m, >CH-CH_3), doublets (6:1) at 4.89 (J = 10 Hz) and 5.23 (J = 6 Hz), together 1H, >CH-OAc, and multiplets at 6.80 (1H), 7.18 (1H), 7.39 (1H), 7.56 (1H) exchangable with D_2O, -CONH_2; (Obs: C, 45.00; H, 6.77. $C_7H_{12}N_2O_4$ requires C, 44.68; H, 6.43%).

5-Acetoxy-6-methyl-dihydro-2,4(1H, 3H)-pyrimidinedione (18)

A suspension of 15 (1.8 g, 9.5 mmol) in DMF (25 ml) was treated with $Pb(OAc)_4$ (7.00 g, 15 mmol) and stirred at 60° for 40 min. DMF was removed under reduced pressure and residue was heated with 10 ml of water at 100° for 5 min. and cooled. Filtered off the solid to furnish (1.35 g), yield: 76%; m.p.258-60°(d), analytically pure sample was obtained by sublimation under vacuum m.p.262-63°(d); IR: 3322, 3125, 1757, 1724, 1667, 1227; PMR (DMSO-d_6): 1.03 (3H, d, J = 8 Hz, >CH-CH_3), 2.08 (3H, s, -OCOCH_3), 3.55 (1H, m, CH_3-CH<), doublets (1:11) at 4.88 (J = 10 Hz) and 5.25 (J = 6 Hz, together 1H, CH-OAc, 7.68 (1H, broad s, NH) 10.15 (1H, broad s, NH); (Obs: C, 45.24; H, 5.52. $C_7H_{10}N_2O_4$ requires C, 45.16; H, 5.41%).

IV 5-Acetoxy-6-ethyl-dihydro-2,4(1H, 3H)-pyrimidinedione (5-Acetoxy-6-methyl-dihydrouracil) (19)

Methyl ethyl-oxaloacetate (10) - It is prepared from methylbutanoate (51 g, 0.5 mol) and dimethyl oxalate (59 g, 0.5 mol) in presence of sodium methoxide (according to procedure as in the case of 9) in 87% yield, b.p.120-25° (bath temp.)/8 mm; IR: 1745 (ester C=O), 1665 (C=O); PMR: 0.93 (3H, t, J = 7 Hz, $-CH_2-\underline{C}H_3$), 1.83 (2H, m, $>CH-\underline{C}H_2-CH_3$), 3.63 (3H, s, $-COOC\underline{H}_3$), 3.72 (3H, s, $-COOC\underline{H}_3$), 3.84 (1H, t, J = 7 Hz, $>\underline{C}H-CH_2-CH_3$).

Dimethyl α-ethyl-β-hydroxy-succinate (13) - $NaBH_4$ (1g, 50mmol) reduction of 10 (9.4g, 50 mmol) in methanol (30 ml) as above furnished 13 (9.00 g), yield: 95%; b.p.140-48°(bath temp.)/8 mm; IR: 3580 (OH), 1742 (ester C=O); PMR: 0.98 (3H, m, $-CH_2-\underline{C}H_3$), 1.71 (2H, m, $-\underline{C}H_2-CH_3$), 2.63 (1H, m, $>\underline{C}H-CH_2-CH_3$), 3.30 (1H, broad d, exchangable with D_2O, O<u>H</u>), 3.60 (3H, s, $-COOC\underline{H}_3$), 3.73 (3H, s, $-COOC\underline{H}_3$), 4.2 (1H, m, $>\underline{C}H-OH$).

Dimethyl α-acetoxy-β-ethyl-succinate (65) - Acylation of 13 (1 g, 5 mmol) using acetic anhydride (2 ml) and pyridine (2 ml) furnished 65 (1.20 g), yield: 98%; b.p.140-48° (bath temp.)/5 mm; PMR: 0.93 (3H, t, $-CH_2-\underline{C}H_3$), 1.63 (2H, m, $-\underline{C}H_2-CH_3$), 2.10 (3H, s, $-OCO\underline{C}H_3$), 2.80 (1H, m, $>\underline{C}H-COOCH_3$), 3.66 (3H, s, $-COOC\underline{H}_3$), 3.73 (3H, s, $-COOC\underline{H}_3$), two doublets (2:1) at 5.13 (J = 6 Hz) and 5.30 (J = 5 Hz),

together 1H, >CH-OAc.

α-Ethyl-β-hydroxy-succinamide (62) - It is prepared according to the procedure as in the case of 61, in 81% yield, m.p.168-70°, recrystalised from methanol; IR:3500, 3300, 1695 to 1639.

α-Acetoxy-β-ethyl-succinamide (16) - Acylation of 62 (2.00 g, 12 mmol) using acetic anhydride (15 ml) acetic acid (5 ml) and sodium acetate (0.1 g) (according to procedure, as in the case of 15), furnished 16 (2.4 g), yield: 95%; recrystalised from water + acetone (2:3), m.p.200-02°(d), IR: 3390, 3226, 1761, 1689, 1639, 1220; PMR (DMSO-d_6); 0.84 (3H, t, $-CH_2-CH_3$), 1.48 (2H, m, $-CH_2-CH_3$), singlets (7:4) at 2.02 and 2.08, together 3H, $-OCOCH_3$, 2.61 (1H, m, $CH_2-CH<$), (doublets (7:4) at 4.88 (J = 10 Hz) and 5.15 (J = 6 Hz), together 1H, >CH-OAc) and multiplet at 6.90(1H) 7.18 (1H), 7.40 (1H), 7.58 (1H), exchangable with D_2O, $CONH_2$;(Found: C, 47.22; H, 6.94. $C_8H_{14}N_2O_4$ requires C, 47.52; H, 6.98%).

5-Acetoxy-6-ethyl-Dihydro-2,4-(1H, 3H)-pyrimidinedione (19)- Action of LTA (7.00 g, 15 mmol) on 16 (2.02 g, 10 mmol) in DMF (20 ml), (as in the case of 18) furnished 19 (1.70 g). Yield: 85%, analytically pure sample was obtained by sublimation under vacuum, m.p.282-285°(d), IR: 3333, 3145, 1754, 1721, 1672; PMR (DMSO-d_6): 1.00 (3H, t, $-CH_2-CH_3$), 1.53 (2H, m, $-CH_2-CH_3$), 2.20 (3H, s,

$-OCOCH_3$), 3.57 (1H, m, $-CH_2-CH<$), doublets (2:5) at 5.27 (J = 10 Hz) and 5.57 (J = 6 Hz), together 1H, $>CH-OAc$, 7.95 (1H, broad s, exchangable with D_2O, -NH-), 10.25 (1H, broad s, exchangable with D_2O, -NH-). (Found: C,48.47; H, 6.03. $C_8H_{12}N_2O_4$ requires C, 48.09; H, 6.04%).

V. 5-Acetoxy-6-phenyl-dihydro-2,4(1H, 3H)- pyrimidine-dione (20) (5-acetoxy-6-phenyl-dihydrouracil)

Methyl phenyl-oxaloacetate (11)- It was prepared from methyl phenylacetate (50 g, 0.33 mol) and dimethyl oxalate (40 g, 0.33 mol) in presence of sodium methoxide, folliwing the procedure as before, yield: 79%; b.p.130-40° (bath temp.)/0.5 mm; IR: 1751 (ester C=O), 1656 (C=O); PMR: 3.37 (3H, s, $-COOCH_3$), 3.43 (3H, s, $-COOCH_3$), 4.76 (1H, s, $>CH-Ph$), 6.60 (5H, s, aromatic).

Dimethyl α-hydroxy--β-phenyl-succinate (14)- Reduction of 11 (11.8 g, 50 mmol) in methanol (40 ml) using $NaBH_4$ (1 g, 26 mmol) in 5 ml of water as abovefurnished 14 (11.00 g), yield: 92.5%; b.p.150-55° (bath temp.)/0.2 mm (lit.[28] 131/0.04 mm for ethyl ester); IR: 3640 (OH), 1748 (ester C=O); PMR: 3.33 (3H, s, $-COOCH_3$), 3.42 (3H, s, $-COOCH_3$), 4.13 (1H, m, $>CH-OH$), 4.45 (1H, d, J = 2 Hz, $Ph-CH<$), 6.73 (5H, s, aromatic).

Dimethyl α-acetoxy-β-phenyl-succinate (66)- Acylation of (14) (0.5 g, 2.1 mmol) using a mixture of pyridine (1 ml) and acetic anhydride (1 ml) furnished 66 (0.51 g),

yield: 86.7%; b.p.140-145°(bath temp.)/0.5 mm; PMR: two singlets (1:1) at 1.83 and 2.00 together 3H, $-OCOCH_3$, 3.60 (6H, s, $-COOCH_3$), 4.70 (1H, d, J = 2 Hz, Ph-CH<), two doublets (1;1) at 5.23 (J = 9 Hz) and 5.63 (J = 8 Hz), >CH-OAc, 7.13 (5H, s, aromatic).

α-Hydroxy-β-phenyl-succinamide (63) - Amidification of 14 (6.00 g, 25 mmol) using methanolic ammonia furnished 63 (3.3 g), yield: 63%; m.p.160-62°, recrystalised from methanol: IR: 3590, 3450, 1684.

α-Acetoxy-β-phenyl-succinamide (17)- Acylation of 63 (2.00 g, 9.6 mmol) using acetic anhydride (12 ml), acetic acid (5 ml) and sodium acetate (0.1 g) (as in the case of 15) furnished (1.6 g), yield: 66.5%; m.p.180-81°; recrystalised from water-acetone (1:2); IR: 3475, 3236, 1761, 1672(broad), 1212, PMR (DMSO-d_6): singlets (10:3) at 1.83 and 2.06 (together 3H, $-OCOCH_3$), 3.00 (1H, d, J = 8 Hz, >CH-Ph), 4.26 (1H, d, J = 8 Hz, >CH-OAc), 7.25 (5H, s, aromatic H); (Found: C, 57.47; H, 5.72. $C_{12}H_{14}N_2O_4$ requires C, 57.59; H, 5.64%).

5-Acetoxy-6-phenyl-dihydro-2,4(1H, 3H)-pyrimidinedione (20)- A suspension of (17) (1.2 g, 4.8 mmol) in DMF (20 ml) was treated with $Pb(OAc)_4$ (4.00 g, 9 mmol) and worked out as in the case of 18, to furnish 20 (0.84 g), yield: 70.5%; m.p.272 (d), recrystalised from water; IR: 3333, 3145, 1779, 1718, 1224; PMR (DMSO-d_6): singlets (3:10) at 1.73 and 2.00 (together 3H, $-OCOCH_3$), 4.76 (1H, d, J = 10 Hz, CH-Ph), 5.40 (1H, d, J = 10 Hz, >CH-OAc), 7.33 (5H, s, aromatic H), (Found: C, 58.42; H, 5.21. $C_{12}H_{12}N_2O_4$ requires C, 58.06; H, 4.91%).

