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I Syntheses of oxytryptamines II Intramolecular phenol alkylations

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I. SYNTHESES OF OXYTRYPTAMINES

II. INTRAMOLECULAR PHENOL ALKYLATIONS

by

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In Charge of Major Work

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Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

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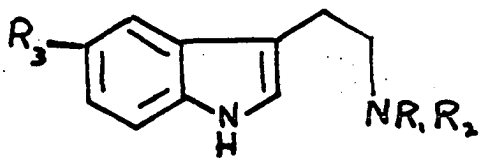
PART I. SYNTHESES OF OXYTRYPTAMINES

INTRODUCTION

An investigation of new methods of synthesis of oxytryptamine and tryptamine derivatives is to be undertaken. These substances are of interest because of their physiological properties and their potential as starting material in the total synthesis of indole and oxindole alkaloids.

HISTORICAL

Tryptamine alkaloids are natural bases containing the tryptamine skeleton (I), where R_1 and R_2 are hydrogen or methyl and where R_3 may be hydrogen, hydroxyl, or methoxyl.



I

a) $R_1 = R_2 = R_3 = H$

b) $R_1 = R_3 = H$; $R_2 = CH_3$

c) $R_1 = R_2 = CH_3$; $R_3 = H$

d) $R_1 = R_2 = H$; $R_3 = OCH_3$

e) $R_1 = H$; $R_2 = CH_3$; $R_3 = OCH_3$

f) $R_1 = R_2 = CH_3$; $R_3 = OCH_3$

g) $R_1 = R_2 = H$; $R_3 = OH$

h) $R_1 = H$; $R_2 = CH_3$; $R_3 = OH$

i) $R_1 = R_2 = CH_3$; $R_3 = OH$

Occurrence and Isolation

Tryptamine (Ia)

In his search for alkaloids in leguminous plants, White (1) found an alkaloid in the hydrochloric acid extract of the tops of *Acacia floribunda*, which was proposed to be tryptamine (Ia). The structure was confirmed by synthesis. Tryptamine has been found also in mushrooms of *Coprinus micaceus* (2).

N-Methyltryptamine (Ib)

In the alcoholic extract of the green parts of dry *Gergensohnia diptera* Bge. (family Chenopodriceae), Yurashevskii and

Stepanov (3, 4) found in 0.25% yield a new alkaloid, which they called dipterine. It was shown to be a secondary base, optically inactive, giving a positive Ehrlich test and yielding skatole on zinc dust distillation. Thus a β -substituted indole structure was indicated. Exhaustive methylation and cleavage yielded trimethyl amine. The structure was proposed to be N-methyltryptamine (Ib) and the structure was confirmed by comparison of the alkaloid with a sample of N-methyltryptamine, prepared by Hoshino and Kobayashi (5).

N-Methyltryptamine was found also to be a constituent of the alkaloid fraction of Anthrophytum leptocladum (family Chenopodiaceae) (6).

N,N-Dimethyltryptamine (Ic)

The Pancaru Indians of Brazil use a beverage in their mystico-religious ceremonies which is described as one that transports individuals to strange worlds and permits them to contact the souls of the dead. The plant, from which the beverage, called Wine of Jurema, is prepared, was obtained by Goncalves de Lima and identified as Mimosa hostilis. The results of Goncalves de Lima's chemical investigation were published in 1946 (7). A single alkaloid, called nigerine, m.p. 45.8-46.8°, was isolated in 0.51% yield and the empirical formula $C_{13}H_9N_2O$ was assigned.

In the hands of Pachter et al. (8), the same plant yielded a single alkaloid, (0.57% yield, m.p. 48-49°) of empirical

formula $C_{12}H_{16}N_2$. The alkaloid was identified as N,N-dimethyltryptamine (Ic) by its ultraviolet and infrared spectra and the preparation of the previously described picrate and methiodide (9).

N,N-Dimethyltryptamine was found also to be a constituent of the alkaloid fraction of other members of the Piptadina species (10) and in Lespedeza bicol var. Japonica (11).

5-Methoxytryptamine (Id)

Of the nine possible alkaloids derivable from the general structure I 5-methoxytryptamine (Id) is the only one which has not been found to be naturally occurring.

5-Methoxy-N-methyltryptamine (Ie)

In 1958 Wilkinson (12) reported the isolation of a crystalline alkaloid hydrochloride, $C_{12}H_{17}N_2O \cdot HCl$, from an extract of canary grass of the species Phalaris arundinacea. It contained no phenolic hydroxyl groups and gave a sodium nitroprusside test indicative of a secondary amine. This suggested the structure of a methoxy-N-methyltryptamine. Comparison of melting point, mixed melting point, and ultraviolet spectrum with authentic 5-methoxy-N-methyltryptamine proved the alkaloid to possess this structure.

5-Methoxy-N,N-dimethyltryptamine (If)

The bark of the Brazilian tree Dictyoloma incandescens (8) has yielded an alkaloid, $C_{13}H_{18}N_2O$. It was identified as

5-methoxy-N,N-dimethyltryptamine (If) by comparison of its ultraviolet spectrum with that of 5-methoxytryptamine, comparison of the melting points of the alkaloid and its picrate with those previously reported (13), and finally by preparation of the methiodide of the alkaloid and comparison of its melting point and infrared spectrum with those of the methiodide prepared by exhaustive methylation of 5-methoxytryptamine.

5-Hydroxytryptamine (Ig)

Two groups of investigators independently identified 5-hydroxytryptamine (Ig) to be naturally occurring. Erspamer et al., as cited by Erspamer (14) investigated the substance, enteramine, which imparts peculiar histochemical properties to the enterochromaffin cells of the gastro-intestinal mucosa. Rapport et al. as cited by Erspamer (14) investigated the principal, serotonin, which is responsible for the vasoconstrictor and moderately hypertensive properties possessed by serum and defibrinated blood. The researches of the two groups met only after enteramine was identified as 5-hydroxytryptamine and serotonin as creatine and 5-hydroxytryptamine. Synthesis confirmed these identifications.

5-Hydroxy-N-methyltryptamine (Ih)

The presence of 5-hydroxy-N-methyltryptamine (Ih) has been reported in the skin of amphibians of the Bufo species (14); however, an extensive investigation does not appear to have been carried out.

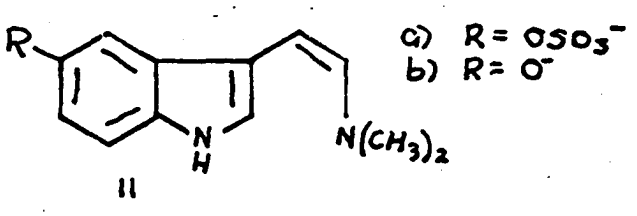
5-Hydroxy-N,N-dimethyltryptamine (Ii)

In addition to the neutral and acidic constituents in the skin secretion of the toad Bufo vulgaris there is a basic substance, bufotenine. The first results of a chemical investigation of this substance were reported by Wieland et al. (15) in 1931, in which the structure was concluded to be N,N-dimethyltryptophan. However, further investigation (16) showed the structure to be either 5- or 6-hydroxy-N,N-dimethyltryptamine. The position of the hydroxyl group was determined to be at C_5 by the synthesis of 5-methoxy-N,N-dimethyltryptamine methiodide, into which bufotenine could be converted.

Bufotenine has also been found in the secretions of toads of other Bufo species (14, 17, 18, 19). It was found in plants for the first time by Wieland et al. (20) and thereafter by others (8, 21).

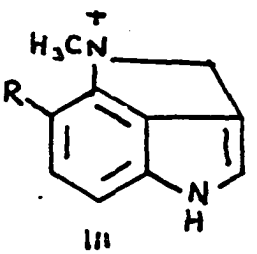
Bufothionine (IIIa) and dehydrobufotenine (IIIb)

The chief isolatable nitrogenous substance from the Bufo bufo bufo species of toads, bufothionine (IIIa), and its hydrolysis product, dehydrobufotenine (IIIb), were first investigated by Wieland and Vocke (22). Structure IIa for bufothionine and IIb for dehydrobufotenine were proposed by Wieland and Wieland (23).



II

a) R = OSO_3^-
b) R = O^-

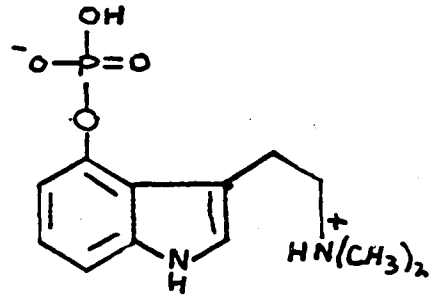


III

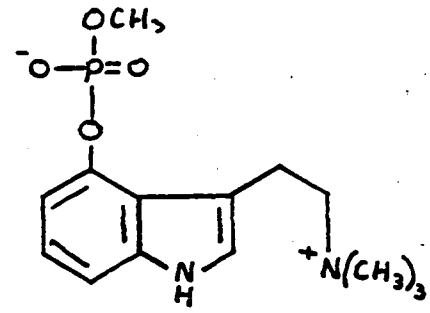
In 1961, two groups (24, 25) independently revised these structures to IIIa and IIIb, respectively, on the basis of nuclear magnetic resonance studies.

Psilocybin (IV)

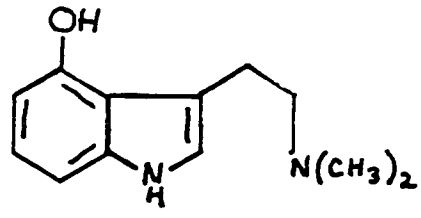
Some native Indians of Mexico use the mushroom Psilocybe mexicana in their ritual ceremonies. Its hallucinogenic effects led Hofman et al. (26) to investigate the active component, psilocybin (IV). It was isolated in crystalline form in 0.4% yield and an empirical formula, $C_{12}H_{17}O_4N_2P$, was proposed (27). Treatment with diazomethane yielded a product with two additional methyl groups (5) and heating this methylated product gave trimethylamine. Hydrolysis of psilocybin yielded phosphoric acid and 4-hydroxy-N,N-dimethyltryptamine (VI). Structure IV was proposed for psilocybin and confirmed by synthesis.



IV



V



VI

Synthesis of Tryptamine Alkaloids

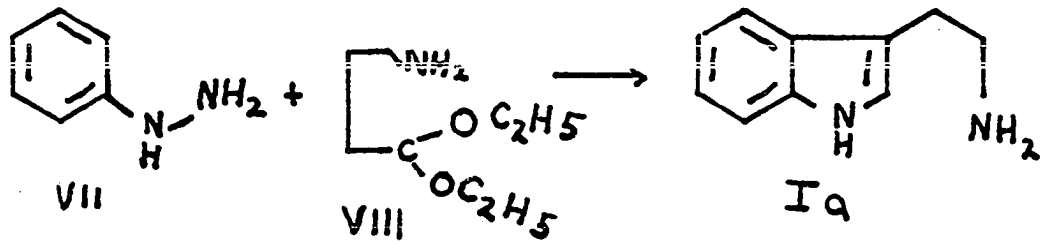
The first synthesis of tryptamine (Ia) (28) utilized a modification of the Fisher Indole Synthesis in which γ-amino butyroacetal (VIII) and phenylhydrazine (VII), on treatment with zinc chloride, yielded tryptamine (Ia). Later, Majima and Hoshino (29) observed that indole on treatment with methylmagnesium iodide gave the N-magnesium iodide salt X, which reacted with chloroacetonitrile, to yield β- indolyl-(3) -acetonitrile (XI). Reduction of the nitrile with sodium and alcohol gave tryptamine (Ia).

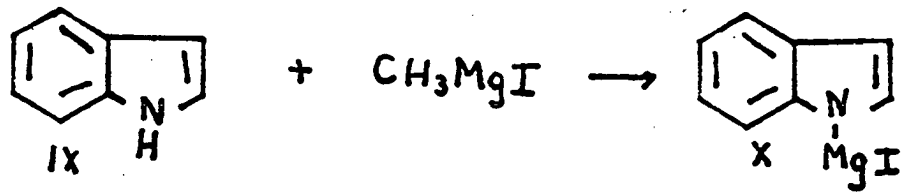
Conversion of tryptamine to N-methyltryptamine and N,N-dimethyltryptamine was accomplished first by Manske (30) by the treatment of tryptamine (Ia) with methyl iodide and separation of the resulting mixture of amines.

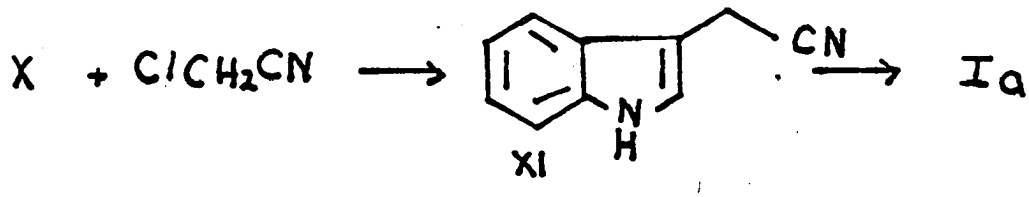
A better synthesis of N-methyltryptamine (Ib) was reported by Hoshino and Kobayashi (5), in which tryptamine (Ia) was converted to the sulfonamide XIII, methylated with methyl iodide, and the product XIV cleaved with aniline and aniline hydrochloride. A modification of this method was utilized by Wilkinson (12) for the synthesis of 5-methoxy-N-methyltryptamine (Ie).