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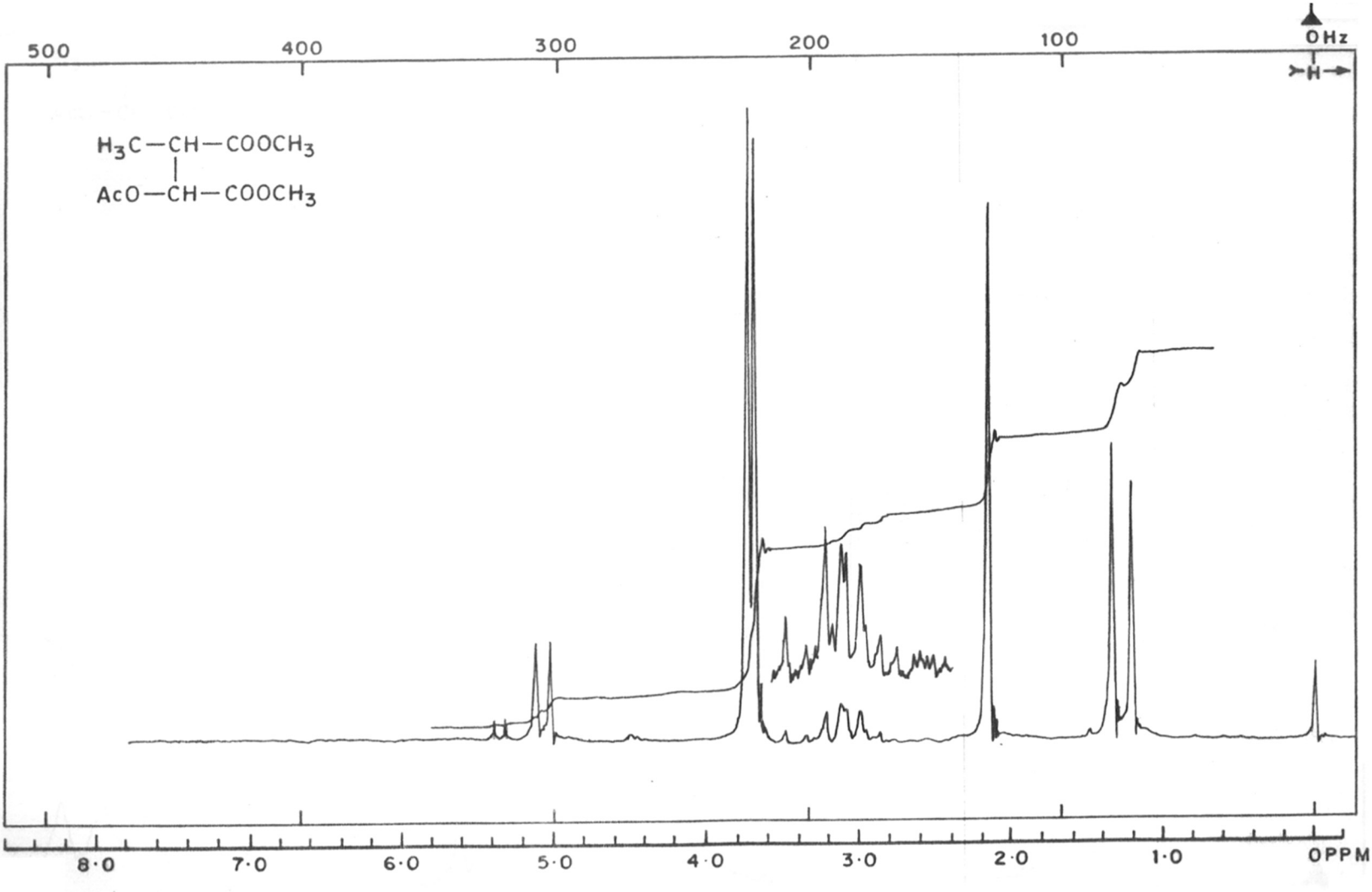
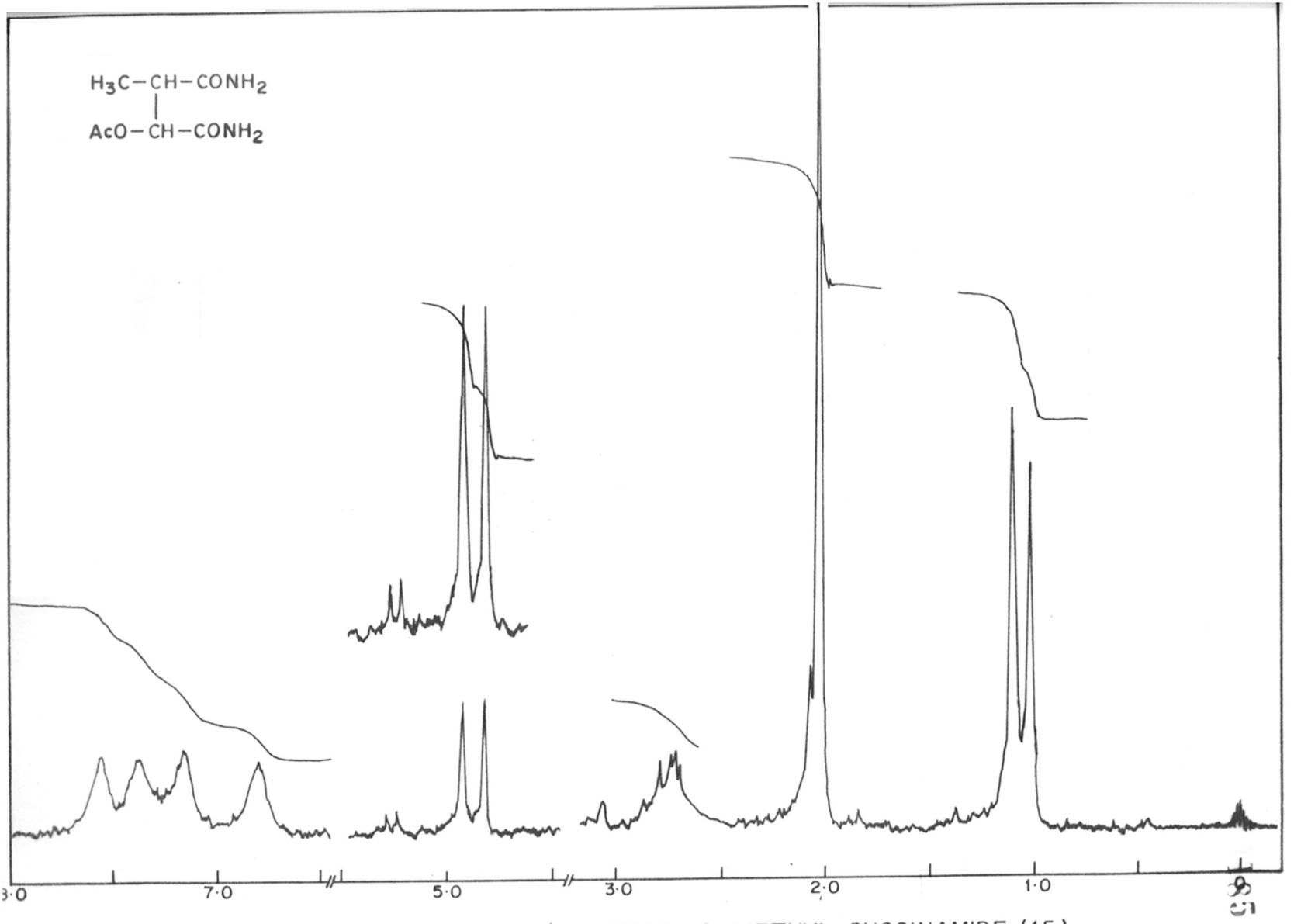
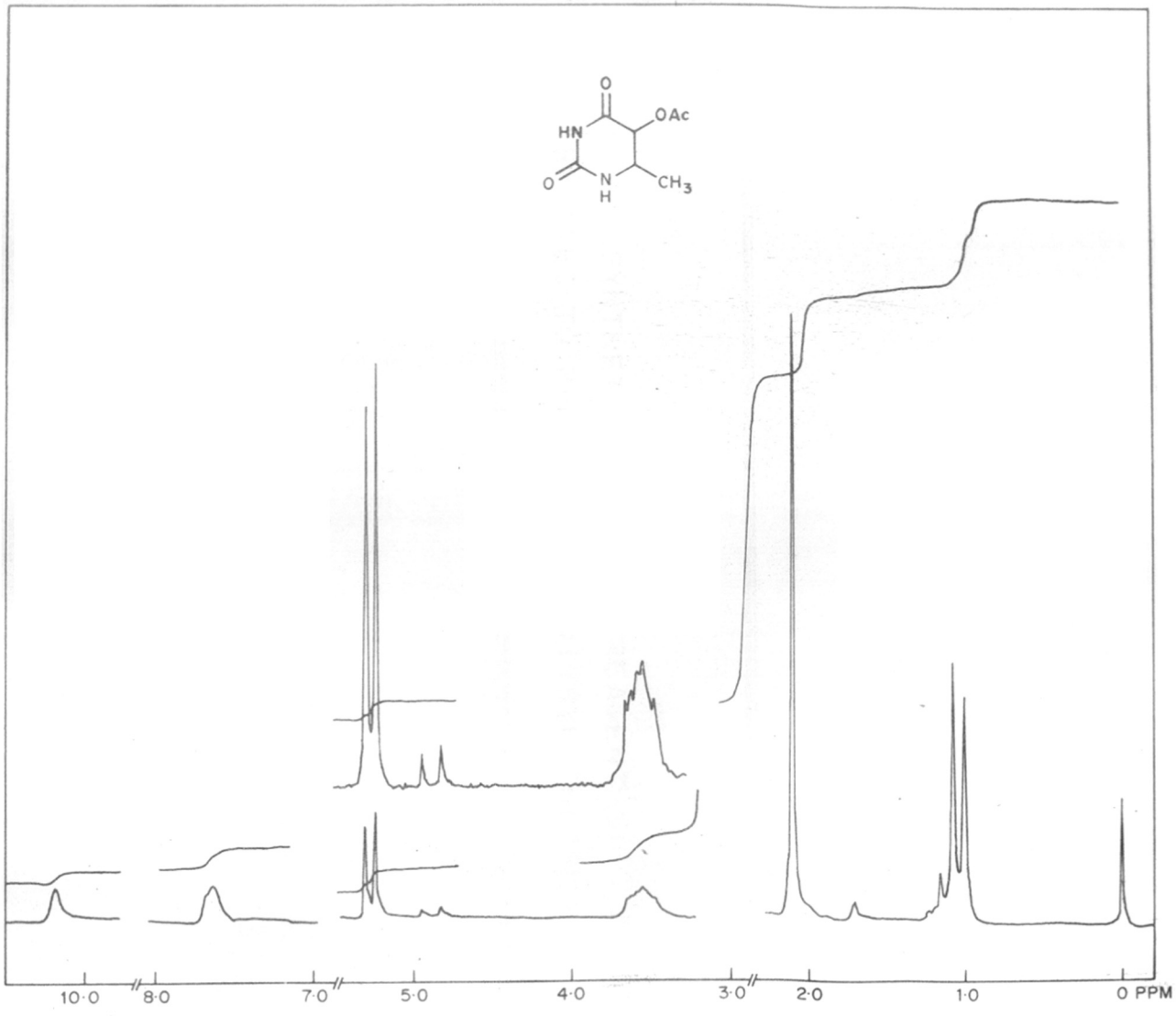


NMR SPECTRUM OF DIMETHYL α-ACETOXY-β-METHYL-SUCCINATE (64)



NMR SPECTRUM OF α-ACETOXY-β-METHYL-SUCCINAMIDE (15)



NMR SPECTRUM OF 5-ACETOXY-6-METHYL-DIHYDROURACIL (18)

CHAPTER-5

SYNTHETIC UTILITY OF REAGENT RELATED TO 2-ACETOXYISOBUTYRYL CHLORIDE

SUMMARY

Reaction of 2-acetoxybenzoyl chloride (2) and 2-acetoxybenzoyl bromide (3) on ethane-1,2-diol in acetic acid furnishes chloro-acetate (7) and bromo-acetate (8) respectively.

Action of reagents 2 and 3 on 1,2,11-undecane-triol (9) in acetic acid affords chloro-diacetate (10) and bromo-diacetate (11) respectively. Further, 10 is also obtained by the action of the reagent, 2-acetoxy-5-nitro-benzoyl chloride (5) on triol (9) in acetic acid. Compounds 10 and 11 on treatment with sodium methoxide solution yield the oxirane (12).

Similarly, 3-phenyl-propan-1,2-diol (13) on reaction with the reagent 3 in acetic acid furnishes the bromo-acetate (14), which on treatment with sodium methoxide solution affords oxirane (15).

Thus, reaction sequences 9 → 11 → 12 and 13 → 14 → 15 provide convenient routes for the preparation of oxiranes (12) and (15) from vicinal 1,2-diols (9) and (13).