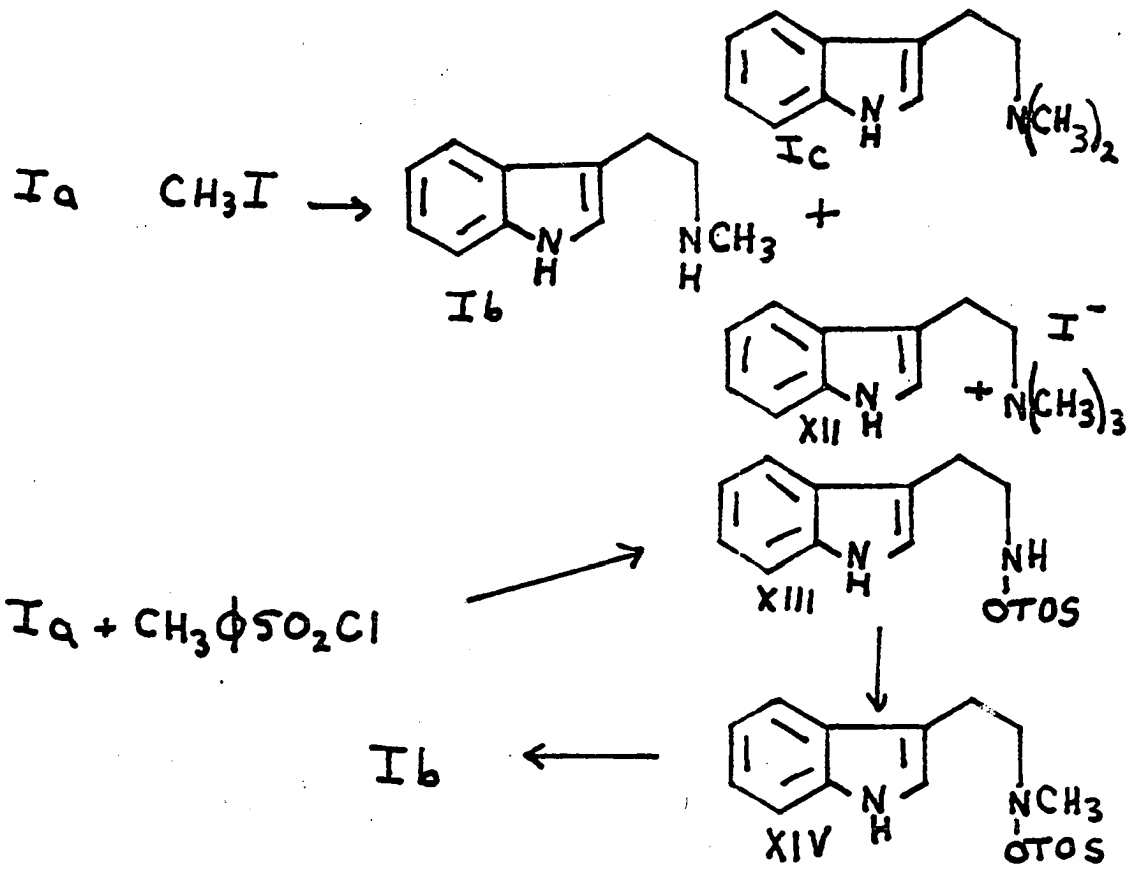
For their synthesis of bufotenine, Hoshino and Shimodaira (13) extended the usefulness of the indole Grignard reagent. Reaction of the N-magnesium iodide salt of 5-ethoxyindole (XV) with chloroacetonitrile gave 5-ethoxy-β-indolyl-(3) -acetonitrile (XVI) which was converted to 5-ethoxy-β- indolyl-

Fig. 1. Reaction Scheme


NH2
NH
VII
NH2
OC2H5
C
OC2H5
VIII
N
H
NH2
Ia


N
H
IX
+ CH3MgI
N
MgI
X


X + ClCH2CN
CN
N
H
XI
Ia

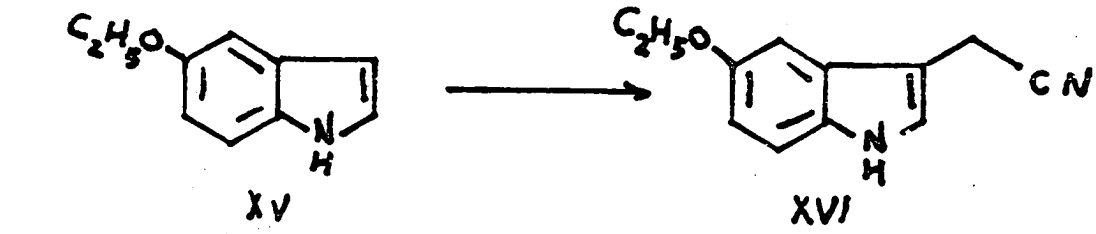

Ia CH3I
N
H
NCH3
Ib
+
N
H
N(CH3)2
Ic
I-
N
H
+N(CH3)3
XII
Ia + CH3φSO2Cl
N
H
NH
OTOS
XIII
Ib
N
H
NCH3
OTOS
XIV

(3) -ethyl bromide (XVIII) via hydrolysis of the nitrile, esterification, reduction and treatment of the resulting alcohol XVII with phosphorous tribromide. Reaction of the bromo compound XVIII with dimethylamine gave 5-ethoxy-N,N-dimethyltryptamine (XIX), and cleavage of the ether with aluminum chloride in benzene gave bufotenine (Ii).

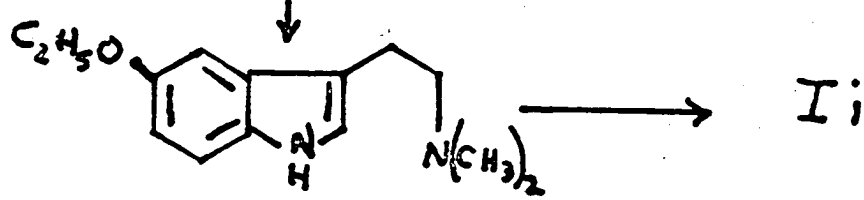
A better preparation of 5-hydroxytryptamines, in which the aluminum chloride ether cleavage was avoided, was introduced by Hamlin and Fischer (31). Hoshino and Kobayashi's method (5) was utilized to obtain 5-benzyloxindole-3-acetonitrile (XXI). Reduction of the nitrile with lithium aluminum hydride and hydrogenolysis of the benzyl ether XXII yielded 5-hydroxytryptamine (Ia). Stoll et al. (32) also utilized the benzyl group as a protecting group for the hydroxyl function. Conversion of 5-benzyloxyindolylacetic acid XXIII to the acid azide XXV and replacement of the azide group with an amine yielded the amide XXVI which, after reduction with lithium aluminum hydride and hydrogenolysis of the benzyl group, yielded 5-hydroxytryptamine XXVIII. Bufotenine (Ii) and 5-hydroxy-N-methyltryptamine (Ih) were synthesized by this method also.

Speeter and Anthony (33) observed that treatment of indole as well as 5-benzyloxyindole with oxalyl chloride yielded 3-indoleglyoxalyl chlorides. Treatment of the acid chlorides XXIX with amines gave amides XXVI which could be reduced by lithium aluminum hydride and debenzylated to yield hydroxytryptamines XXVIII. In this manner 5-hydroxytryptamine (Ig)

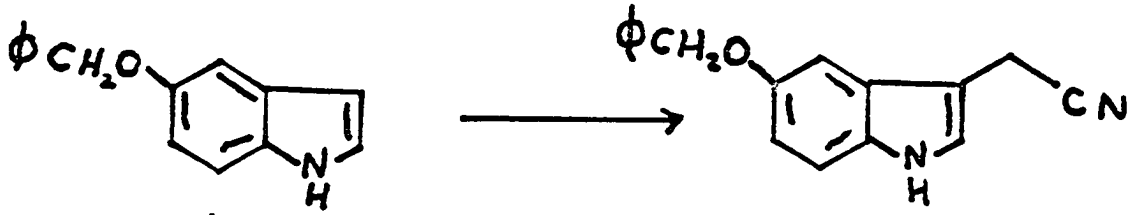
Fig. 2. Reaction Scheme



XV XVI XVII XVIII



XIX



XX XXI

and bufotenine (Ii) were synthesized. Kondo et al. (34, 35) utilized the oxalyl chloride method for the synthesis of various hydroxytryptamines and Hofman et al. (27) synthesized psilocybin by utilizing this method. Speeter also demonstrated the amines could equally well be obtained by reaction of the Grignard salt of 5-benzyloxyindole with halogenoacetamides (36).

A rather novel synthesis of 5-hydroxytryptamine (Ig) and bufotenine (Ii) was reported by Harley-Mason and Jackson (37). Alkylation of 2,5-dimethoxybenzyl cyanide (XXXI) with 2-dimethylaminoethyl chloride (XXXII) yielded 1-(2,5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide (XXXIII), which on hydrogenation and hydrobromic acid ether cleavage gave 2-(2,5-dihydroxyphenyl)-4-dimethylaminobutylamine (XXXIV). Oxidation of XXXIV with potassium ferricyanide yielded bufotenine (Ii).

Synthesis of Oxytryptamine Analogues of Tryptamine Alkaloids

Julian et al. (38) demonstrated that acylation of oxindoles (XXXV) by Claisen condensation with esters produced 3-acyloxindoles (XXXVII) which could be hydrogenated catalytically to give oxytryptamine derivatives (XXXVIII). The oxytryptamines XXXVIIIa and b were synthesized in this manner.

Sugasawa and Murayama (39) obtained the oxytryptamine XLI by heating XXXIX with aluminum chloride and cleaving the product XL with hydrazine hydrate.

Freter et al. (40) obtained the oxytryptamines from the

Fig. 3. Reaction Scheme

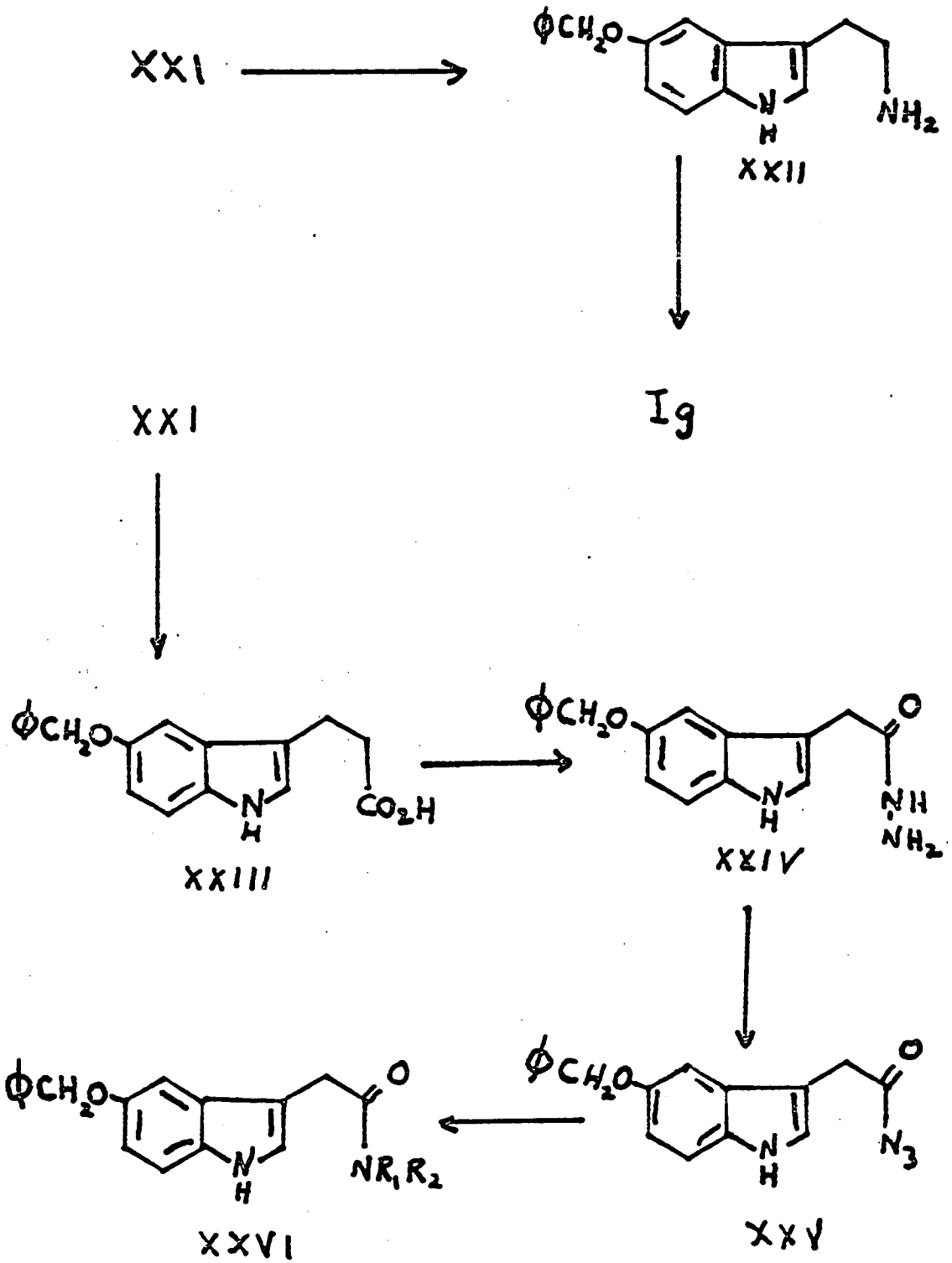
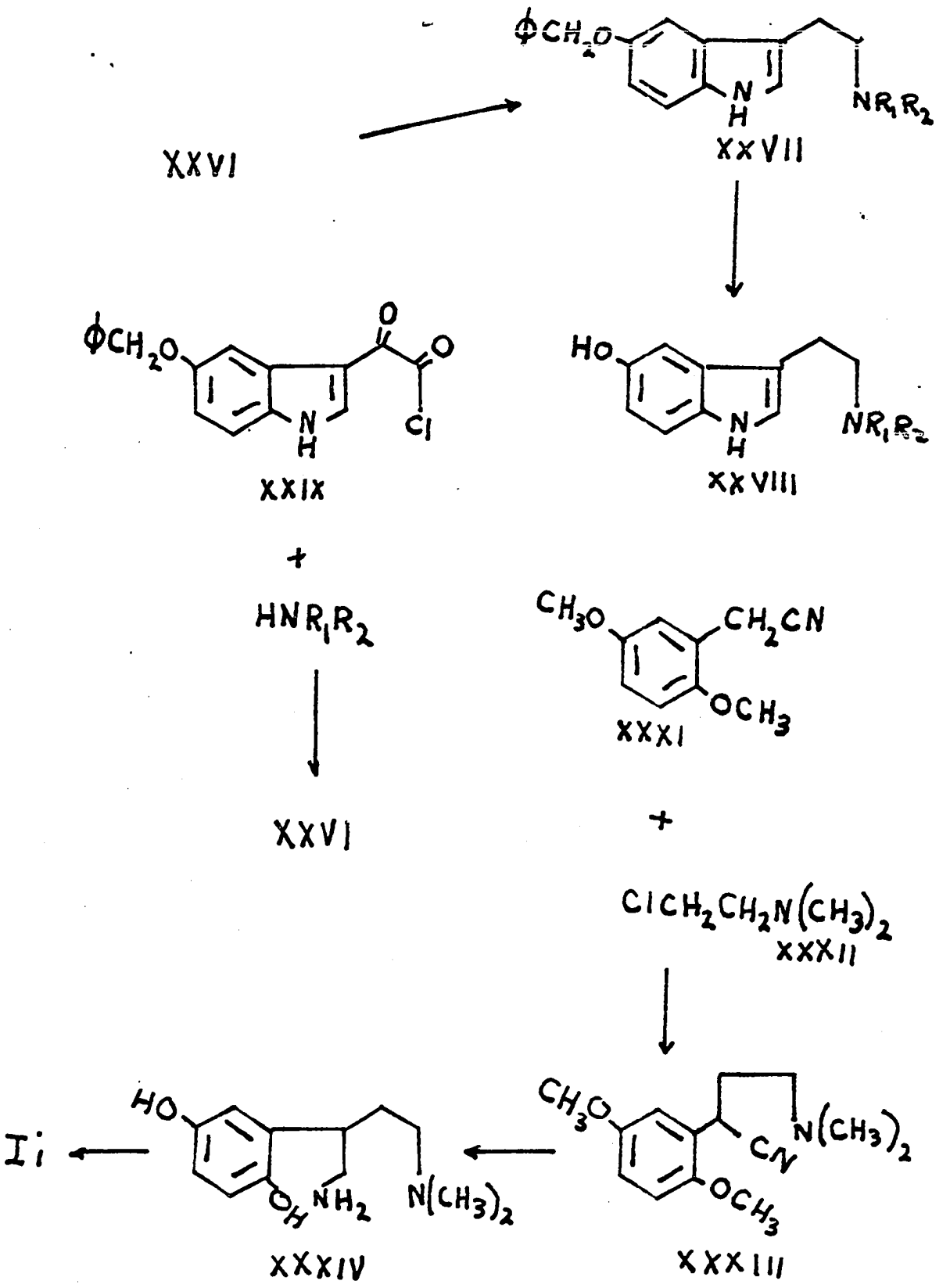

XXI
φCH2O
NH2
XXII
Ig
XXI
φCH2O
CO2H
XXIII
φCH2O
O
NH
NH2
XXIV
φCH2O
O
N3
XXV
φCH2O
O
NR1R2
XXVI

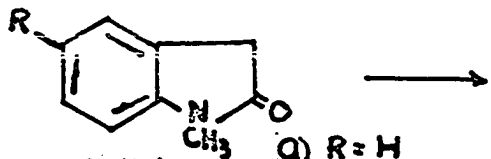
Fig. 4. Reaction Scheme


ΦCH2O
NR1R2
XXVII
XXVI
HO
XXVIII
ΦCH2O
O
O
Cl
XXIX
+
HNR1R2
XXVI
CH3O
CH2CN
OCH3
XXXI
+
ClCH2CH2N(CH3)2
XXXII
CH3O
N(CH3)2
CN
OCH3
XXXIII
HO
NH2
N(CH3)2
XXXIV
Ii

corresponding tryptamines. Treatment of Ia with sulfur monochloride gave XLII which on reduction with zinc and hydrochloric acid gave the corresponding oxindole derivatives.

Harley-Mason and Ingleby (41) obtained oxytryptamine (XLI) by starting with isatin. Condensation with cyanoacetic ester and hydrolysis and decarboxylation of the product XLIV gave the nitrile (XLV). Its hydrogenation yielded oxytryptamine (XLI).

Fig. 5. Reaction Scheme



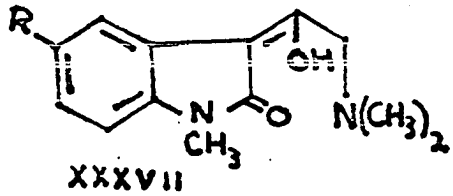
XXXV

a) R = H
b) R = OC_2H_5

+

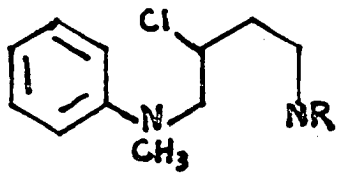
$C_2H_5O_2CCH_2N(CH_3)_2$

XXXVI



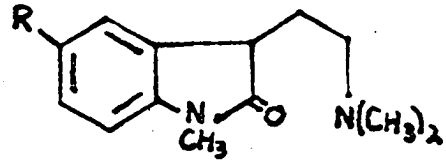
XXXVII

a) R = H
b) R = OC_2H_5



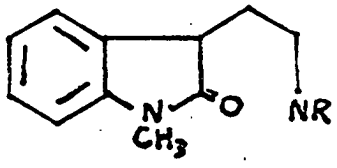
XXXIX

NR = phthalimido



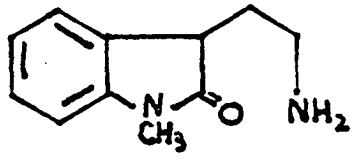
XXXVIII

a) R = H
b) R = OC_2H_5

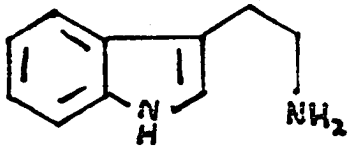


XL

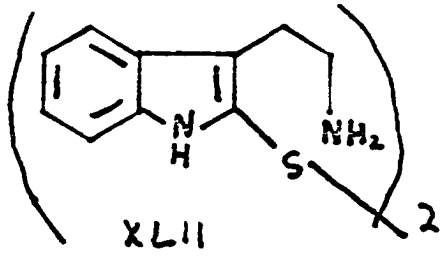
NR = phthalimido



XLI

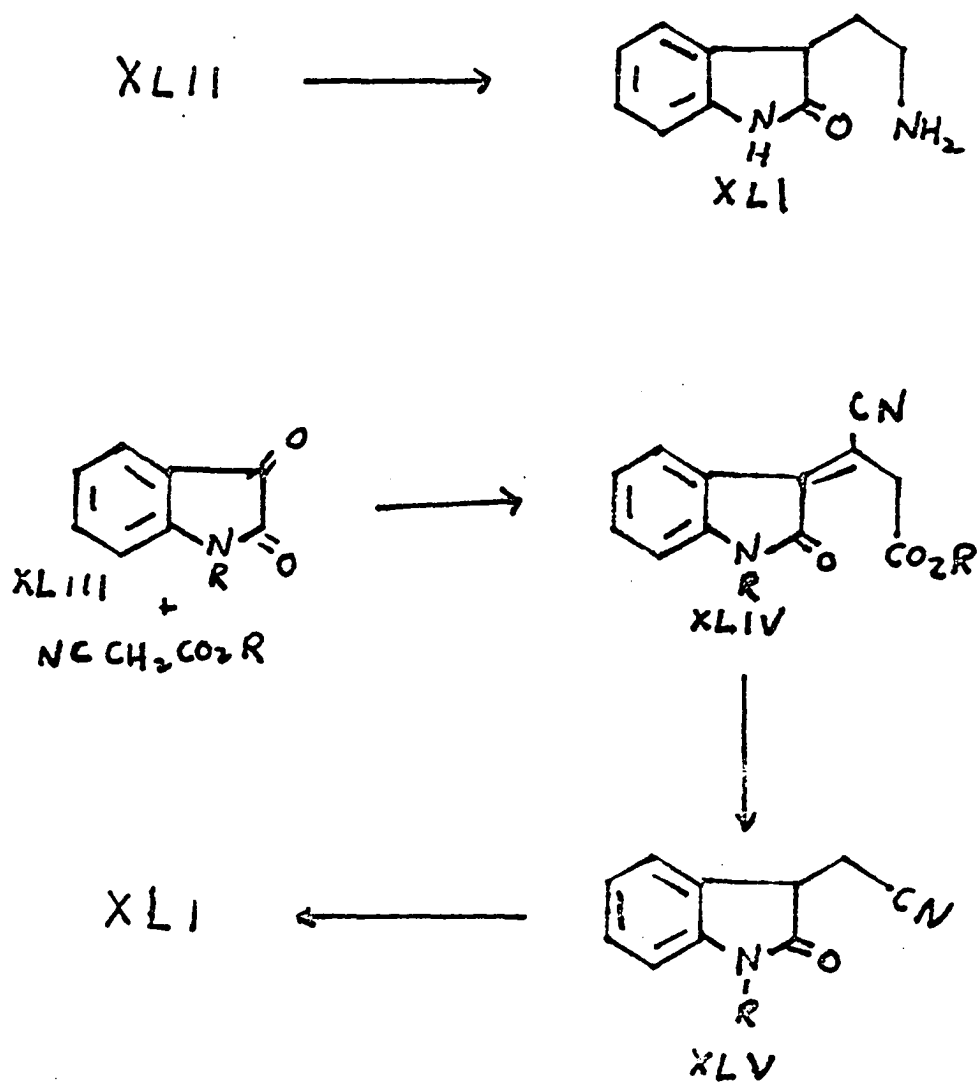


Ia



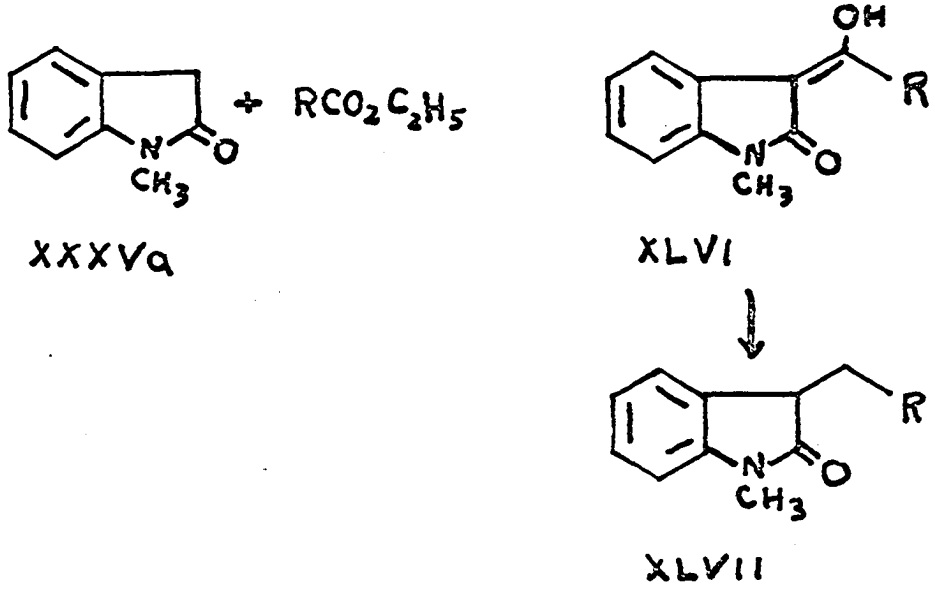
XLII

Fig. 6. Reaction Scheme


XLII
XLI
XLIII
+
NCCH2CO2R
XLIV
XLV
XLI

DISCUSSION

Julian et al. (38) reported the synthesis of 3-alkyloxindoles (XLVII) by the Claisen condensation of N-methyloxindole (XXXVa) with esters and the hydrogenation of the resulting 3-acyloxindoles (XLVI). Horner (42) used the same method for the preparation of N-unsubstituted 3-alkyloxindoles.



Since Wenkert et al. (43) reported the synthesis of an oxytryptamine (LXIIIc) by the above method, it was decided to investigate this route as a general method of synthesis of oxytryptamine and tryptamine derivatives.

The Claisen condensation of oxindole (LVIIIa) with ethyl N,N-dimethylglycinate (LIXa) produced the 3-acyloxindole LXa in excellent yields. First attempts to prepare a perchlorate salt of LXa proved unsuccessful and hydrogenation of LXa by Julian's method (38) as well as a variety of other conditions

led only to intractable products.

Since Wenkert et al. (43) had succeeded in reducing the perchlorate of the 3-acyloxindole LXb, reduction of LXa was attempted under acidic conditions. In the presence of sufficient hydrochloric acid, to insure complete hydrochloride formation, a solution of LXa in ethanol was hydrogenated over 30% palladium on charcoal catalyst. The hydrogen uptake ceased after two moles were absorbed. A white crystalline hydrochloride was obtained, which could not be purified through crystallization. As a consequence it was converted to a crystalline perchlorate. The infrared spectrum showed a single carbonyl absorption band at 5.97μ and the ultraviolet spectrum showed absorption maxima at 250 mμ and 280 mμ, characteristic of oxindoles. Hence the perchlorate was assigned structure LXIIIa. Attempts to liberate the free base resulted in oils which decomposed fairly rapidly on standing.

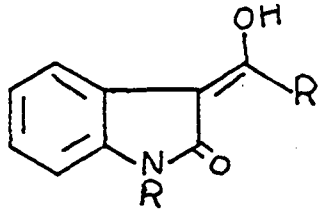
The fact that the reported ultraviolet spectrum of XLIIIc (43), λ_{max} 252 mμ (log ε 4.07) and 296 mμ (log ε 3.68) differed from that of oxindole XLIIIa led us to reinvestigate the structure of the former compound. The perchlorate salt of LXb was prepared and hydrogenated by the identical process used by Wenkert et al. (43). The hydrogen uptake ceased after one mole had been absorbed. When after filtration of the catalyst the solvent was evaporated on the steam bath, the solution noticably turned from colorless to yellow. After the solvent had been removed completely, an oily yellow solid

was obtained, which after several crystallizations melted at 200-204°. This melting point was considerably higher than the reported melting point of 170° but the infrared and ultraviolet spectra were identical with those of an authentic sample. It was later found that the melting point of the authentic sample could be raised to 200-204° by further crystallization.