Further, reaction of uridine (16) with 2 and 5 in acetic acid furnishes 3',5'-di-O-acetyl-2'-chloro-2'-deoxyuridine (17) and action of 16 with reagent 3 in acetic acid yields 3',5'-di-O-acetyl-2'-bromo-2'-deoxyuridine (18). The transformation of 17 and 18 to 2'-deoxyuridine (19) is known[1].

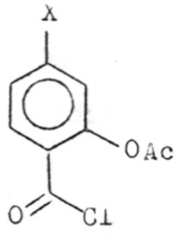
Thus transformation of 16 → (17 or 18) → 19 presents a convenient route for the preparation of 2'-deoxyuridine (19) from uridine (16).

The formation of acetates (21) and (23) by the action of reagent 2 on decyl alcohol (20) and menthol (22) in acetonitrile, is also observed.

During the reactions of 1,2-diol (9) and uridine (16) with reagents 2, 3 and 5, it has been observed that, reagents 2, 3 and 5 are comparable as far as yields of the resulting chloro-acetates (10 and 17) and bromo-acetates (11 and 18) are concerned. However, in the transformation of the bromo-acetate (11) to oxirane (12) the yield is 86%, while in the transformation of chloro-acetate (10) to oxirane (12), the yield is only 47%. Hence the reagent 3 is better than reagents 2 and 5, for the transformation of the 1,2-diol (9) to the oxirane (12).

The reaction of reagents 3 and 5 with 1,2-diol system has not been reported in literature so far.

CHART - I



1. X = H, Y = OH

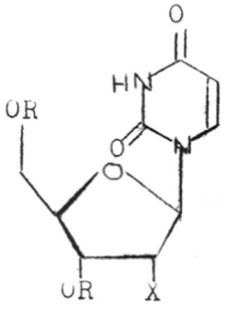
2. X = H, Y = Cl

3. X = H, Y = Br

4. X = NO_2, Y = H

5. X = NO_2, Y = Cl

6. X = H, Y = H



16 X = OH, R = H

16a. X = OAc, R = Ac

17. X = Cl, R = Ac

18. X = Br, R = Ac

19. X = H, R = H

$CH_3-(CH_2)_8-CH_2-OR$

20. R = H

21. R = Ac

CH_2-X
CH_2-OAc

7. X = Cl

8. X = Br

$CH_2-CH-(CH_2)_8-CH_2OH$
OH OH
9

$CH_2-CH-(CH_2)_8-CH_2-OAc$
OAc

10. X = Cl

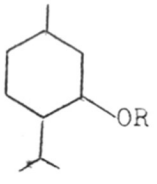
11. X = Br

$CH_2-CH-(CH_2)_8-CH_2OH$
O
12

$Ph-CH_2-CH-CH_2$
OH OH
13

$Ph-CH_2-CH-CH_2$
OAc X
14

$Ph-CH_2-CH-CH_2$
O
15

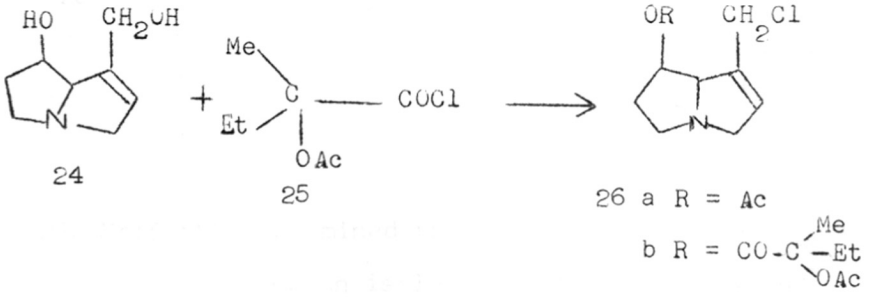


22. R = H

23. R = Ac

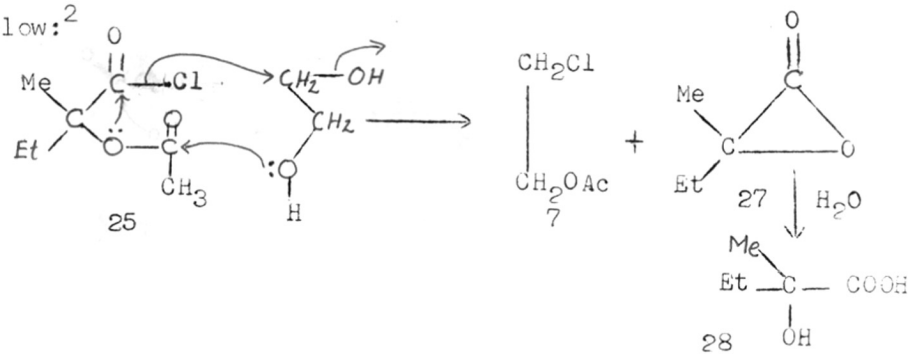
INTRODUCTION

During studies by Mattocks on the chemistry of pyrrolizidine alkaloid, an abnormal reaction was observed between the 1,4-diol (24) and 2-acetoxy-2-methylbutyryl chloride (25), the unexpected products of this reaction being the chloroesters (26a and 26b) in yields of 54 and 20%[2].



Mattocks also showed that the acetoxyacyl chloride (25) reacts abnormally with 1,2- and 1,3-diols to form chloroacetates for example, ethylene glycol reacting to form chloroethylacetate. It was also reported that predominantly trans-cyclohexane-1,2-diol reacted to give four products, the major one of which was identified by vapour phase chromatography as cis-2-chlorocyclohexyl acetate, the reaction thus proceeding with inversion of one center. On the basis of these and other considerations it was suggested that nucleophilic attack upon -acyloxy

acid chlorides bearing bulky substituents on the positions occurred primarily at the acetoxy carbonyl group rather than at the acyl chloride function. A favoured mechanism for these reactions is represented below:[2]

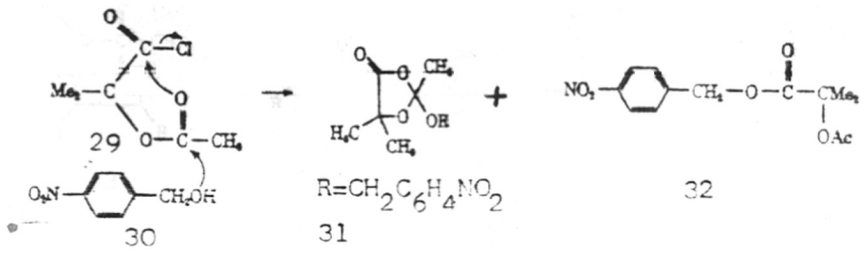


J.G. Moffatt[3] reexamined this unusual reaction and extended the studies on isolated hydroxyl groups and vicinal 1,2-diols.

Since the reagent 25 contains an asymmetric center, Moffatt et al. used the closely related 2-acetoxyisobutyryl chloride (29) in their work.

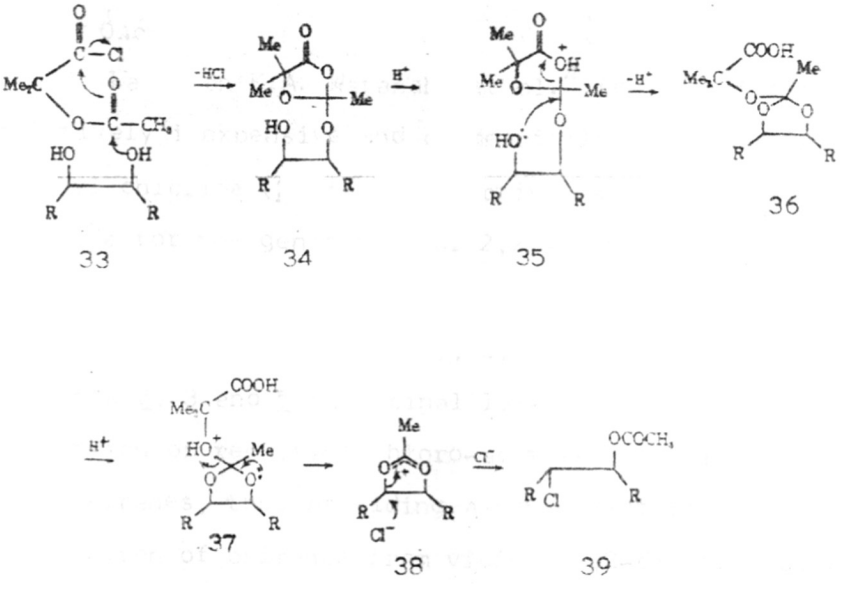
Moffatt reported[3] that, isolated hydroxyl groups are usually converted into 2,5,5-trimethyl-1,3-dioxolan 4-on-2-yl ethers or under certain conditions, 2-acetoxyisobutyryl esters. For example, 29 with p-nitrobenzyl alcohol (30) in acetonitrile furnished 2,5,5-trimethyl-2-p-nitrobenzyloxy-1,3-dioxolan-4-one (31) as the major product and 32 as the minor product. The formation of 32

involves the pathway shown below, once again via initial nucleophilic attack upon the acetoxyl group[2].

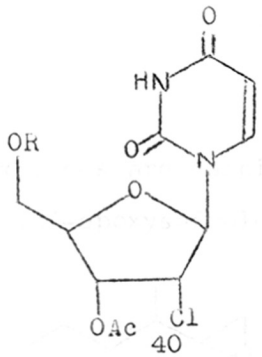


30 31 32

Further, cis-cycloalkane-1,2-diols were converted almost quantitatively into trans-2-chlorocycloalkyl acetates, while the corresponding trans-1,2-diols gave many products with little incorporation of chlorine, indicating that the formation of chloroacetates is characteristic of only cis-diols and proceeds with inversion of configuration of one of the centers. On the basis of these results they[3] proposed a mechanism for the formation of chloroacetates involving the intermediate formation of acetoxonium ion (38) as shown in the following page.



The reaction of 29 with uridine (16) or with 5'-protected uridine derivatives, led to the formation of high yield of 3'-O-acetyl-2'-chloro-2'-deoxyuridine (40) by way of a 2',3'-acetoxonium ion and then a 3'-O-acetyl-O2,2'-cyclonucleoside (41). They studied the reaction of uridine (16) with reagent 29 in a number of solvents (e.g. acetonitrile, DMF and acetic acid) and concluded that the nature of the resulting 5'-substituent is solvent dependent.



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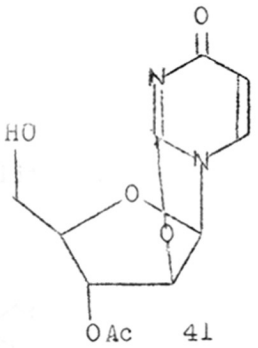


41

Later on K.A. Watanabe et al.[4] found that the relatively inexpensive and commercially available 2-acetoxybenzoyl chloride (2) is as effective as α-acetoxyisobutyryl chloride for the generation of 2,2'-anhydro pyrimidine nucleosides from ribo nucleosides.

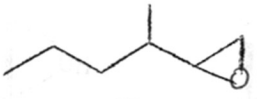
We extended this study, by examining the action of reagents 2, 3 and 5 on vicinal 1,2-diols and subsequent conversion of resulting chloro-acetates and bromo-acetates into oxiranes, thus providing a convenient route for the preparation of oxiranes from vicinal 1,2-diols. Further a convenient route for the conversion of uridine (16) into 2'-deoxyuridine (19) using reagents 2, 3 and 5 is described.

Oxiranes

Oxiranes are very reactive intermediate compounds and are susceptible to attack by carboxylic acids to form the mono-esters of 1,2-diols, a reaction catalysed by mineral acids[5]. Hence formation of epoxides should be under mild conditions or exclusion of mineral acids.

Further, some of the oxiranes (e.g. 42 and 43) are synthetically important intermediates[6] and some of the

oxiranes are carcinogenic metabolities, for example 2',3'-epoxysafrole (44).