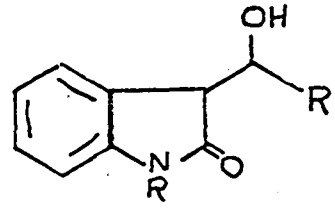
Since there was a definite color change in workup, the hydrogenation of XLb was repeated using the same conditions for hydrogenation as before, except the temperature was not allowed to exceed 40° when the solvent was evaporated. Under these conditions, a white crystalline salt was obtained in quantitative yield, whose infrared spectrum (Fig. 10) showed both OH and NH bands and whose melting point was different from the compound obtained by Wenkert et al. (43). It appeared likely the compound was the hydrochloride salt of the oxindole alcohol (XLIb). Thus the Wenkert compound is the dehydration product of XLIb, the alkylideneoxindole perchlorate XLIIb.

Heating (100°) of a solution of the perchlorate salt of the oxindole alcohol XLIb in acetic acid containing 1 drop of 70% perchloric acid led to a yellow perchlorate identical in all respects with the substance of Wenkert et al. (43). Hydrogenation of this compound yielded an oily salt, which could be converted quantitatively to a solid picrate. The latter was identical in all respects with the picrate of oxindole LXIIIc, obtained by the one-step hydrogenation of the 3-acyloxindole LXb. The three-step reduction of 3-acylox-

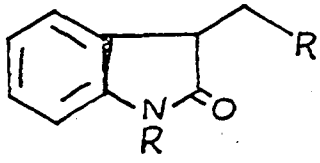
indoles to 3-alkyloxindoles has been reported by Julian and Printy (44), e.g. the conversion of XLVIII into LI by way of the oxindole alcohol LXIX and 3-alkylideneoxindole L. The oxindole LI could be prepared also by a one-step hydrogenation of the acyloxindole XLVIII.



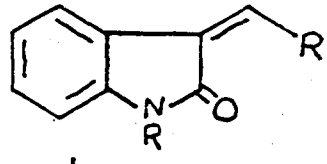
XLVIII



XLIX



LI



L

Application of the above procedure to the acyloxindole perchlorate LXa permitted its hydrogenation to the hydroxy oxindole LXIa, dehydration to LXIIa and hydrogenation to the alkyloxindole LXIIIa. The latter was identical with the product of a single-step hydrogenation of LXa.

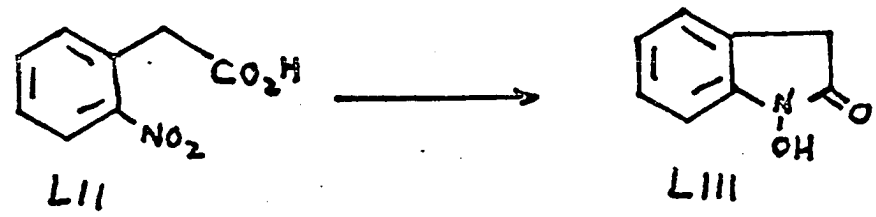
Treatment of o-nitrophenylacetic acid (LII) with zinc and sulfuric acid produced N-hydroxyoxindole (LIII) (45). Exposure of the latter to refluxing 4 N sulfuric acid (46, 47, 48) gave 5-hydroxyoxindole in 60% yield. Wright and Collins observed a similar rearrangement (49). Their treatment of LIII

with hydrobromic acid had yielded LVb in 21% yield; with hydrochloric acid LVa had been obtained in 18% yield. Treatment of the bromooxindole (LVI) with hydrochloric acid had yielded LVII.

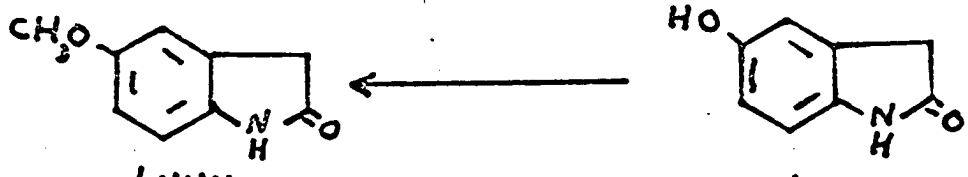
Methylation of LIV with diazomethane gave LVIIIb which appeared to be an excellent starting material for the synthesis of 5-methoxytryptamines and possibly also 5-hydroxytryptamines. Condensation of LVIIIb with ethyl N,N-dimethylglycinate (LIXa) yielded the acyloxindole LXc. Catalytic hydrogenation of LXc gave the oxindole LXIIIb without difficulty.

Attempts to reduce the oxindole perchlorates (LXIIIa and LXIIIb) with lithium aluminum hydride in ether, tetrahydrofuran and N-methylmorpholine were unfruitful. However, reduction of the free bases LXIIIa and LXIIIb in tetrahydrofuran with lithium aluminum hydride produced the indoles XLIVa and XLIVb in approximately 50% yield. Increased reaction times (24 hours) left the yields unaffected. Thus it appeared that the formation of insoluble intermediate complexes interfered in the reduction process. As a consequence two consecutive lithium aluminum hydride reductions were run. The infrared spectra of crude, twice reduced products showed almost no carbonyl absorption. This procedure led to good yields of N,N-dimethyltryptamine (XLIVa) and 5-methoxy-N,N-dimethyltryptamine (XLIVb), identical in all respects with an authentic sample supplied by Dr. Pachter (8).

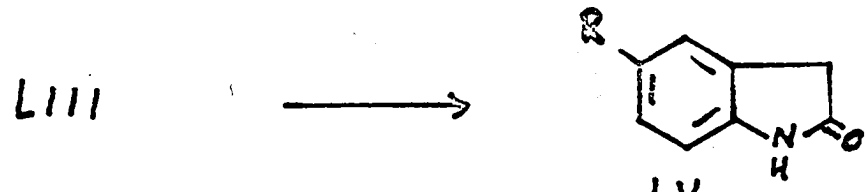
Fig. 7. Reaction Scheme



LII LIII

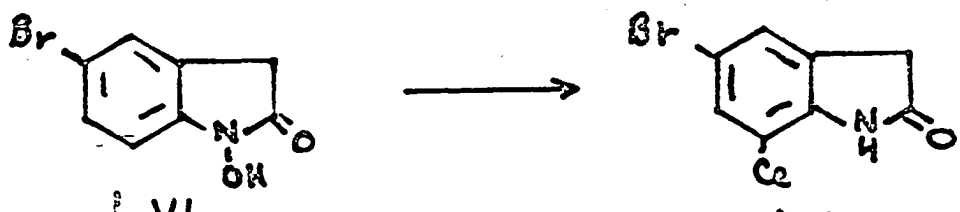


LVIIIb LIV



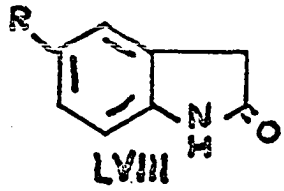
LV

a) R = Cl
b) R = Br



LVI LVII

Fig. 8. Reaction Scheme



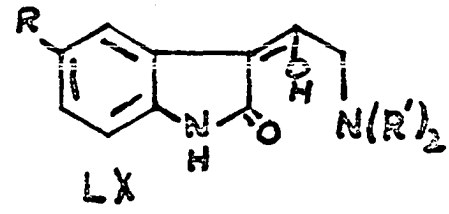
LVIII

a) R=H
b) R=OCH$_3$

+

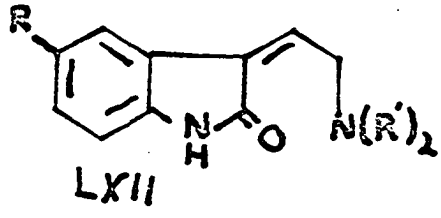
$(R')_2 CH_2 CO_2 C_2H_5$

a) R'=CH$_3$
b) $(R')_2$=N-PIPERIDINO



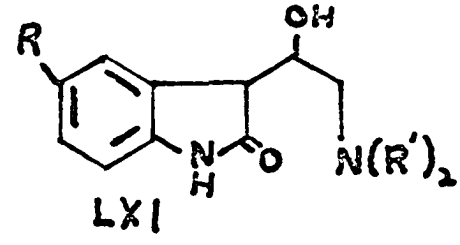
LX

a) R=H, R'=CH$_3$
b) R=H, $(R')_2$=N-PIPERIDINO
R=OCH$_3$, R'=CH$_3$



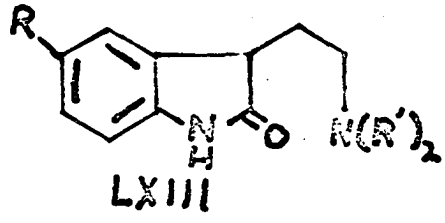
LXII

a) R=H, R'=CH$_3$
b) R=H, $(R')_2$=N-PIPERIDINO



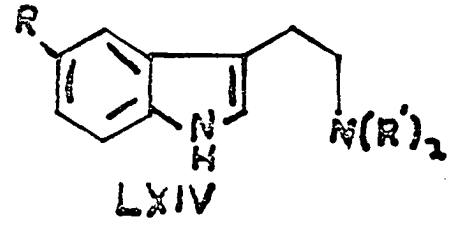
LXI

a) R=H, R'=CH$_3$
b) R=H, $(R')_2$=N-PIPERIDINO



LXIII

a) R=H, R'=CH$_3$
b) R=OCH$_3$, R'=CH$_3$
c) R=H, $(R')_2$=N-PIPERIDINO



LXIV

a) R=H, R'=CH$_3$
b) R=OCH$_3$, R'=CH$_3$

SPECTRA

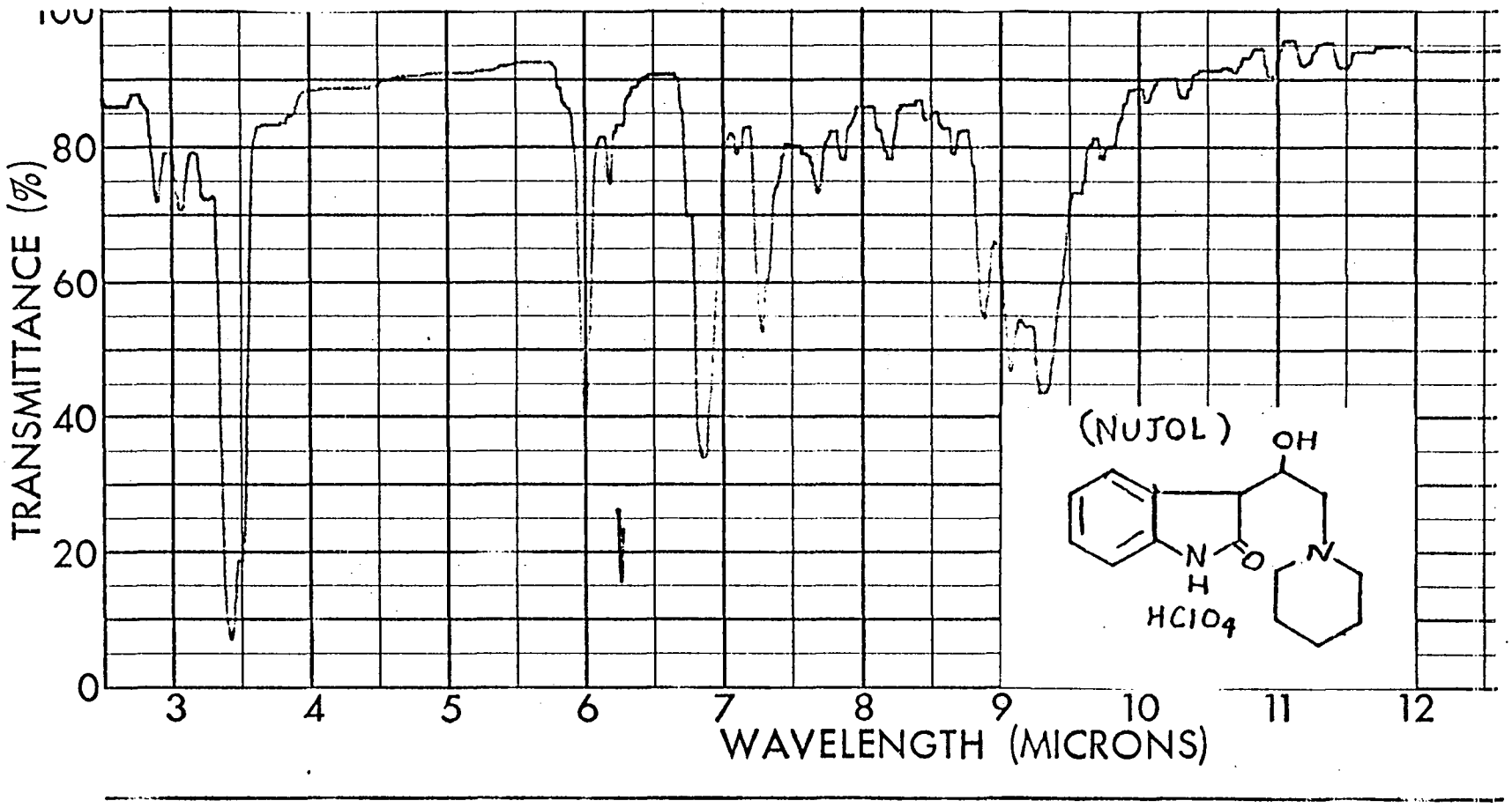


FIG 9. INFRARED SPECTRUM

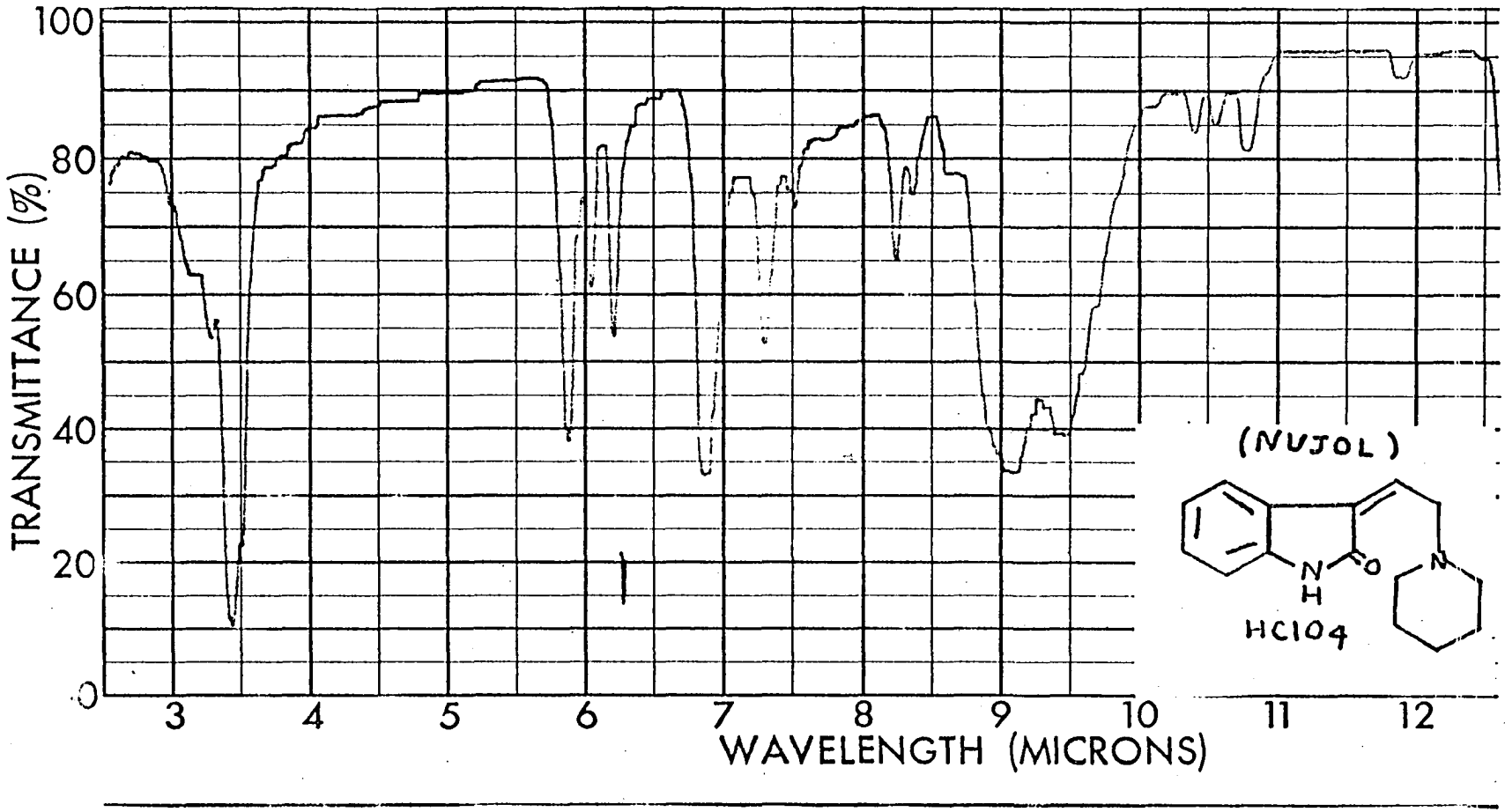


FIG. 10 INFRARED SPECTRUM

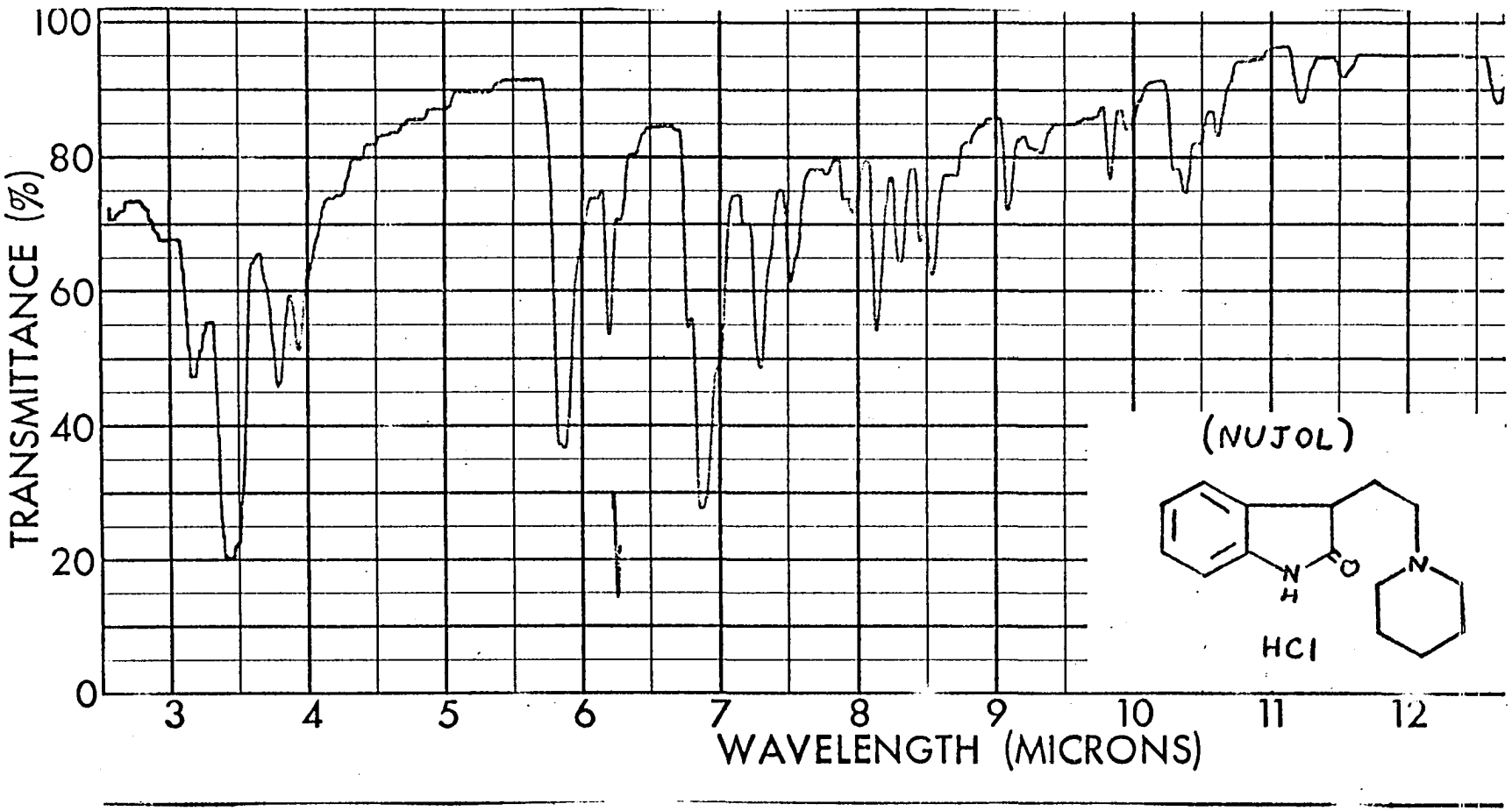


FIG. 11 INFRARED SPECTRUM

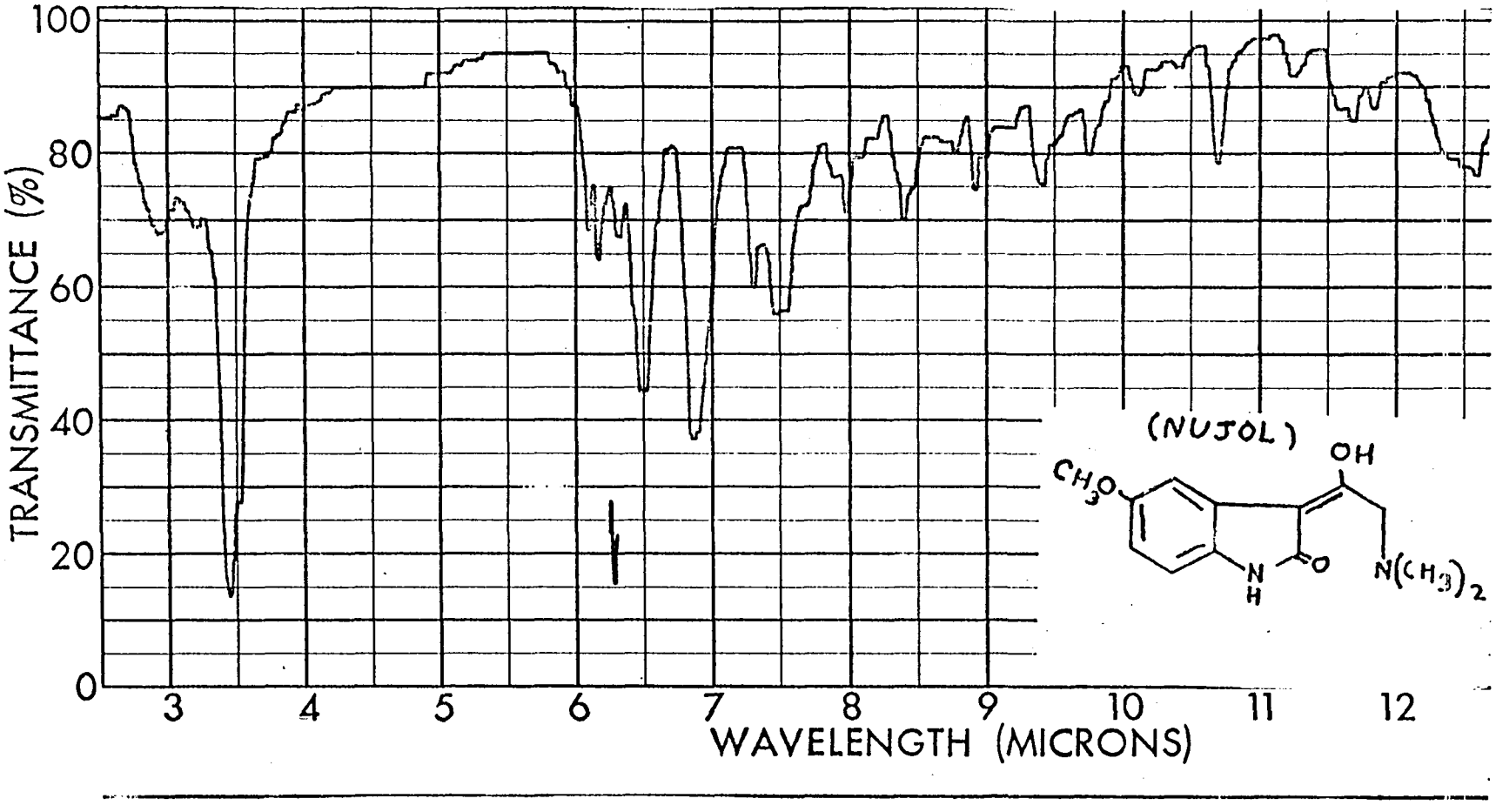


FIG. 12 INFRARED SPECTRUM

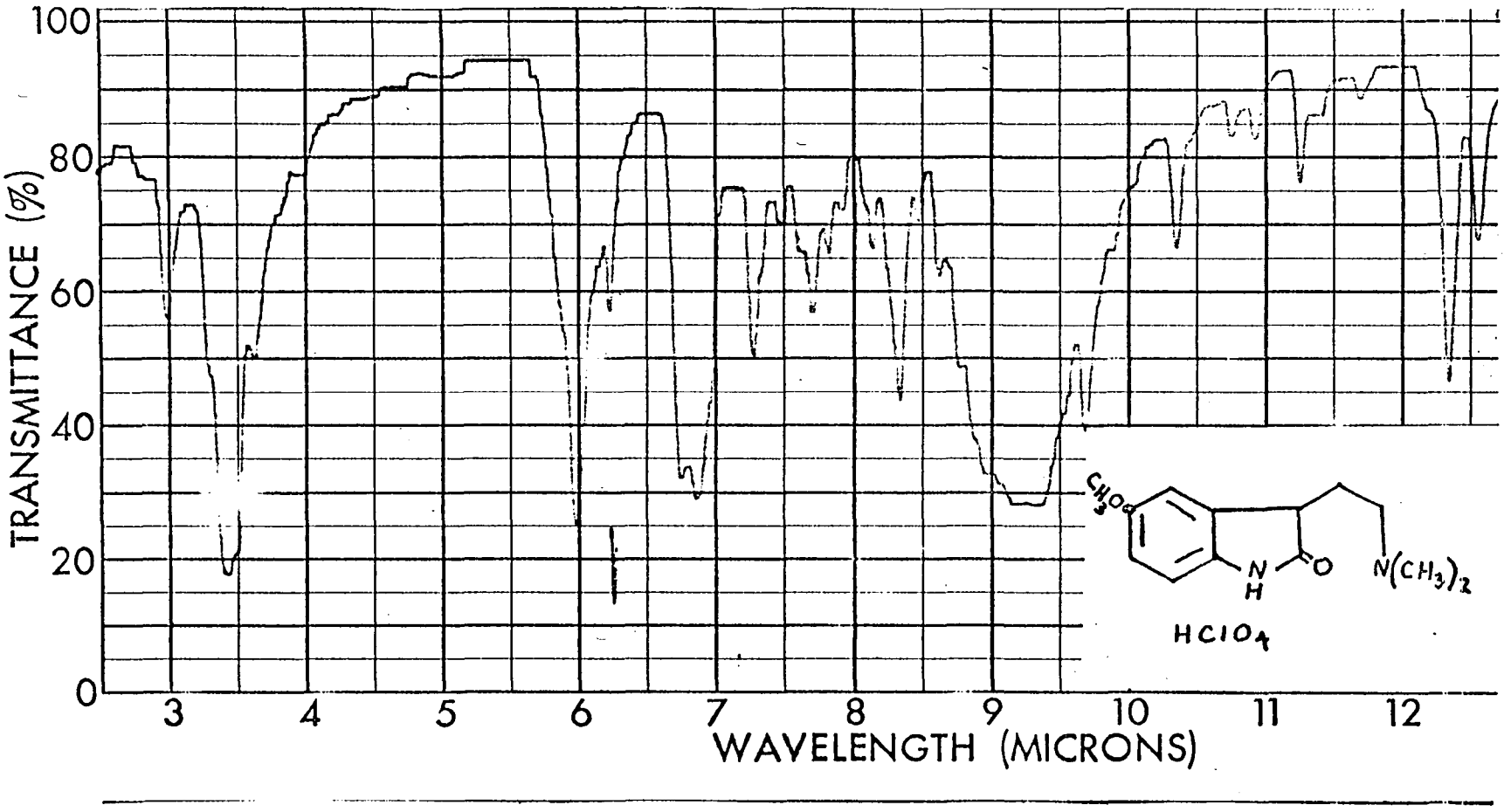


FIG. 13 INFRARED SPECTRUM

Fig. 14. Ultraviolet Spectra

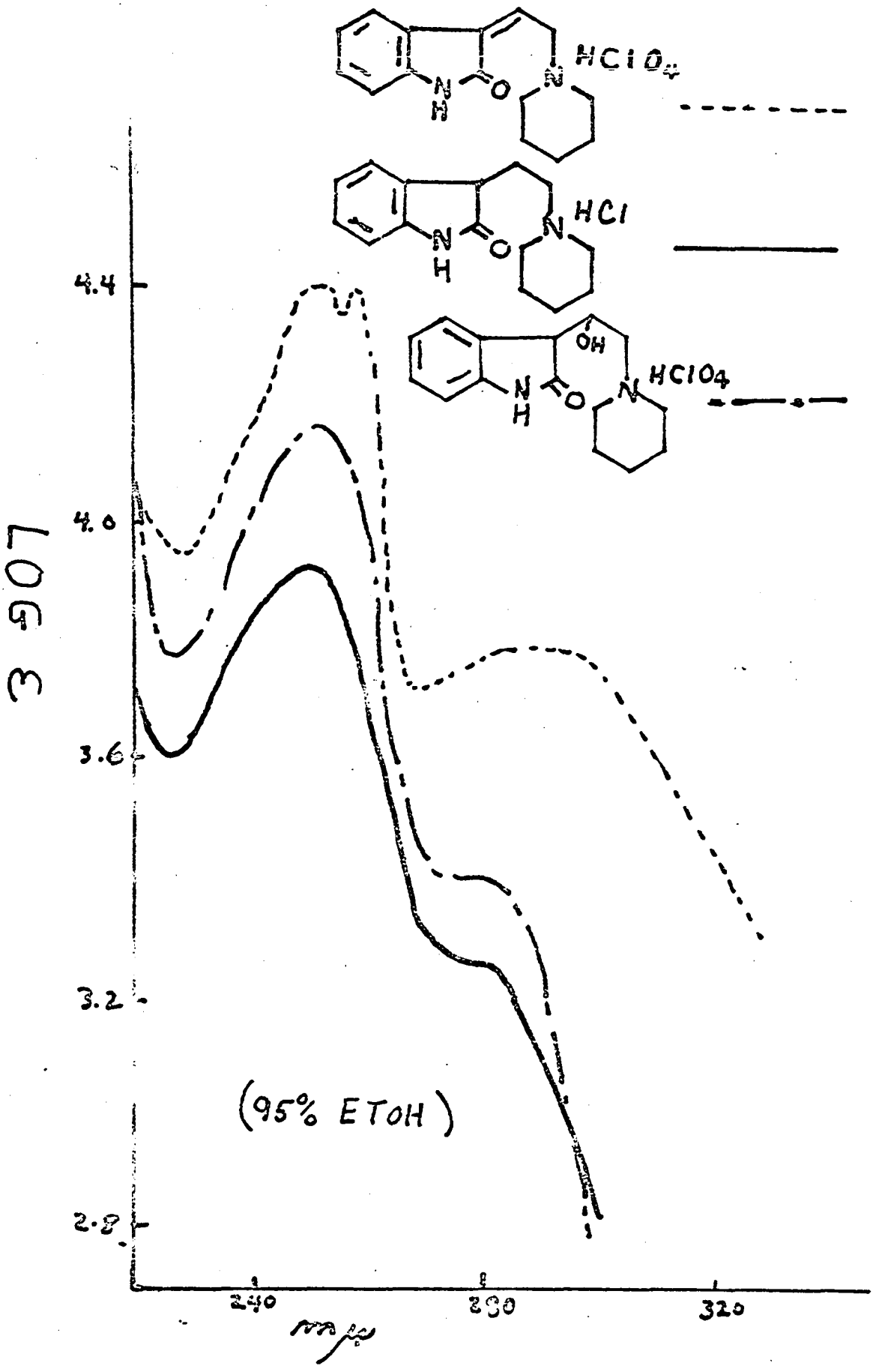
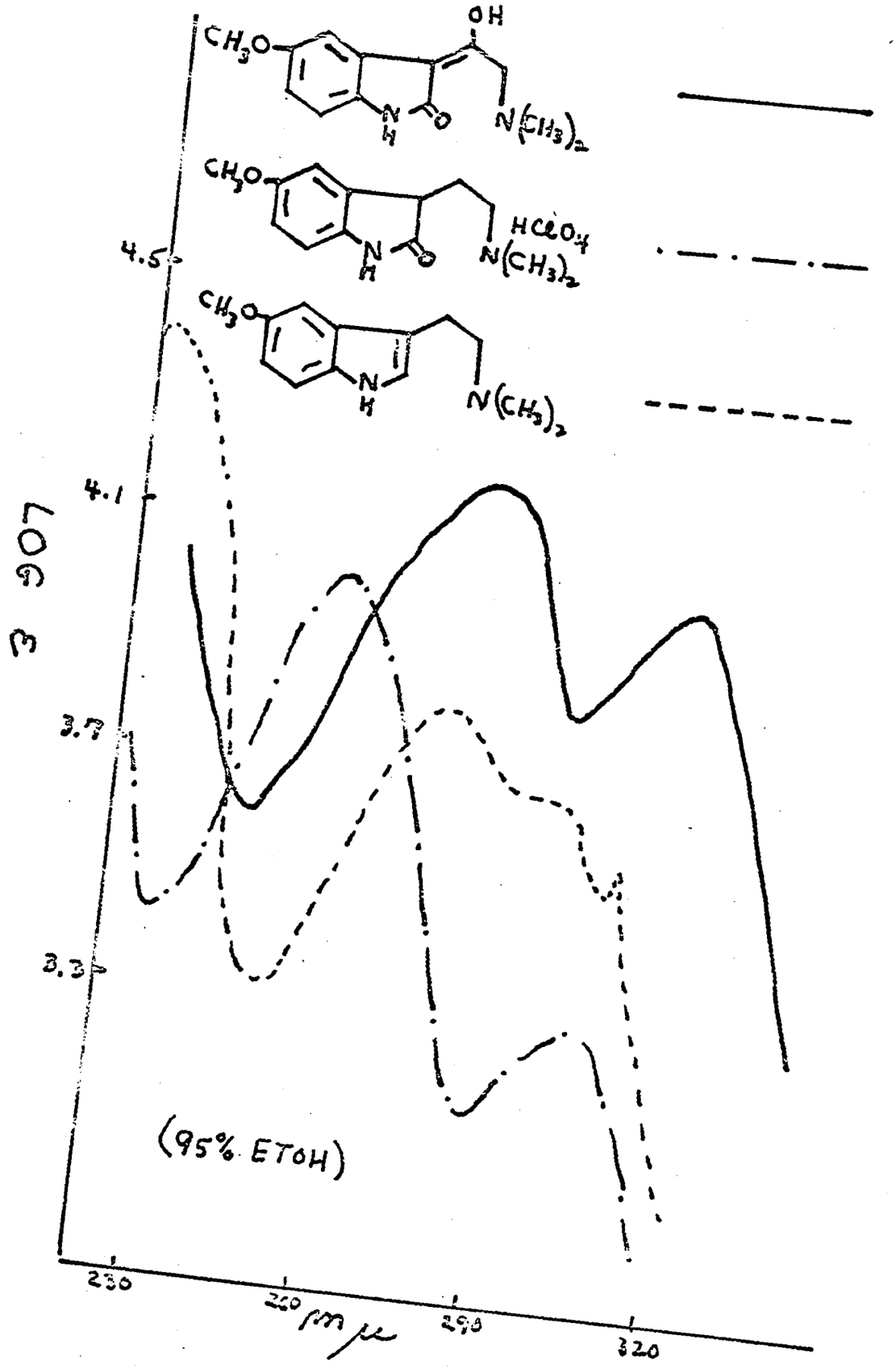

HClO4
HCl
OH
HClO4
4.4
4.0
3.6
3.2
2.8
LOG ε
(95% ETOH)
240
280
320
mμ

Fig. 15. Ultraviolet Spectra


OH
CH3O
N(CH3)2
HClO4
4.5
4.1
3.7
3.3
log ε
(95% EtOH)
230
240
290
320
mμ

EXPERIMENTAL

The microanalyses were performed by Mr. L. Dorfman of the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

All melting points given are uncorrected.

Ultraviolet spectra were measured in 95% ethanol solution using a Cary 14 spectrophotometer. All infrared spectra were taken on a Perkin-Elmer model "Infracord" infrared spectrophotometer.

The use of silica gel in the text refers to that supplied by G. F. Smith Chemical Co., Columbus, Ohio, and thin layer silica to that supplied by Research Specialties Co., Richmond, California.

N-Hydroxyoxindole (LIII)

This compound was prepared in 35% yield by the method of M. S. Kisteneva (45). The compound melted at 198-200° after crystallization from water. [Lit. value, m.p. 196-197° (45)].

5-Hydroxyoxindole (LIV)

A solution of 2.0 g. of N-hydroxyoxindole (LIII), 6 ml. of concentrated sulfuric acid and 25 ml. of water was refluxed 1 hour under nitrogen. Charcoal was added and a yellow solid, 0.6 g., precipitated on cooling. After sublimation it melted at about 265°, with some prior decomposition. [Lit. value, m.p.

about 270° with some previous decomposition (50).] Concentrating the mother liquor yielded an additional 0.40 g. of product.*

5-Methoxyoxindole (LVIIIb)

A solution of diazomethane in ether was added to 0.50 g. of 5-hydroxyoxindole (LIV) in methanol. The mixture was kept in the freezer for 9 days, checking periodically to insure presence of diazomethane. Two further additions of diazomethane were required during this period. The solvent was evaporated on the steam bath and the residue solidified. The product, m.p. 149-151°, was crystallized from acetone-cyclohexane. [Lit. value, m.p. 152-154° (51).]

3-[α-Hydroxy-β-(N,N-dimethylamino)-ethylidene]-oxindole (LXa)