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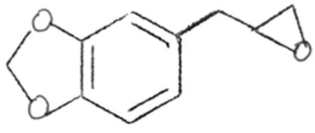
43



44

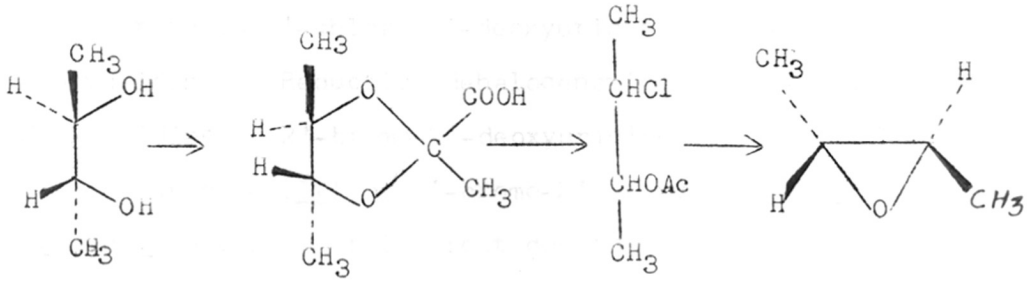
Methods are known to convert 1,2-diols into corresponding oxiranes, of which some are given below.

1. B.T. Golding et al.[8] obtained acetoxy-bromopropane (49) by reacting propane 1,2-diol (46) with 6M hydrogen bromide in acetic acid; alkali treatment of acetoxy-bromide (49) furnished propylene oxide (51).

$HO\text{-}CH_2\text{-}CH(R)\text{-}OH$	$Br\text{-}CH_2\text{-}CH(R)\text{-}OAc$	$CH_2\text{-}CH\text{-}CH_3$ (O)
45. R = H	48. R = H	51
46. R = Me	49. R = Me	
47. R = Ph	50. R = Ph	

Similarly vicinal diols (45) and (47) were converted to acetoxy-bromides (48) and (50), which can give the corresponding epoxides by treatment of alkali.

2. M.S. Newman et al.[9] prepared 2,3-epoxybutane (55) from 2,3-butanediol (52). Diol (52) was protected as



53 54 55

ketal (53), which upon treatment with thionyl chloride or phosphorous pentachloride at 20-25° furnished chloroacetate (54). Action of strong base on 54 furnished epoxide (55).

3. S. Hanessian et al.[10] showed that benzylidene derivatives prepared from 1,2-diols react with NBS in CCl_4 under free-radical conditions to form bromobenzoates which on treatment with alkali furnish corresponding epoxides.

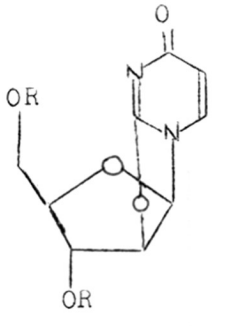
2'-Deoxyuridine

2'-Deoxyuridine (19) is a naturally occurring compound. It is useful as intermediate for the preparation of antivirus and anticancer drugs[11].

A few procedures[12] are available for the synthesis of 2'-deoxyuridine (19). Uridine (16) is initially transformed to 2'-chloro-2'-deoxyuridine or 2'-bromo-2'-deoxyuridine. Reductive dehalogenation[1] of 2'-chloro-2'-deoxyuridine or 2'-bromo-2'-deoxyuridine furnishes 2'-chloro-2'-deoxyuridine (17) or 2'-bromo-2'-deoxyuridine (18). 17 and 18 are also of interest due to their biological activity.

Some of the literature methods for the preparation of 2'-halogeno-2'-deoxyuridine are reviewed here.

Generally preparation of 2'-halogeno-2'-deoxyuridine involves two steps starting from uridine. First step is the conversion of uridine (16) into cyclouridine (2,2'-anhydro-1-β-D-arabinofuranosyluracil (56) and second step is the opening of the cyclouridine using suitable halo-acids or acetyl halides to 2'-halogeno-2'-deoxyuridine.



56 R = H

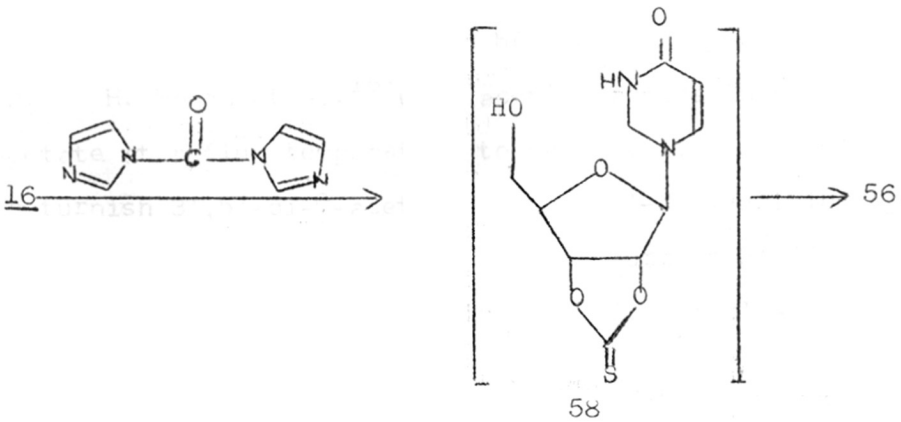
57 R = $COCH_3$

Preparation of cyclouridine (56)

1. Action of partially hydrolysed $POCl_3$ (1 mole of $POCl_3$: 1 mole of water) on uridine in ethylacetate at reflux temperature furnished 57. The use of dichlorophosphoric acid or a mixture of phosphorous oxychloride and t-butanol (1:1) in place of partially hydrolysed $POCl_3$ also gave 57 in good yield[13]. Hydrolysis of 57 using methanolic ammonia furnished cyclouridine (56).

16 —(i) $POCl_3$ + H_2O or (ii) $POCl_3$ + t-Bu-OH or (iii) Cl_2PO_2H→ 57

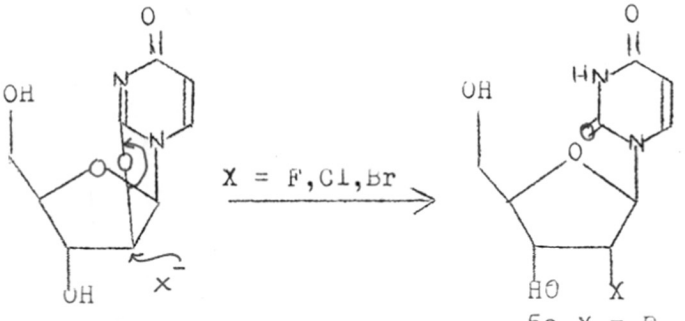
2. J.J. Fox et al.[14] showed that reaction of uridine (16) with thicarbonyldiimidazole in anhydrous toluene at reflux temperature yields cyclouridine (56) directly as shown below:.



58

Opening of cyclouridine (56) to 2'-halogeno-2'-deoxyuridine

(a) J.J. Fox et al.[15] found that under anhydrous conditions hydrogen halides cleave the 2,2'-anhydro bond of cyclouridine (56) with a nucleophilic attack by halide ion at C_2, to yield 2'-halogeno derivatives. For example, 2-fluoro-2'-deoxyuridine (59) was obtained by the reaction of hydrogen fluoride on 56 as shown below.



56

59 X = F
60 X = Cl
61 X = Br

Similarly, 60 and 61 were prepared by reacting hydrogen chloride and hydrogen bromide with 56.

2. H. Honjo et al.[16] used acetyl bromide in ethyl-acetate at reflux temperature to open cyclic nucleoside (56) to furnish 3',5'-di-O-acetyl-2'-bromo-2'-deoxyuridine (18). Similarly acetyl chloride was used to furnish 3',5'-di-O-acetyl-2'-chloro-2'-deoxyuridine (17) from cyclouridine (56).

Later on it was shown that both the stages viz. (1) transformation of uridine (16) to cyclouridine (56) and (2) oxazole ring opening of cyclouridine (56) can be combined as "one pot reaction" by treating uridine (16) with acetyl bromide or acetyl chloride when the bromo compound (18) or chlorocompound (17) were obtained in good yields[16]; however besides the bromocompound (18) or chlorocompound (17) considerable amount of the byproduct 2',3',5'-tri-O-acetyluridine (16a) was also formed.

PRESENT WORK

A convenient route for the preparation of oxiranes (12) and (15) from vicinal 1,2-diols (9) and (13) is presented. Further a synthetic route for 2'-deoxy-uridine (19) starting from uridine (16) is discussed.

Synthesis of reagents 2, 3 and 5

2-Acetoxybenzoyl chloride (2) is prepared by the action of thionyl chloride on 2-acetoxybenzoic acid (1)[17].

2-Acetoxy-5-nitrobenzoyl chloride (5) is prepared from 2-acetoxy-5-nitrobenzoic acid (4) (prepared by the method of Grimme and Schmitz[18]) using thionyl chloride[19].

2-Acetoxybenzoyl bromide (3) is prepared by the action of N-bromosuccinimide on 2-acetoxybenzaldehyde (6) in 59% yield . (N-bromosuccinimide is known[20] to convert aldehyde into corresponding acid bromide in CCl_4 using catalytic amount of benzoyl peroxide).

From the earlier reports[3], it is evident that reaction of 2-acetoxyisobutyryl chloride (29) with 1,2-diol system is solvent dependent; solvents like acetonitrile, DMF and acetic acid have been used. Reaction in acetic acid medium has been shown to furnish a single product in high yield. Hence in our study we used acetic acid as solvent.

As the ethylene glycol is available easily, we chose it as the starting material for the preliminary studies.

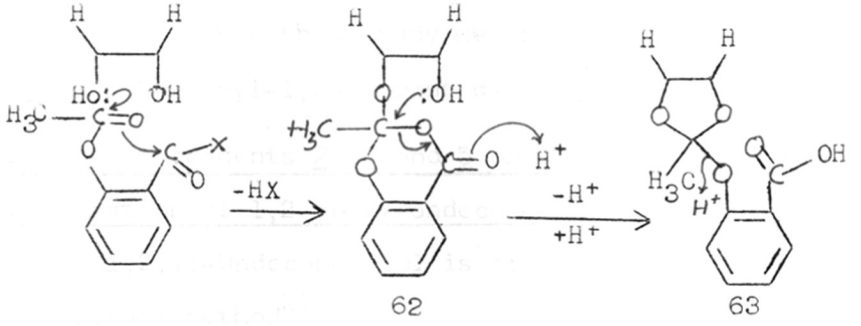
Action of reagents 2 and 3 on ethylene glycol

2-Acetoxybenzoyl chloride (2) is reacted with ethylene glycol in acetic acid at 100° for 2 hr., reaction mixture after work-up (removed the acetic acid under reduced pressure, residue treated with aqueous sodium carbonate (5%), extracted with ether, ether extract washed with water, dried and concentrated) furnished a single compound (by TLC), characterised as chloroethyl acetate (7) by elemental analysis, IR and PMR spectral data. IR Spectrum shows bands at 1740 and 1235 cm^{-1} characteristic of acetate. PMR spectrum shows signals at δ 2.16 (3H, s), 3.75 (2H, t, J = 6 Hz) and 4.33 (2H, t, J = 6 Hz) assignable to $-OCOCH_3$, $-CH_2-Cl$ and $-CH_2-OAc$ respectively.

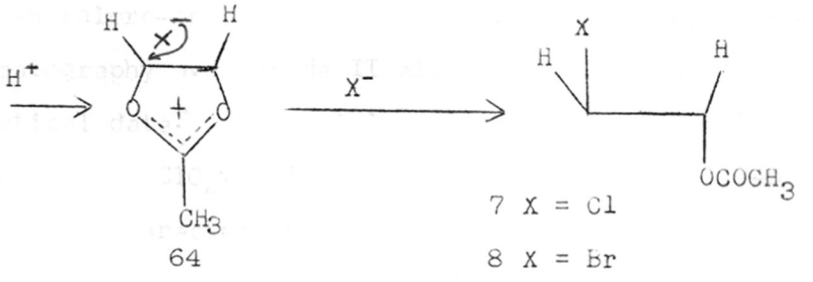
Similarly 2-acetoxybenzoyl bromide (3) is reacted with ethylene glycol in acetic acid at 100° for 2 hr to furnish bromoethyl acetate (8), characterised through analytical data.