A slurry of 2.4 g. (0.018 mole) of oxindole (LVIIIa), 3.0 g. (0.023 mole) of ethyl N,N-dimethylglycinate (LIXa) in 10 ml. of absolute ethanol was added to a refluxing solution of sodium ethoxide, prepared from 0.60 g. (0.026 mole) of sodium and 15 ml. of absolute ethanol. After 3.5 hours the precipitated sodio salt was dissolved in water, neutralized with solid carbon dioxide and the white precipitate, 3.4 g. (70%), filtered.

---

*This compound was first prepared in this manner by Dr. N. V. Bringi.

After several crystallizations from methanol-benzene the 3-[α-hydroxy-β-(N,N-dimethylamino)-ethylidene]-oxindole (LXa) melted at 250-255° with decomposition.

Infrared spectrum

(Nujol) NH, 3.10(w)μ; C=O, C=C, 6.18(m)μ, 6.50(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 264 mμ (log ε 4.25), 310 mμ (log ε 4.25).

Analysis

Calculated for $C_{12}H_{14}N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.90; H, 6.56; N, 12.74.

The perchlorate salt was formed by dissolving the base in a few milliliters of acetic acid and adding 70% perchloric acid dropwise. After several crystallizations of the precipitate from methanol-benzene the compound melted at 177-182°.

3-[α-Hydroxy-β-(N,N-dimethylamino)ethylidene]-5-methoxyoxindole (LXc)

This compound was prepared by the above procedure. After several crystallizations from methanol-benzene, the compound melted at 225-228° with decomposition.

Infrared spectrum

See Fig. 12.

Ultraviolet spectrum

See Fig. 15.

Analysis

Calculated for $C_{13}H_{15}N_2O_3$: N, 11.28. Found: N, 11.58.

3-[α-Hydroxy-β-(N-piperidino)-ethylidene]-oxindole

(LXb)

This compound was prepared in 80% yield, m.p. 225-260° with decomposition, by the procedure described above. Its perchlorate salt melted at 242-245°. [Lit. value gives m.p. 260° for the base and 245° for the perchlorate salt (43).]

Infrared spectrum

(Nujol) NH, 3.02(m)μ; C=O, C=C, 6.08(s)μ, 6.15(s)μ, 6.3(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 285 mμ (log ε 4.16), 3.8 mμ (log ε 4.00)

3-[α-Hydroxy-β-(N,N-dimethylamino)-ethyl]-oxindole

Perchlorate (LXIa)

A solution of 0.20 g. (0.00063 mole) of LXa was hydrogenated at atmospheric pressure over 0.03 g. of 30% palladium on charcoal. The hydrogen uptake ceased after one mole was ab-

sorbed. After filtration of the catalyst and evaporation of the solvent in vacuo at 40° there was obtained a quantitative yield of a white solid, m.p. 170-185°. After several crystallizations from absolute alcohol the compound turned yellow on melting (presumably with formation of the alkylidene LXIIa). The melting point range was 173-185°.

Infrared spectrum

(Nujol) OH, NH, 2.9(w)μ, 3.06(w)μ; C=O, 6.0(s)μ; C=C, 6.17(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 252 mμ (log ε 4.01), 282 mμ (log ε 3.45).

Analysis

Calculated for $C_{12}H_{16}N_2O_2 \cdot HClO_4$: N, 8.74. Found: N, 8.63.

3-[α-Hydroxy-β-(N-piperidino)-ethyl]-oxindole Perchlorate (LXIb)

This compound was prepared from 3-[α-hydroxy-β-(N-piperidino)-ethylidene]-oxindole (LXb) by the above procedure. After several crystallizations from methanol-benzene the compound melted at 165-185° with decomposition (presumably into the alkylidene (LXIIb).

Infrared spectrum

See Fig. 9.

Ultraviolet spectrum

See Fig. 14.

Analysis

Calculated for $C_{15}H_{20}N_2O_2 \cdot HClO_4$: C, 49.93; H, 5.87; N, 7.77. Found: C, 50.07; H, 6.00; N, 7.64.

When the solvent was evaporated at steam bath temperature rather than at 40°, a yellow solid was obtained, m.p. 200-204° after crystallization, which had identical infrared and ultraviolet spectra as that of Wenkert et al. (43) reported 3-[β-(N-piperidino)-ethyl]-oxindole perchlorate.

3-[β-(N,N-Dimethylamino)-ethylidene]-oxindole (LXIIa)

One drop of 70% perchloric acid was added to a slurry of 0.200 g. (0.000630 mole) of perchlorate LXIa in 5 ml. of acetic acid. The mixture was heated on the steam bath until solution was effected. On cooling a yellow precipitate of 3-[β-(N,N-dimethylamino)-ethylidene]-oxindole perchlorate (LXIIa), 0.110 g. (55%), m.p. 147-154°, precipitated. A second crop, 0.018 g. (9%), was obtained by the addition of ether to the mother liquor. After several crystallizations from absolute ethanol the yellow solid melted at 152-155°.

Infrared spectrum

(Nujol) NH, 3.06(m)μ; C=O, C=C, 5.91(s)μ, 6.07(m)μ, 6.17(m)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 253 mμ (log ε 4.43), 293 mμ (log ε 3.72).

Analysis

Calculated for $C_{12}H_{14}N_2O \cdot HClO_4$: C, 47.61; H, 5.00; N, 9.25. Found: C, 47.69; H, 5.20; N, 9.23.

3-[β-(N-Piperidino)-ethylidene]-oxindole Perchlorate (LXIIb)

This compound was prepared by the above procedure from LXIb. The yellow crystals melted at 200-204° after several crystallizations from methanol.

Infrared spectrum

See Fig. 10.

Ultraviolet spectrum

See Fig. 14.

Analysis

Calculated for $C_{15}H_{19}N_2O \cdot HClO_4$: C, 52.56; H, 5.59; N, 8.17. Found: C, 52.23; H, 5.60; N, 8.50.

3-[β-(N,N-Dimethylamino)-ethyl]-oxindole (LXIIIa)

a) A solution of 0.80 g. (0.0037 mole) of 3-[α-hydroxy-β-(N,N-dimethylamino)-ethylidene]-oxindole (LXa) was hydrogenated at atmospheric pressure over 0.08 g. of 30% palladium on carbon in 50 ml. of absolute ethanol containing enough concentrated hydrochloric acid to insure complete hydrochloride salt formation. After 24 hours the hydrogenation was stopped. The catalyst was filtered and the solvent evaporated in vacuo at 40°. The hydrochloride, a viscous oil, solidified on standing and was crystallized from methanol-ether. Conversion to the perchlorate gave 3-[β-(N,N-dimethylamino)-ethyl]-oxindole perchlorate (LXIIIa), 0.75 g. (71%) which melted at 130-132° after one crystallization from methanol-benzene.

Infrared spectrum

(Nujol) NH, 3.03(m)μ; C=O, 5.97(s)μ; C=C, 6.19(m)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 250 mμ (log ε 3.86), 280 mμ (log ε 3.10)

Analysis

Calculated for $C_{12}H_{16}N_2O \cdot HClO_4$: C, 47.29; H, 5.62; N, 9.13. Found: C, 47.58; H, 5.72; N, 9.04.

b) When 3-[β-(N,N-dimethylamino)-ethylidene]-oxindole (LXIIa) perchlorate was hydrogenated in absolute ethanol over

30% palladium on carbon at atmospheric pressure, a quantitative yield of 3-[β-(N,N-dimethylamino)-ethyl]-oxindole perchlorate (LXIIIa) was obtained, m.p. 130-132°.

3-[β-(N,N-Dimethylamino)-ethyl]-5-methoxy-oxindole (LXIIIb)

When 3-[α-hydroxy-β-(N,N-dimethylamino)-ethylidene]-5-methoxy-oxindole (LXc) was hydrogenated, 3-[β-(N,N-dimethylamino)-ethyl]-5-methoxyoxindole perchlorate (LXIIIb) was obtained as a white solid which melted at 180-181° after several crystallizations from methanol.

Infrared spectrum

See Fig. 13.

Ultraviolet spectrum

See Fig. 15.

Analysis

Calculated for $C_{13}H_{18}N_2O \cdot HClO_4$: C, 46.66; H, 5.73; N, 8.37. Found: C, 46.53; H, 5.83; N, 8.19.

3-[β-(N-Piperidino)-ethyl]-oxindole (LXIIIc)

a) When 3-[α-hydroxy-β-(N-piperidino)-ethylidene]-oxindole (LXb) was hydrogenated, crude 3-[β-(N-piperidino)-ethyl]-oxindole (LXIIIc) was isolated as the picrate salt.

After several crystallizations from methanol it melted at 195-198°.

Analysis

Calculated for $C_{15}H_{20}N_2O \cdot C_6H_4N_3O_7$: C, 53.27; H, 4.89; N, 15.79. Found: C, 53.32; H, 5.01; N, 15.77.

Oxindole LXIIIc could be obtained as the hydrochloride salt by neutralization of the picrate and treatment of the free base with anhydrous hydrogen chloride in ether. It melted at 193-196° after crystallization from absolute ethanol-ether.

Infrared spectrum

See Fig. 11.

Ultraviolet spectrum

See Fig. 14.

b) When 3-[β-(N-piperidino)-ethylidene]-oxindole perchlorate (LXIIb) was hydrogenated in ethanol over palladium on carbon, a quantitative yield of 3-[β-(N-piperidino)-ethyl]-oxindole (LXIIIc), isolated as the picrate, m.p. 195-198°, was obtained.

General Method for Reduction of Oxindoles to Indoles

The oxindolic amine salt was dissolved in anhydrous methanol and made basic with methanolic potassium hydroxide. The

solvent was evaporated in vacuo at room temperature and the residue was taken up in tetrahydrofuran. To this solution lithium aluminum hydride was added in excess and the slurry refluxed under nitrogen for a 0.5 hour. After removal of the solvent and subjection of the residue to a second lithium aluminum hydride reduction identical with the above, the crude product was converted to the picrate salt.

N,N-Dimethyltryptamine (LXIVa)

This indole was obtained from the structurally related oxindole by the above procedure. Its picrate, m.p. 168-170° [Lit. value, m.p. 170-171° (52)], was obtained in 50% yield. The free base was obtained by passing a methanolic solution of the picrate through a basic ion-exchange resin. After crystallization from ligroin it melted at 45-47°. [Lit. value, m.p. 49-50° (52)].

Infrared spectrum

(CCl_4) NH, 2.87(s) .

Ultraviolet spectrum

(95% Ethanol) λ_{max} 222 mμ (log ε 4.58), 275 mμ (log ε 3.77), 282 mμ (log ε 3.80), 292 mμ (log ε 3.74).

N,N-Dimethyl-5-methoxytryptamine (LXIVb)

This compound was prepared from its oxindole in 58% yield (based on the picrate). Its picrate melted at 175-177° [Lit. value, m.p. 176-177.5° (8)]. The free base was obtained by passing a solution of the picrate salt, dissolved in methanol, through a basic ion-exchange resin. It was crystallized from ligroin and melted at 66-68° Lit. value, m.p. 67.5-68.5° (8). The ultraviolet and infrared spectra were identical with those of an authentic sample. A mixed melting point gave no depression.

Infrared spectrum

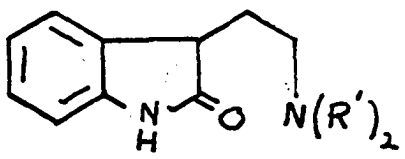
(CCl_4) NH, 2.89(s)μ.

Ultraviolet spectrum

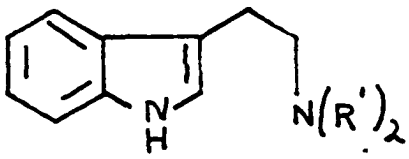
See Fig. 15.

SUMMARY

The method of Julian et al. (38) was applied to the synthesis of several new oxytryptamines (LXIII).



LXIII



LXIV

The oxytryptamines were reduced to tryptamines (LXIV) by lithium aluminum hydride.

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PART II. INTRAMOLECULAR PHENOL ALKYLATIONS

INTRODUCTION

The purpose of the present research is the investigation of the base-catalyzed intramolecular alkylation of meta-substituted phenol salts as a method of synthesis of eudesmane-type sesquiterpene intermediates.

HISTORICAL

The only widespread study on the alkylation of phenol salts was conducted by Kornblum et al. in a series of papers (1, 2, 3, 4, 5) starting in 1959. The results of the study, conducted under a wide variety of conditions are summatized below.

Factors Influencing the Ratio of Oxygen to Carbon Alkylation

Heterogeneous alkylation vs. homogeneous alkylation

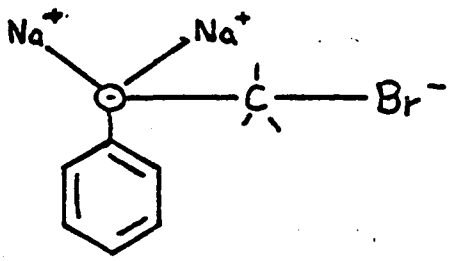
As early as 1925, Claisen (6, 7, 8) made the observation that carbon alkylation of phenoxide ion with alkyl halides is maximized under heterogeneous reaction conditions. In 1959 Kornblum and Lurie (1) investigated this phenomenon. It was found that the alkylation of sodium phenoxide with either benzyl or allyl bromide in ether, under heterogeneous conditions, gave considerable carbon alkylation whereas homogeneous alkylation in ethylene glycol dimethyl ether (EGDE) gave only oxygen alkylation (Fig. 16).

The possibility that the difference in alkylation products of the same reaction, run in different solvents, results from specific solvation effects was ruled out by the following set of experiments (Fig. 17).

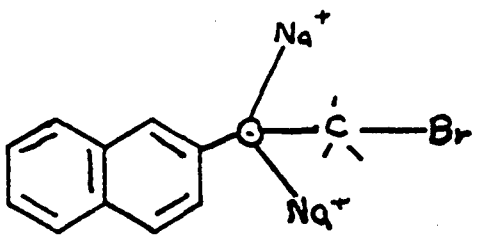
Sodium p-t-octylphenoxide, which dissolved readily in both ethylene glycol dimethyl ether and diethyl ether, gave exclusively oxygen alkylation with benzyl and allyl bromide, whereas alkyla-

tion of potassium p-t-octylphenoxide, which was insoluble in diethyl ether, yielded both oxygen (74%) and carbon alkylation (21%) on treatment with benzyl bromide in this solvent (Fig. 17).

An explanation for the preference of carbon alkylation of phenoxide ion in heterogeneous media, based on the crystal structure of sodium phenoxide, was offered by Kornblum and Lurie (1). Oxygen alkylation of a phenoxide ion which is part of a crystal lattice would seem to proceed through linear transition state (LXV) with the negative charge on oxygen being progressively transferred to the halogen. Two factors seem to oppose this transition state: 1. in non-polar solvents, used to maximize carbon alkylation, the departing halide would be poorly solvated; 2. the removal of the charge from oxygen deprives the sodium ion of the negative charge which brought it close to the oxygen.



LXV



LXVI

Thus the loss of the charge on oxygen gives rise to electrostatic repulsion forces between sodium ions and since they are held in a crystal lattice and cannot move, the energy of the system would increase.