These observations (i.e. conversion of ethylene glycol to chloro-acetate (7) and bromo-acetate (8) using reagents 2 and 3) indicate that acid bromide (3) and acid chloride (2) can be used for the conversion of 1,2-diols into corresponding halo-acetates.

Based on existing literature, the following mechanism is suggested for the transformation of ethylene glycol to 7 and 8.



2 X = Cl
3 X = Br



64

7 X = Cl
8 X = Br

This mechanism involves the formation of hydroxy dioxane (62) which undergoes acid-catalysed rearrangement involving the cis hydroxyl group to give the carboxyl substituted orthoester (63). 63 on protonation can collapse to the acetoxonium ion (64) which opens by halide ion to the haloacetates 7 and 8.

As the oxiranes are synthetically and biologically important compounds (as discussed in introduction, page No. 194), we thought of using these reagents, viz. 2 and 3 for the synthesis of oxiranes from vicinal 1,2-diols. For this study we chose 1,2,11-undecanetriol (9) and 3-phenyl-1,2-propane diol (13) as 1,2-diol systems.

Action of reagents 2, 3 and 5 on undecane triol (9) : preparation of 1,2-epoxy-undecane-11-ol (12)—

1,2,11-Undecanetriol is prepared according to literature method[21].

2-Acetoxybenzoyl chloride (2) reacts with 1,2,11-undecanetriol (9) in acetic acid at 100° for 2 hr to furnish chloro-acetate (10) which is purified by column chromatography over grade II alumina and characterised by analytical data. Elemental analysis shows the molecular formula $C_{15}H_{27}ClO_4$. IR spectrum shows bands at 1745 and 1245 cm^{-1}, characteristic of acetate, PMR spectrum exhibits signals at δ 1.42 (m, 16H), 2.00 and 2.09 (singlets, together 6H), 3.56 (d, 2H, J = 5 Hz), 3.96 (t, 2H, J = 6 Hz), 4.93 (t, 1H, J = 5 Hz). Multiplet at 1.42 is assignable to $(-C\underline{H}_2)_8-CH_2OAc$. Singlets at 2.00 and 2.09 are assignable to $-OCOC\underline{H}_3$. Further, 2H doublet, 2H triplet and 1H triplet are assignable to $-C\underline{H}_2-Cl$, $-C\underline{H}_2-OAc$ and $C\underline{H}$ OAc respectively. Hence the reaction product is assigned the structure 10 (1,10-di-acetoxy-11-chloro-undecane).

Moreover, Maltocks has shown that the reaction of 25 with propane-1,2-diol gave almost exclusively 3-chloropropyl acetate with replacement of only the primary hydroxyl group by halide[1]. This and our observations above, shows that under normal conditions the regioselectivity of the reaction is controlled mainly by steric factors; the acetoxonium ion (65) (likely intermediate during reaction between triol (9) and reagent 2 according to reaction mechanism described previously) may open by chloride ion attack from the less hindered side to furnish primary chloride (66). Then other primary alcohol moiety can get acylated to furnish chloro-diacetate (10).

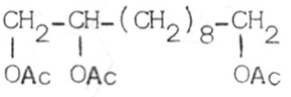
Similarly 2-acetoxybenzoyl bromide (3) reacts with triol (9) in acetic acid at 100° for 2 hr to furnish 1,10-di-acetoxy-11-bromo-undecane (11); it is purified by column chromatography over grade II alumina and characterised through elemental analysis. IR and PMR spectral data (see experimental).

As the above reaction mechanism involves, nucleophilic attack at the acetoxy carbonyl grouprather than at the acyl chloride function and in view of literature reports (Jencks et al.[22] reported that rate of alkaline hydrolysis of p-nitrophenylacetate is much faster than that of phenylaceta te), we expect the rate of reaction of reagent (5) with 1,2-diol systems will be greater than the rate of

reaction of reagent 2 with 1,2-diol systems.

In view of this, the reaction of triol (9) with reagents 2 and 5 are carried out separately for 40 min. under similar conditions to furnish chloro-acetate (10); reagent 2 furnished 10 in 66% yield, whereas reagent 5 furnished 10 in 70% yield. This observation shows that there is a slight increase in reaction rate of triol (9). with reagent 5, in comparison with that of reagent 2.

The comparison of PMR spectrum of triacetate (67) (prepared from triol (9) using pyridine and acetic anhydride) with the spectral data of chloro-diacetate (10)



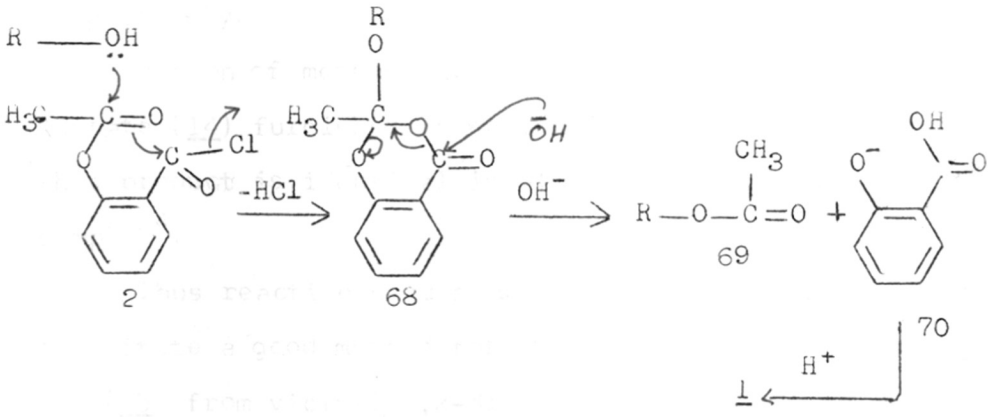
67

or bromo-diacetate (11) indicates the absence of triacetate (67) in the reaction products of triol (9) with reagents 2, 3 and 5.. PMR spectrum of 67 shows signals at δ 1.4 (m, 16H, $-(CH_2)_8-CH_2-OAc$), 2.04 and 2.09 (two singlets, together 9H, $-OCOCH_3$), 4.36 (m, 4H, $-CH_2-OAc$), 5.00 (m, 1H, CH-OAc).

Further, action of reagent 2 on triol (9) in acetonitrile at room temperature, after work-up (removed acetonitrile under reduced pressue , diluted the residue with aqueous sodium carbonate (5%), extracted with ether, ether extract washed with water, dried and concentrated)

furnished chloro-diacetate (10) in 75% yield. Furthermore decyl alcohol (20) and menthol (22) react with reagent 2 (under similar conditions as above) to furnish acetates 21 and 23.

This indicates the acylation of primary and secondary alcohol group possibly via acetolysis of the intermediate dioxane (68), as shown below:



Action of methanolic sodium methoxide (1M) on chloro-diacetate (10) and bromo-diacetate (11) furnishes known epoxide (12) in 50 and 86% yield respectively. Epoxide (12) is characterised by comparison of spectral data with authentic sample[23].

Action of reagent 3 on 3-phenyl-propan-1,2-diol (13): Preparation of 1,2-epoxy-3-phenyl-propane

3-Phenyl-propan-1,2-diol (13) reacts with reagent 3 in acetic acid, to furnish bromo-acetate (14), which is

purified by column chromatography and characterised through analytical data. IR spectrum shows bands at 1745 and 1235 cm^{-1} characteristic of acetate. PMR spectrum exhibits signals at δ 1.96 (s, 3H), 2.93 (d, 2H, J = 7 Hz), 3.33 (dd, 2H, J = 6 Hz and 2 Hz), 5.00 (m, 1H) and 7.13 (s, 5H). Signals at 1.96 and 7.13 are assigned to $-OCOCH_3$ and aromatic H, whereas signals at 2.93, 3.33 and 5.00 are assignable to $-CH_2-\emptyset$, $-CH_2-Br$ and CH-OAc respectively.

Action of methanolic sodium methoxide (1M) on bromoacetate (14) furnishes known epoxide (15) in 90% yield. This product is identical in all respect with an authentic sample[24].

Thus reaction sequences 9 → 11 → 12 and 13 → 14 → 15 constitute a good method for the preparation oxiranes (12) and (15) from vicinal 1,2-diols (9 and 13).

2'-Deoxyuridine (19)

Since 2'-deoxyuridine (19) and the nucleosides derived from it[25,26] are biologically important, we thought of making use of reagents 2,3 and 5 for the preparation of 2'-deoxyuridine (19) from uridine (16).

2-Acetoxybenzoyl chloride (2) reacts with uridine (16) in acetic acid at 100°, to furnish 3',5'-di-O-acetyl-2'-chloro-2'- deoxyuridine (17) in 95% yield, characterised by optical rotation and PMR spectral data. PMR spectrum

of 17 exhibits signals at δ 2.13 (3H, s), 2.20 (3H, s), 4.46 (3H, m), 4.73 (1H, t, J = 5 Hz), 5.33 (1H, m), 5.83 (1H, d, J = 9 Hz), 6.07 (1H, d, J = 5 Hz), 7.50 (1H, d, J = 9 Hz), 9.8 (1H, broad singlet, exchangable with D_2O), which are in good agreement with the data given in lit.[2].

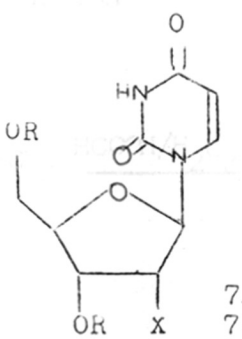
Similarly 2-acetoxy-5-nitrobenzoyl chloride (5) reacts with uridine (16) in acetic acid at 100°, to furnish 17 in 96% yield; product (17) thus obtained is identical in all respect with the sample prepared above.

Action of 2-acetoxybenzoyl bromide (3) on uridine (16) in acetic acid at 100°, furnishes in 96% yield of 3',5'-di-O-acetyl-2'-bromo-2'-deoxyuridine (18), characterised by optical rotation and PMR spectral data. PMR spectrum of 18 shows signals at 2.13 (3H, s), 2.20 (3H, s), 4.43 (3H, m), 4.63 (1H, t, J = 5 Hz), 5.26 (1H, m), 5.80 (1H, d, J = 8 Hz), 6.20 (1H, d, J = 5 Hz), 7.40 (1H, d, J = 8 Hz), 9.63 (1H, broad singlet, exchangable with D_2O), which are consistant with the data given in lit.[16]

Uridine (16) is treated with reagents 2 and 5 in acetic acid for 40 min. under identical conditions to furnish 17; reagent 2 furnished 17 in 65% yield, whereas reagent 5 furnished 17 in 73% yield indicating the slight increase in reaction rate of uridine with reagent 5 in comparison with that of reagent 2.

This one-step method for the preparation of chloro-diacetate (17) and bromo-diacetate (12) using reagents 2, 3 and 5 is more efficient than the literature methods even though one-pot reaction of uridine to 17 or 18 using acetyl chloride or acetyl bromide is supposed to be a good method, besides 17 or 18 considerable amount of a byproduct the triacetate (16a) is also formed[1,16]. In our method even detectable amount of triacetate (16a) is not formed, as revealed by the study of PMR spectra of 17, 18 and 16a.

Further, action of methanolic sodium methoxide (0.5 N) on chloro-diacetate (17) and bromo-diacetate (18) furnishes known chloro-diol (71) and bromo-diol (72), characterised by comparison of m.p. and optical rotation with the available data in literature.



71 X = Cl, R = H
72 X = Br, R = H
73 X = H, R = OAc

Based on the literature dealing with the reactions of ribonucleosides with acid chlorides and acid bromides related to 2 and 3 it is suggested that cyclic

CHART II

Scheme A

Preparation of triol 9

$$CH_2 = CH-(CH_2)_8-COOH \xrightarrow{CH_3OH/H^+} CH_2=CH-(CH_2)_8-COOCH_3$$

74 75

$$\xrightarrow{LAH} CH_2=CH-(CH_2)_8-CH_2OH \longrightarrow \underset{OH}{\overset{CH_2}{|}}-\underset{OH}{\overset{CH}{|}}-(CH_2)_8-CH_2OH$$

76 9

Scheme B

Preparation of diol 13

$$Ph-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-COOH \xrightarrow[\text{reduction}]{\text{Wolff Kishner}} Ph-CH_2-CH_2-CH_2-COOH$$

77 78

$$\xrightarrow{Pb(OAc)_4} Ph-CH_2-CH=CH_2 \xrightarrow{HCOOH/H_2O_2} Ph-CH_2-\underset{OH}{\overset{CH}{|}}-\underset{OH}{\overset{CH_2}{|}}$$

79 13

nucleoside (56) is involved in the transformation of uridine (16) by reagent 2, 3 and 5 to 17 and 18.

The transformation of chloro-diacetate (17) and bromo-diacetate (18) to diacetate (73) by selective reductive dehalogenation using tributyltinhydride and 2,2'-azobis (2-methylpropionitrile) is known[1]. Action of methanolic ammonia solution on 73 furnishes 2'-deoxy-uridine (19)[16].

In the reactions of 1,2-diol (9) and uridine (16) with reagents 2, 3 and 5, it has been observed that reagents 2, 3 and 5 are comparable as far as yields of the resulting chloro-acetates (10 and 17) and bromoacetates (11 and 18) are concerned. However, in the transformation of the bromo-acetate (11) to oxirane (12) the yield is 86%, while in the transformation of chloro-acetate (10) to oxirane (12), the yield is only 47%. Hence the reagent 3 is better than reagents 2 and 5, for the transformation of the 1,2-diol (9) to the oxirane (12).

EXPERIMENTAL

(A) Preparation of reagents 2,3 and 5

2-Acetoxy-benzoyl chloride (2) - A mixture of 2-acetoxy-benzoic acid (1) (10 g, 56 mmol) and thionyl chloride (25 ml) was kept at room temperature for 5 hr and excess of thionyl chloride was taken off under reduced pressure. Residue was distilled under vacuum to furnish (2), b.p. 150-55°(bath temp.)/0.5 mm (lit.[17] 134-35°/14 mm).

2-Acetoxy-5-nitrobenzoyl chloride (5)

A mixture of 2-acetoxy-5-nitrobenzoic acid (4) (5 g, 22 mmol) and thionyl chloride (20 ml) was heated under reflux for 2 hr and excess of thionyl chloride was taken off under reduced pressure. Residue was distilled under vacuum to furnish 5, b.p. 165-170 (bath temp.)/0.5 mm (lit.[19] 150°(bath temp.)/0.01).

2-Acetoxy-benzoyl bromide (3)

A mixture of O-acetylsalicylaldehyde (6) (12.5 g, 76 mmol), N-bromo succinimide (14.00 g, 78 mmol), benzoyl peroxide (0.20 g) and carbon tetrachloride (120 ml) was heated under reflux with continuous stirring in N_2 atmosphere for 1 hr; during heating reaction mixture was irradiated with 250 W I.R. lamp. Reaction mixture was cooled, filtered off the solid and filtrate was concentrated. Residue was distilled under vacuum to furnish (3) (11 g), yield 50%; b.p. 160-70(bath temp.)/0.3 mm.

(B) Reaction of ethylene glycol with reagents 2 and 3

2-Chloroethylacetate (7)

A mixture of ethylene glycol (0.5 g, 8 mmol), reagent 2 (2.5 g, 12 mmol) and acetic acid (5 ml) was heated at 100° (bath temp.) for 2 hr, removed the excess of acetic acid under reduced pressure. Residue was treated with aqueous sodium carbonate (5%) and extracted with ether. Ether extract was washed with water, dried and concentrated to furnish 7 (0.93 g). Yield: 94.3%; b.p.140-142° (lit.[27] 145°); IR: 1740 and 1235 (acetate); PMR: 2.16 (3H, s, $-OCOCH_3$), 3.75 (2H, t, J = 6 Hz, $-CH_2-Cl$), 4.33 (2H, t, J = 6 Hz, $-CH_2OAc$).

2-Bromoethyl acetate (8)

Ethylene glycol (0.5 g, 8 mmol) was reacted with with reagent 3 (3 g, 12 mmol) in acetic acid (as in the case of 7) to furnish 8, (1.2 g); yield: 89%; b.p.156° (lit.[28] 159-64°); IR: 1742 and 1238 (acetate); PMR: 2.16 (3H, s, $-OCOCH_3$), 3.86 (2H, t, J = 6 Hz, $-CH_2-Br$), 4.33 (2H, t, J = 6 Hz, $-CH_2OAc$).

(C) Preparation of undecane 1,10,11-triol (9)

Esterification of undecenoic acid (74) using methanol and sulfuric acid furnished methyl undecenoiate (75) in 85% yield, b.p.140-45°(bath temp.)/15 mm (reported[29] 140-141°/20 mm. IR: 1745 (ester C=O), 1645 (C=C);

PMR: 1.43 (12H, m, $-(CH_2)_6-$) 2.20 (4H, m, $-\underline{CH_2}-COO-$, $-\underline{CH_2}-CH=CH_2$), 3.66 (3H, s, $-COOC\underline{H_3}$), 5.00 (2H, m, $C\underline{H_2}=CH-$), 5.80 (1H, m, $CH_2=C\underline{H}-$).

LAH reduction of (75) according to literature method[29] furnished 10-undecen-1-ol (76) in 95% yield b.p.138-40°/20 mm (lit.[29] 134-35/18 mm), IR: 3435 (OH), 1642 (C=C); PMR: 1.36 (14H, m, $-(CH_2)_7-$), 2.03 (2H, m, $CH_2=CH-C\underline{H_2}-$), 3.53 (2H, m, $-\underline{CH_2}-OH$), 4.13 (1H, m, exchangable with D_2O, O$\underline{H}$), 4.93 (1H, m, $C\underline{H_2}=CH-$), 5.70 (1H, m, $CH_2=C\underline{H}-$).

Hydroxylation of (76) using formic acid and H_2O_2, according to literature method[21] furnished 9 in 75% yield, b.p.155-65°(bath temp.)/0.2 mm; m.p.72-74°(lit.[21] 74-75°). IR: 3460 (OH).

(D) 1,10,11-Tri-O-acetyl-undecan 1,10,11-triol (67)

A mixture of triol (0.20 g), acetic anhydride (5 ml) and pyridine (5 ml) was kept overnight and worked out as usual to furnish 67 in 95% yield; b.p.160-165° (bath temp.)/ 1 mm (lit.[21] 176°/8 mm); IR: 1742 and 1228 (acetate); PMR: 1.4 (16H, m, $-(CH_2)_8-$), 2.04 and 2.09 (singlets, together 9H, $-OCOC\underline{H_3}$), 4.36 (4H, m, $-\underline{CH_2}-OAc$), 5.00 (1H, m, $C\underline{H}-OAc$).

(E) Reaction of undecane-1,2,11-triol (9) with reagent 2, 3 and 5

(a) Reaction in acetic acid medium

1,10-Di-acetoxy-11-chloro-undecane (10) A mixture of triol (0.5 g, 2.5 mmol), reagent 2 (1.5 g, 7.5 mmol) and acetic acid (15 ml) was stirred at 100° for 2 hr. Acetic acid was distilled off under reduced pressure and residue was treated with sodium carbonate solution (5%). Extracted with ether, organic extract washed with water, dried and concentrated to furnish 10, purified through column chromatography over grade II alumina. Fraction eluted with 2% acetone in pet.ether furnished analytically pure sample of 10 (0.64 g); yield: 86%; b.p.140-145°(bath temp.)/0.5 mm; IR: 1745 and 1245 (acetate); PMR: 1.42 (16H, m, $-(CH_2)_8-CH_2OAc$), 2.00 and 2.09 (singlets, together 6H, $-OCOCH_3$), 3.56 (2H, d, J = 5 Hz, $-CH_2-Cl$), 3.96 (2H, t, J = 6 Hz, $-CH_2OAc$), 4.93 (1H, t, J = 5 Hz, $>CH-OAc$).

1,10-Diacetoxy-11-bromo-undecane (11)

Reaction of triol (9) with reagent 3 in acetic acid (as in the case of 10), furnished crude 11; analytically pure sample of 11 (0.71 g) was obtained by column chromatography over grade II alumina; yield: 83%; IR: 1742 and 1235 (acetate); PMR: 1.43 (16H, m, $-(CH_2)_8-CH_2-OAc$), 2.00 and 2.10 (singlets, together 6H, $-OCOCH_3$), 3.50 (2H, d, J = 5 Hz, $-CH_2-Br$), 4.06 (2H, t, J = 6 Hz. $-CH_2-OAc$),

4.97 (1H, t, J = 5 Hz, >CH-OAc); (Found: C, 51.56; H, 8.46. $C_{15}H_{27}BrO_4$ requires C, 51.42; H, 8.08%).

Action of reagent (5) on triol (9): 1,10-Di-acetoxy-11-chloro-undecane (10)

A mixture of triol (9) (0.5 g, 2.5 mmol), reagent 5 (1.2 g, 7.5 mmol) and acetic acid (5 ml) was heated at 100° for 2 hr and worked out as above to furnish crude chloro-diacetate (10), which was purified through column chromatography over grade II alumina. Fraction eluted with 2% acetone in pet.ether furnished pure 10 (0.66 g); yield: 88%; b.p.140-145°(bath temp.)/0.5 mm; this sample is identical in all respect with the sample prepared above.

(b) Reaction in acetonitrile medium

Action of reagent 2 on triol (9)

A mixture of triol (9) (0.5 g, 2.5 mmol), reagent 2 (1.7 g, 8.6 mmol) and acetonitrile was kept overnight. Removed the acetonitrile under reduced pressure and residue was treated with aqueous sodium carbonate (5%). Extracted with ether, ether extract was washed with water, dried and concentrated to furnish crude 10. Analytical sample of 10 (0.56 g) was obtained by column chromatography over grade alumina, yield: 75%. IR and PMR spectral data were matching with those of sample prepared above.

Action of reagent 3 on triol (9)

A mixture of triol (9) (0.5 g, 25 mmol), reagent 3 (2.00 g, 8.2 mmol) and acetonitrile (8 ml) was kept overnight and worked as above to furnish crude (11). Chromatography of crude product furnished analytically pure sample of 11 (0.66 g) yield: 77%. Thus prepared bromo-diacetate (11) was identical in all respect with the sample prepared above.

(F) 10,11-Epoxy-undecan-1-ol (12)

(a) The bromo-diacetate (11) (0.35 g, 1 mmol) was treated with sodium methoxide solution (4 ml, 1M) and kept at room temperature for 2 hr. Reaction mixture was neutralised with H^+ resin, extracted with ether, organic extract was washed with water, dried and concentrated. Residue was distilled under vacuum to furnish pure 12 (0.16 g), yield: 86%; b.p.120-125° (bath temp.)/0.5 mm (lit.[30] 91-7°/0.04 mm); IR: 3540 (OH), 1464, 1408, 1258, 1053, 916, 833, 725; PMR: 1.40 (16H, m, $-(CH_2)_8-$), 2.33 (1H, m, CH_2—O—CH-), 2.66 (2H, m, CH_2—O—CH-), 3.16 (1H, m, exchangable with D_2O, OH), 3.50 (2H, m, $-CH_2OH$).

(b) The chloro-diacetate (10) (0.30 g, 9.8 mmol) was treated with sodium methoxide solution (4 ml, 1M) and kept at room temperature for 2 hr and worked out as above to furnish distilled, pure 12 (0.09 g); yield 47%; b.p.120-25°/(bath temp.)/0.5 mm; IR and PMR spectral data

are identical with those of the sample prepared above.

(G) Action of reagent 2 on n-decyl alcohol (20)

A mixture of 20 (0.30 g, 1.9 mmol), reagent 2 (0.57 g, 2.9 mmol) and acetonitrile (5 ml) was kept overnight. Removed the acetonitrile under reduced pressure and residue was treated with aqueous sodium carbonate (5%). Extracted with ether, ether extract was washed with water, dried, concentrated and chromatographed over grade II alumina to furnish decylacetate (21) (0.34 g) in 90% yield. R_f value, IR and PMR spectral data are matching with those of authentic sample prepared from n-decyl alcohol using pyridine-acetic anhydride.

(H) Action of reagent on menthol (22)

A mixture of menthol (0.30 g, 1.95mmol) reagent (2) (0.57 g, 2.9 mmol) and acetonitrile (5 ml) was kept overnight and worked out as in the case of 20 to furnish 23 (0.33 g); yield: 87%; R_f value, IR and PMR spectral data were matching with those of authentic sample prepared from menthol (22) using pyridine-acetic anhydride.

I. Preparation of 3-phenyl-propane-1,2-diol (13)

To a stirred mixture of Y-phenyl butyric acid (78)[31] (8.2 g, 50mmol) (obtained by Wolff-Kishner reduction of β-benzoylpropionic acid (77) cupric acetate (1 g), pyridine (2 ml) and benzene (120 ml), lead tetraacetate

(33.3 g, 75 mmol) was added. Reaction mixture was stirred under reflux for 8 hr. Excess of lead tetraacetate was destroyed by the addition of ethylene glycol (10 ml), diluted with water, separated the benzene layer. Organic layer was washed with aqueous sodium carbonate (5%), water and dried. Removal of the benzene furnished 3-phenyl-prop-1-ene (79) (4.2 g, 35 mmol), yield: 71%, b.p.100-05° (bath temp.)/20 mm (lit.[32] 153-4°); IR: 1658 (C=C); PMR: 3.33 (2H, d, J = 7 Hz, Ø -C$\underline{H}_2$), 4.80 (1H, m, = C$\underline{H}_2$), 5.10 (1H, m, = C$\underline{H}_2$), 5.56 to 6.23 (1H, m, -C$\underline{H}$=CH$_2$), 7.10 (5H, s, aromatic).

To a solution of 79 (3.5 g, 30 mmol) and formic acid (90%, 10 ml), hydrogen peroxide (30%, 18 ml) was added under vigorous stirring at 40°. After 8 hr. at the same temperature, the solvent was removed under diminished pressure and residue was treated with 10% alcoholic sodium hydroxide. Mixture was heated under reflux for 1 hr. Ethanol was removed under diminished pressure and residue was extracted with ether. Ether extract was washed with water, dried and concentrated. Residue was distilled under vacuum to furnish 13 (3.2 g, 21 mmol), yield: 70%; b.p.125-30° (bath temp.)/ 0.5 mm (lit.[33] 147-49°/6 mm): IR: 3450 (OH); PMR: 2.50 (2H, m, Ø-C$\underline{H}_2$-), 3.20 to 3.80 (3H, m, -C$\underline{H}$(OH)-C$\underline{H}_2$(OH), 3.96 (2H, broad s, exchangable with D_2O, O$\underline{H}$), 7.05 (5H, s, aromatic).

(J) Action of reagent 3 on 13: 2-Acetyl-1-bromo-3-phenyl-propan-2-ol (14)

A mixture of 13 (0.82 g, 5.3 mmol), reagent 3 (2.00 g, 8.2 mmol) and acetic acid (5 ml) was stirred at 100° for 2 hr. and worked out as in the case of 10 to furnish crude 14. Analytically pure sample was obtained through column chromatography over grade II alumina; fraction eluted with 1% acetone in pet.ether furnished pure 14 (1.3 g), yield: 89.5%; b.p.120-30°(bath temp.)/0.5 mm; IR: 1745 and 1235 (acetate); PMR: 1.96 (3H, s, $-OCOCH_3$), 2.93 (2H, d, J = 7 Hz, Ø $-CH_2-$), 3.33 (2H, dd, J = 6 Hz, 2 Hz, $-CH_2-Br$), 5.00 (1H, m, CH-OAc), 7.13 (5H, s, aromatic H). (Found: C, 52.43; H, 5.32. $C_{11}H_{13}BrO_2$ requires C, 52.12; H, 5.17%).

(K) 1,2-Epoxy-3-phenyl-propane (15)

Bromo-acetate (14) (0.5 g, 1.9 mmol) was treated with sodium methoxide solution (5 ml, 1M) and kept at room temperature for 1.5 hr. Reaction mixture was worked out as in case of 12, to furnish 15 (0.25 g), yield: 90%; b.p.110°(bath temp.)/10 mm (lit.[34] 92-93°/10 mm); IR: 1504, 1458, 847, 739, 702; PMR: 2.33 (1H, m, $-CH\overset{O}{\diagup\diagdown}CH_2$, 2.73 (4H, m, $-CH_2-CH\overset{O}{\diagup\diagdown}CH_2$), 7.03 (5H, s, aromatic H).

(L) Reaction of uridine with reagents 2,3 and 5

3',5'-Di-O-acetyl-2'-chloro-2'-deoxyuridine (17)

Method A: A mixture of uridine (16) (0.6 g, 2.4 mmol), acetic acid (5 ml) and 2-acetoxybenzoyl chloride (1.5 g, 7.6 mmol) was stirred at 100° for 1.5 hr. Acetic acid was taken off under reduced pressure at 70-80° (bath temp) and residue was extracted with ether. Ether extract was washed with aqueous sodium carbonate (5%, 50 ml), water and dried. Removal of ether furnished chloro-compound (17) (0.82 g), which was chromatographically homogeneous, yield: 96% TLC (solvent system): R_f: 0.51; $(\alpha)_D^{25}$ + 5.8 (c 1.5, ethanol) [lit.[36] $(\alpha)_D^{25}$ + 6 (c, 0.6, ethanol)]; IR (Nujol): 3390 (NH), 1760 (broad, C=O of acetate), 1704 (C=O of uracil), 1645 (C=C), 1235 (broad, acetate); PMR ($CDCl_3$): 2.13 (3H, s, $-OCOCH_3$), 2.20 (3H, s, $-OCOCH_3$), 4.46 (3H, m, $H_{4'}$, $2H_{5'}$), 4.73 (1H, t, J = 5 Hz, $H_{2'}$), 5.33 (1H, m, $H_{3'}$), 5.83 (1H, d, J = 9 Hz, H_5), 6.07 (1H, d, J = 5 Hz, $H_{1'}$), 7.50 (1H, d, J = 9 Hz, H_6) 9.8 (1H, broad s, exchangable with D_2O, HN_3).

Method B: A mixture of uridine (16) (0.6 g, 2.4 mmol), acetic acid (5 ml) and 2-acetoxy-4-nitrobenzoyl chloride (1.8 g, 8 mmol) was stirred at 100° for 1 hr and worked out (as above) to furnish chloro-compound (17) (8.2 g), whose TLC was matching with the sample prepared above. Yield: 96%; IR and PMR spectral data were in good

agreement with the data given above.

Reaction of uridine with 2 and 5 for 40 min -

A mixture of uridine (16) (0.4 g, 1.6 mmol), acetic acid (5 ml) and acid-chloride (5) was stirred at 100° for 40 min. and worked out as above to furnish 17 (0.42 g), yield: 73%.

A mixture of uridine (16) (0.4 g, 1.6 mmol), acetic acid (5 ml) and acid-chloride (2) was stirred at 100° for 40 min. and worked out as above to furnish 17 (0.37 g), yield: 65%.

3',5',Di-O-acetyl-2'-bromo-2'-deoxyuridine (18)

A mixture of uridine (16) (0.66 g, 27 mmol), acetic acid (6 ml) and 2-acetoxybenzoyl bromide (2 g) was stirred at 100° for 1.5 hr. Acetic acid was taken off under reduced pressure at 70-80° (bath temp.) and residue was extracted with ether. Ether extract was washed with aqueous sodium carbonate (5%, 50 ml), water and dried. Removal of ether furnished (18) (1.01 g), which was chromatographically homogeneous, yield: 96%; TLC (solvent system C): R_f, 0.52; $(\alpha)_D^{25}$ + 8.5 (c, 0.4, ethanol) [lit. $^{35}(\alpha)_D^{25}$ + 8.9° (c, 0.4 ethanol)]; IR: 3400 (N-H), 1765 (broad, C=O of acetate) 1709 (C=O of uracil), 1653 (C=C), 1233 (acetate). PMR ($CDCl_3$): 2.13 (3H, s, $-OCOCH_3$), 2.20 (3H, s, $-OCOCH_3$) 4.43 (3H, m, $H_{4'}$, $2H_{5'}$), 4.63 (1H, t, J = 5 Hz, $H_{2'}$) 5.26 (1H, m, $H_{3'}$), 5.80 (1H, d,

J = 8 Hz, H_5), 6.20 (1H, d, J = 5 Hz, $H_{1'}$), 7.40 (1H, d, J = 8 Hz, H_6), 9.63 (1H, broad s, exchangable with D_2O, HN_3).

2'-Chloro-2'-deoxyuridine (71)

A mixture of 17 (0.50 g, 14 mmol) and methanolic sodium methoxide (0.5 N, 10 ml) was stirred at room temperature for 2 hr, neutralised with H^+ resin and concentrated under reduced pressure to furnish 71 (0.33 g) which after crystallisation from methanol-pet.ether (3:1) showed m.p.202-3° (decomp.), $(\alpha)_D^{25}$ + 17.5° (c, 1.5, water) [lit.[36] m.p. 206-7°, $(\alpha)_D^{25}$ + 18° (c, 1.5, water)]: IR (nujol): 3600, 3550, 3333, 3175, 1701, 1618.

2'-Bromo-2'-deoxyuridine (72)

Hydrolysis of (18) (0.80 g, 2 mmol) using methanolic sodium methoxide (0.5 N, 10 ml) (as in the case of compound (71) furnished 72. (0.51 g), which after crystallisation from ethanol-pet.ether (2:1) showed m.p.183-85(d); $(\alpha)_D^{25}$ + 14.1° (c, 0.6, water) [lit.[37] m.p.183-86° (d); $(\alpha)_D^{25}$ + 15° (c, 0.6, water)].

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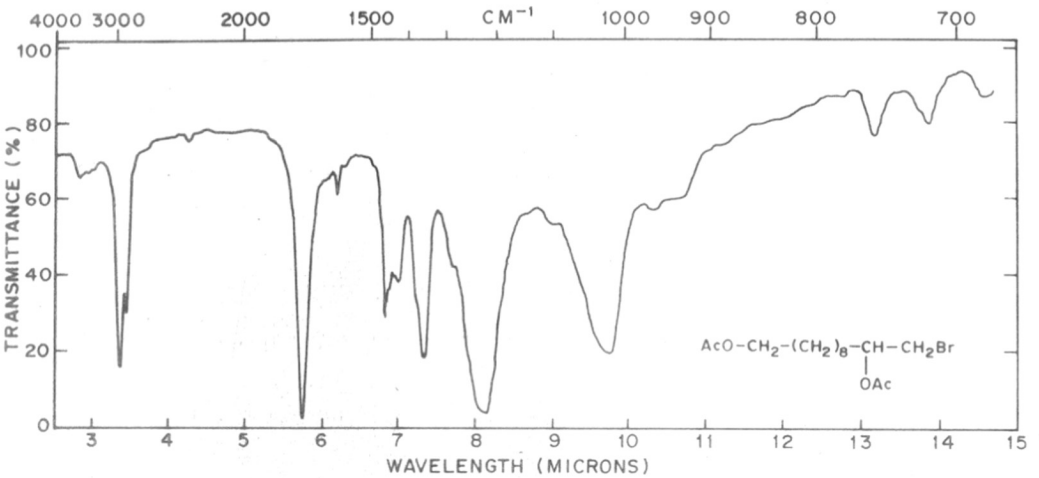
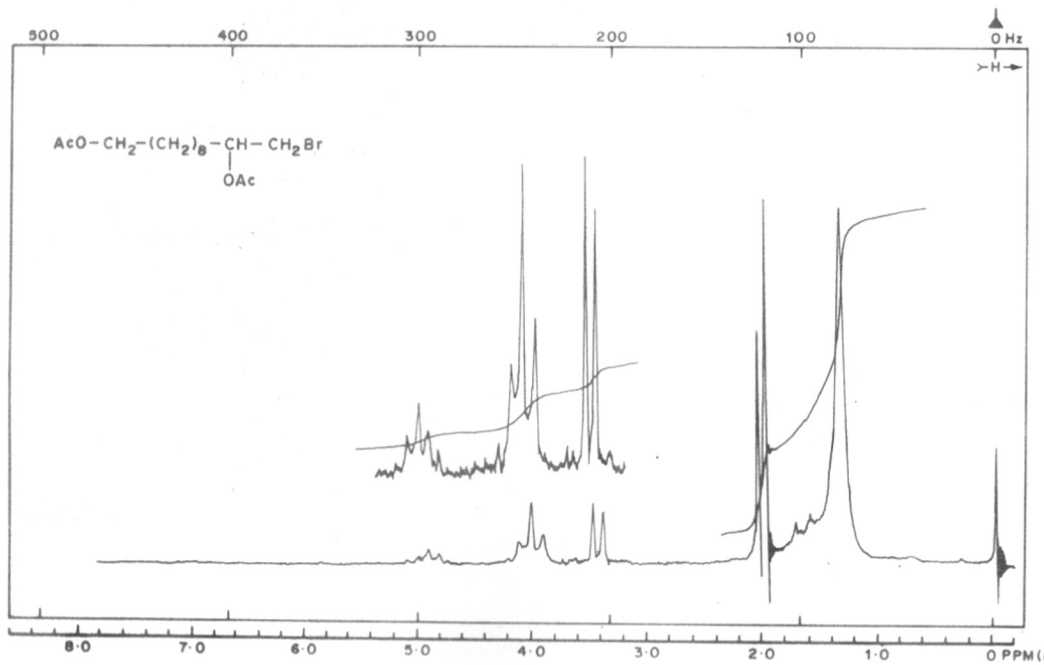
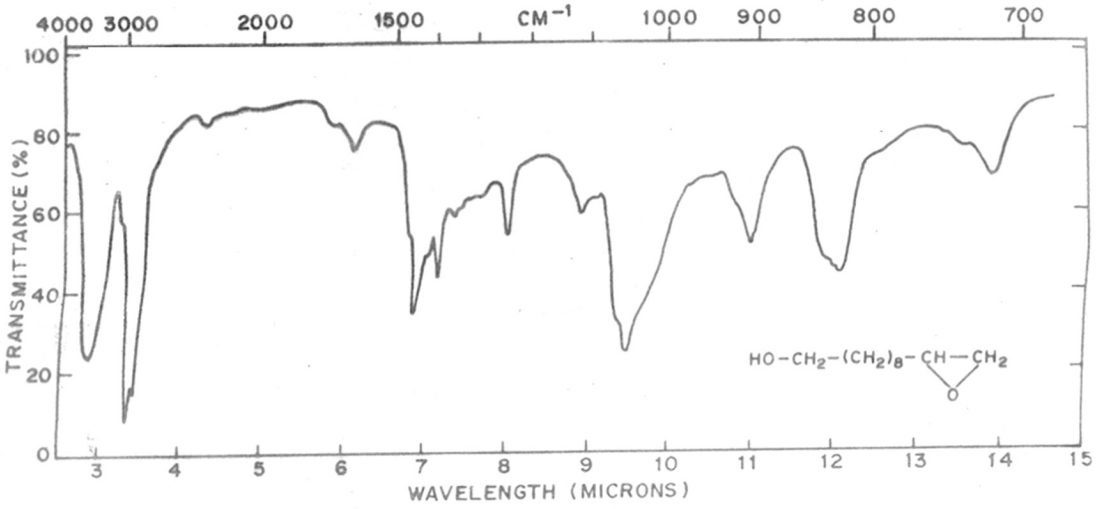
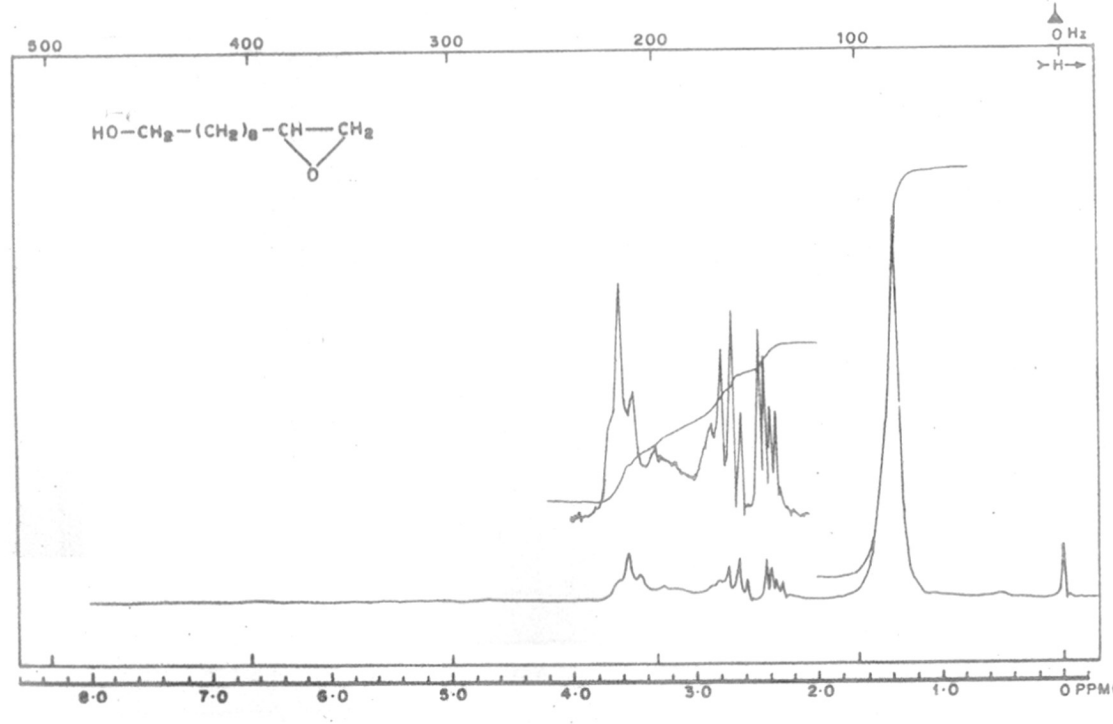




IR & NMR OF 1, 10-Di-ACETOXY-11-BROMO-UNDECANE (11)





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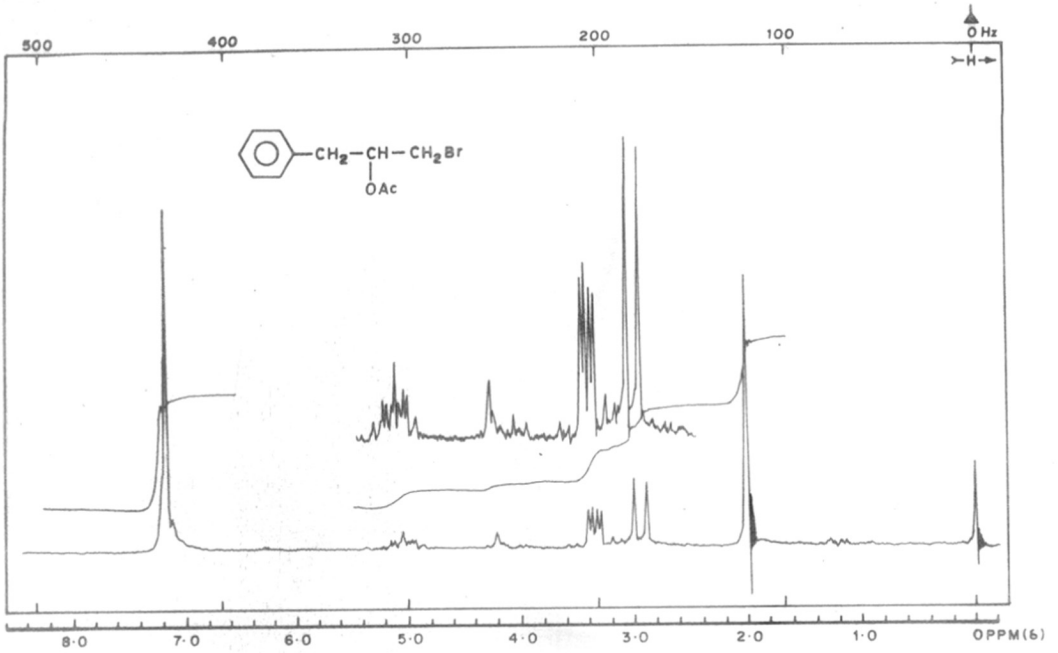
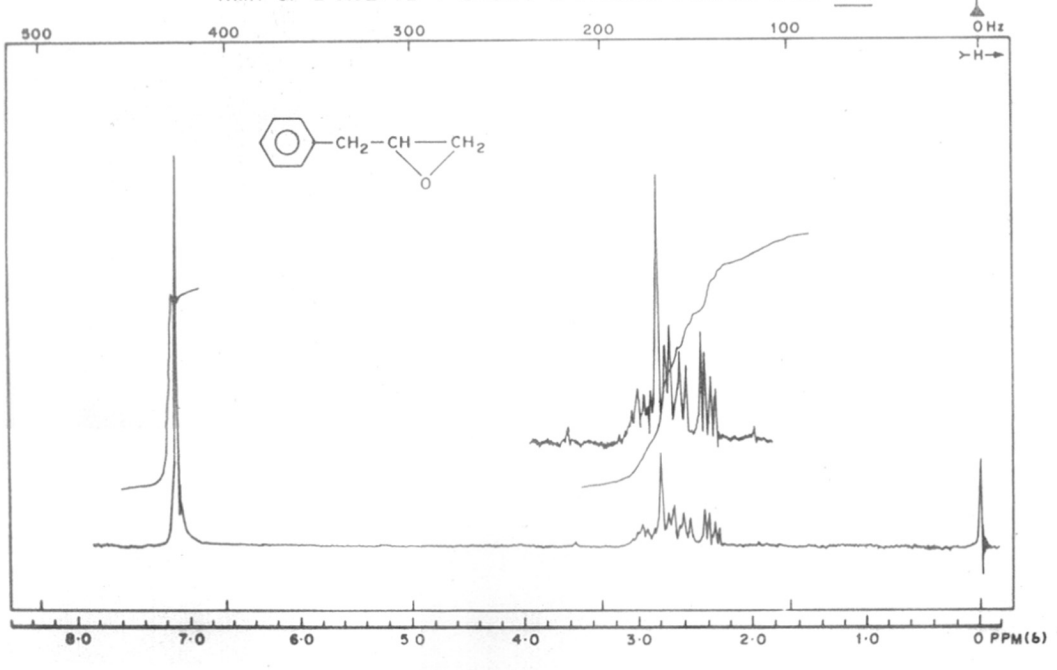


NMR OF 2-ACETYL-1-BROMO-3-PHENYL-PROPAN-2-OL (14)



NMR OF 1, 2-EPOXY-3-PHENYL-PROPANE (15)

LIST OF PUBLICATIONS

1. Preparation and rearrangement of cis-methyl 3,4-epoxy-4-(4'-methylphenyl)butanoate, Bhat, K.S. and Rao, A.S., Ind.J.Chem., 20B (1981), 355.
2. Synthesis of 2-deoxy-(±)-erythropentose, Bhat, K.S. and A.S. Rao, Ind.J.Chem., 21B (1982), 140.
3. Preparation of 5-(2-benzoyloxymethyl-4-methoxy)phenyl-2(5H)-furanone, Bhat K.S. and A.S. Rao, Ind.J.Chem. (in press).
4. A convenient route for the preparation of 2'-deoxyuridine, Bhat, K.S. and A.S. Rao, Ind.J.Chem. (in press).
5. Synthesis of uracil, 6-methylurancil and some dihydrouracils (under communication).