In the case of carbon alkylation, the transition state would

Fig. 16. Reaction Scheme

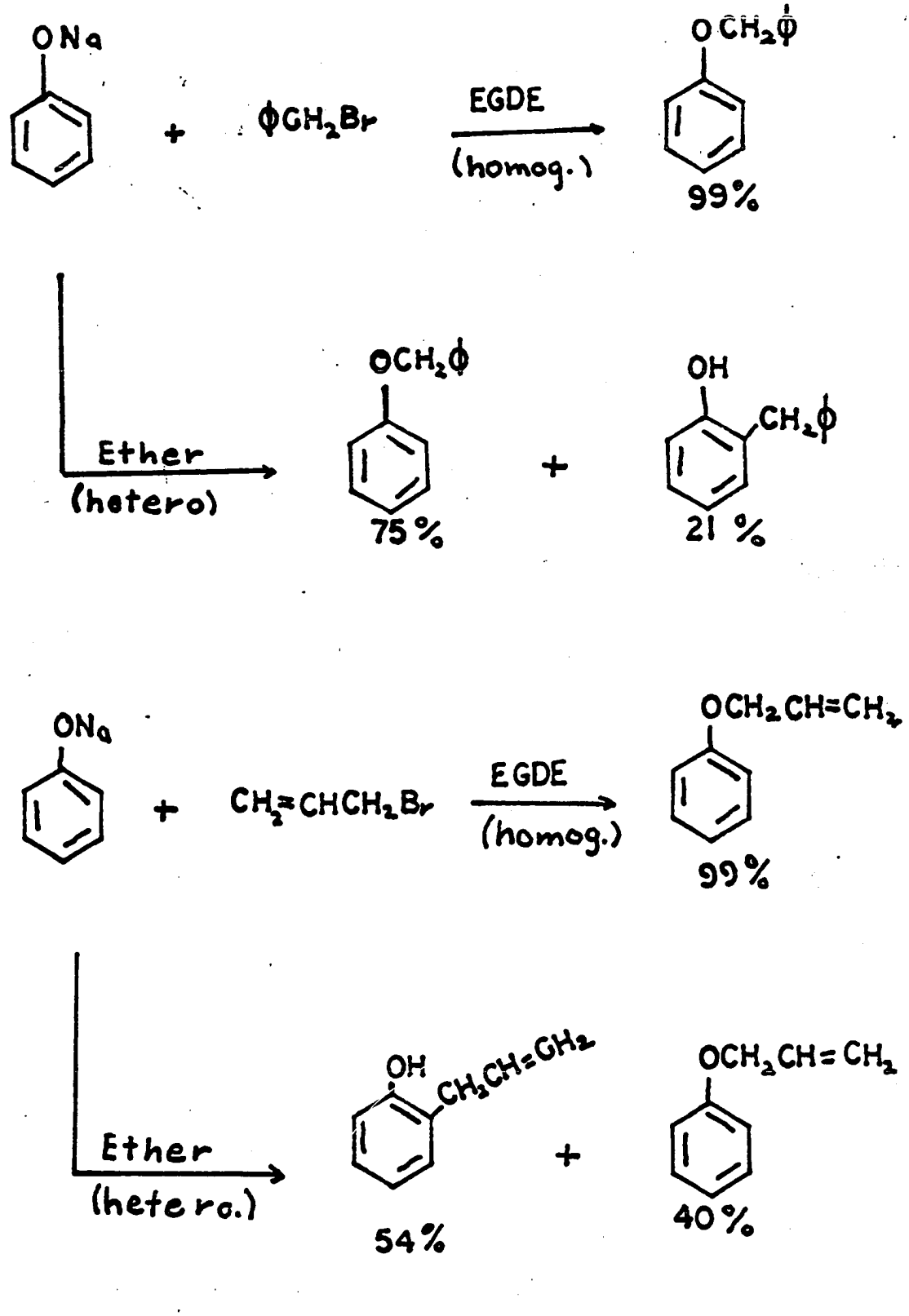
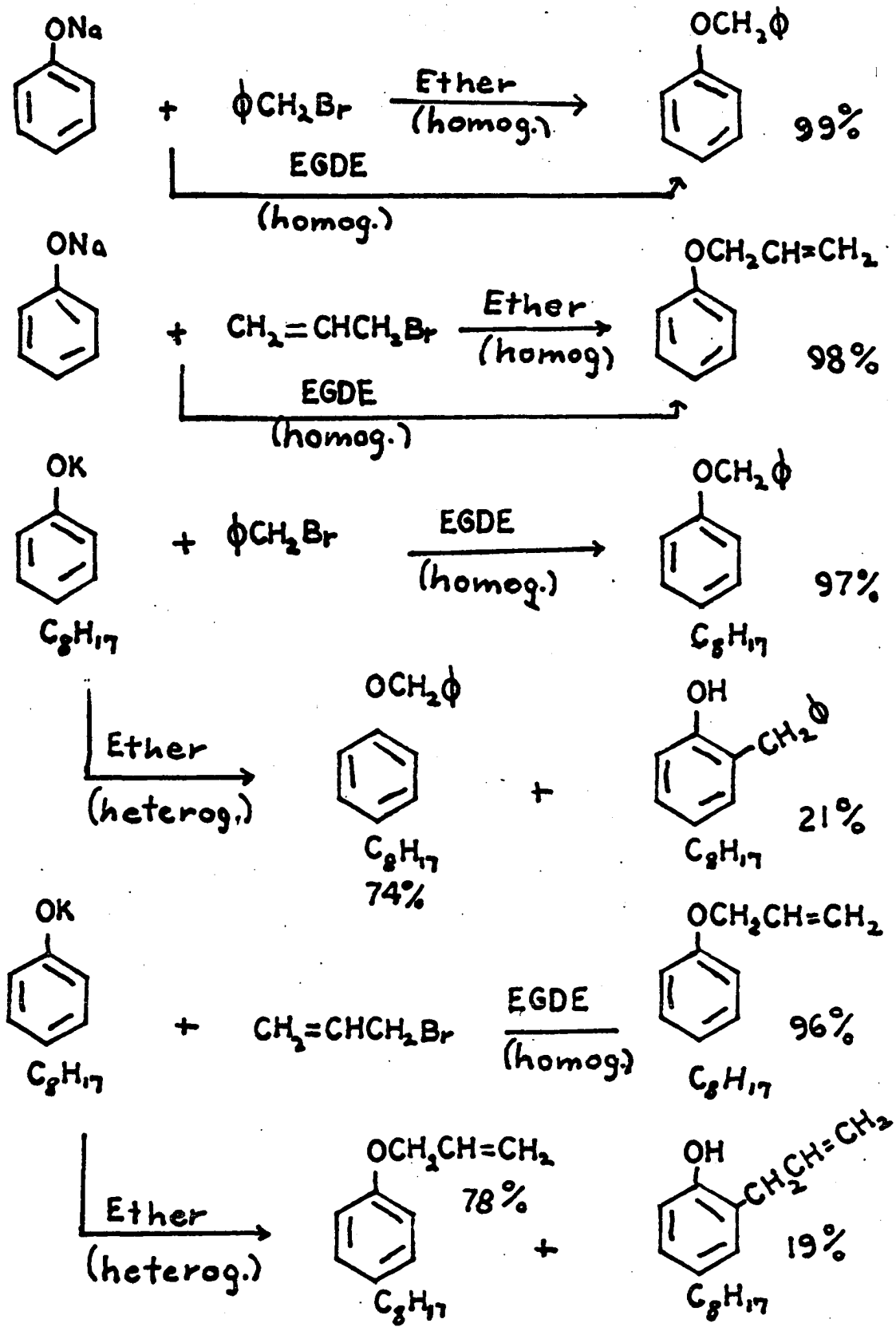
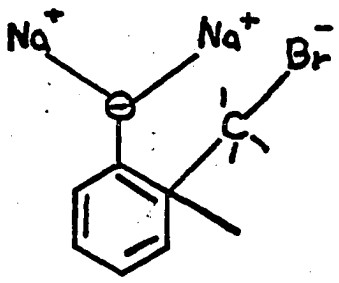

ONa
+ ϕCH2Br
EGDE
(homog.)
OCH2ϕ
99%
Ether
(hetero)
OCH2ϕ
75%
+
OH
CH2ϕ
21%
ONa
+ CH2=CHCH2Br
EGDE
(homog.)
OCH2CH=CH2
99%
Ether
(hetero.)
OH
CH2CH=CH2
54%
+
OCH2CH=CH2
40%

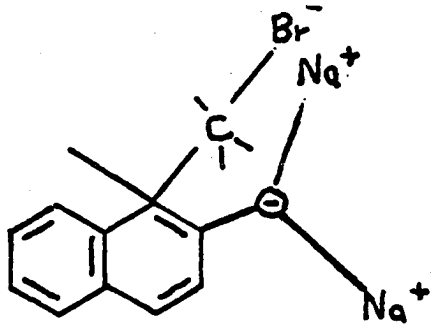
Fig. 17. Reaction Scheme


ONa
+ ϕCH2Br
Ether (homog.)
EGDE (homog.)
OCH2ϕ
99%
ONa
+ CH2=CHCH2Br
Ether (homog)
EGDE (homog.)
OCH2CH=CH2
98%
OK
+ ϕCH2Br
EGDE (homog.)
OCH2ϕ
C8H17
97%
Ether (heterog.)
OCH2ϕ
C8H17
74%
+
OH
CH2ϕ
C8H17
21%
OK
C8H17
+ CH2=CHCH2Br
EGDE (homog.)
OCH2CH=CH2
C8H17
96%
Ether (heterog.)
OCH2CH=CH2
78%
C8H17
+
OH
CH2CH=CH2
C8H17
19%

not be linear (LXVII). Instead, the sodium ion would be between



LXVII



LXVIII

oxygen and halogen, yielding the following advantages: 1. the departing halide is solvated by ion pair formation; 2. ion pair formation, as a feature of the transition state, results in the removal of a positive charge from the ions surrounding the negative oxygen at the same time as the oxygen is losing its negative charge. This prevents the build-up of repulsive forces between sodium ions.

In the case of homogeneous alkylation reactions, the barrier to oxygen alkylation is eliminated, even when the solution consists of ionic aggregates. As the charge on oxygen is lost, the sodium ions are not constrained to remain rigid but can increase in distance from one another and neutralize any coulombic repulsion forces arising.

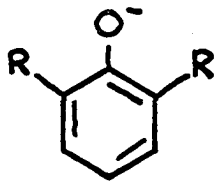
Variations in nucleophilicity of oxygen and carbon

In different phenoxide ions, the nucleophilicity of oxygen and carbon are different and thus the amount of oxygen to carbon alkylation will differ. While sodium phenoxide yields only

oxygen alkylation with benzyl bromide in ethylene glycol dimethylether under homogeneous reaction conditions (Table 1), sodium β-napthoxide gives 22% carbon alkylation under the same reaction conditions (Table 2).

Steric hindrance

It is to be expected that in phenoxide ions of type LXIX, as the series R = H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, is



LXIX

ascended, oxygen alkylation becomes more difficult. Although there is hindrance to carbon alkylation, it does not appear to be as great as in the case of oxygen alkylation. Sodium 2,6-dimethylphenoxide gives small amounts of carbon alkylation products on reaction with allyl bromide. In the case of potassium 2,6-di-t-butylphenoxide with methyl iodide the major product is ether, while with ethyl and isopropyl iodide carbon alkylation predominates (3).

Carbonium ion attack

When carbonium ions are generated in solutions of phenoxide ion, both carbon and oxygen alkylation are observed. Unpublished work (9) shows that in going from t-butyl to benzhydryl to trityl carbonium ions the reaction with phenoxide gives

progressively more oxygen alkylation. Thus it appears that with carbonium ions of very high reactivity, there results less specificity in position of reaction and thus both oxygen and carbon alkylation take place.

Nature of the solvent

In the view of Kornblum et al. (5) two transition states LXV and LXVII leading to oxygen and carbon alkylations in reactions of ambident anions in protic solvents are influenced by a combination of the solvent power (hydrogen bonding ability) and dielectric factors. In aprotic solvents the two transition states are influenced by the dielectric factors and the capacity of the solvent for solvating either anion or cation.

It was observed that in certain solvents, namely water, trifluoroethanol and phenol, carbon alkylation of phenoxide ion in both the ortho and para positions occurs along with oxygen alkylation (Table 2), whereas in a wide variety of other solvents only oxygen alkylation is observed (Table 1). It was established that carbon alkylation was not the result of a carbonium ion process since the rate of reaction between alkyl halide and phenoxide in water approached second order kinetics. The same kinetic order was assumed to hole for the other cases. The difference in the amount of oxygen to carbon alkylation in different solvents presumably arose because of selective solvation effects and enhanced solvation of the leaving group. Kornblum et al. (4) explained selective solvation as the process whereby the dissolved phenoxide ion can be solvated so tightly

that the nucleophilic properties of the oxygen decreases significantly. As a result, ortho and para substitution can compete favorably.

In the case of β-napthoxide ion, it was found that the reaction course also depended on the solvent (Table 3). Alkylations run in dimethylformamide gave 97% oxygen alkylation and in dimethyl sulfoxide 95% oxygen alkylation. In contrast, alkylations run in water gave 84% carbon alkylation, and in 2,2,2-trifluoroethanol 85% carbon alkylation. These results correlated well with similar observations with phenol salts (Table 2).

Carbon alkylation (36%) of sodium β-napthoxide (Table 3) in tetrahydrofuran cannot be attributed to hydrogen bonding. Kornblum et al. (5) consider this fact to be due to the ability of the solvent to decrease electrostatic interactions, a consequence of the dielectric constant. Of the four aprotic solvents used (Table 3), two have high dielectric constants, dimethylformamide (ε = 37) and dimethyl sulfoxide (ε = 45). These strongly favor oxygen alkylation while tetrahydrofuran (ε = 7) and ethylene glycol dimethylether (ε = 7) bring about a shift towards carbon alkylation. In a medium of low dielectric constant, e.g. tetrahydrofuran (ε = 7), it is reasonable to assume that sodium β-napthoxide exists completely as ion pairs and higher aggregates. In the transition state for oxygen alkylation (LXVI) charge transfer from oxygen to halogen is involved. Since the halogen atom is relatively remote from the sodium ion, the transfer must be accomplished against the attractive force

of the sodium ion. This factor disfavors oxygen alkylation and is important in media of low dielectric constant. In contrast, carbon alkylation, involving little removal of charge from the proximity of the sodium ion, is relatively insensitive to dielectric factors. Hence, solvents of low dielectric constant favor carbon alkylation by hindering oxygen alkylation.

When the alkylation is run in aprotic solvents of high dielectric constant, the reacting species again may be ion pairs or free napthoxide ions if the solution is sufficiently dilute. If the reaction involves ion pairs, it goes through the transition states previously described (LXVI, LXVIII). However, in the case of oxygen alkylation the transition state is of significantly lower energy in solvents of high dielectric constant because of their shielding of the departing halide ion from the attractive force of the sodium ion. Thus the coulombic force, which acted as a deterrent to oxygen alkylation, is minimized in solvents of high dielectric constants.

Alternately, in solvents of high dielectric constants, alkylation conceivably can involve free β -napthoxide ions. If this is the case, the sodium ions are effectively removed and the force which resists the charge transfer from oxygen to halogen in transition state LXVI for oxygen alkylation is absent. Hence the β-napthoxide ions can exert their preference for displacements involving oxygen.

Among some solvents of similar dielectric constant, e.g. methanol ($\mathcal{E}$ = 33) and dimethylformamide ($\mathcal{E}$ = 37), quite dif-

ferent proportions of oxygen to carbon alkylation are observed (Table 3). This difference is attributed to hydrogen bonding. Its importance is shown by a comparison of alkylation of β-napthoxide in 2,2,2-trifluoroethanol and ethanol (Table 3). The two alcohols have similar dielectric constants but the trifluoroethanol has the greater hydrogen bonding tendency. As a consequence, alkylation of sodium β-napthoxide by benzyl bromide in 2,2,2-trifluoroethanol gives 85% carbon alkylation, but only 28% in ethanol.

Nature of the cation

In aprotic solvents having low dielectric constants the reacting phenoxide anion is likely to be part of an ion aggregate. With a small cation, such as lithium ion, the ion pairs will be associated closely and the electrostatic restraing to oxygen alkylation large. In the series Li^+, Na^+, K^+, and R_4N^+ ion pairs are associated progressively less closely causing the tendency for oxygen alkylation to increase. Thus it would be expected that the influence of the cation is greatest in solvents of low dielectric constant and that carbon alkylation decreases in the series Li^+, Na^+, K^+, and R_4N^+(5).

Cationic solvation

Certain solvents are especially effective at solvating cations, e.g. ethylene glycol dimethyl ether, dimethylformamide, dimethyl sulfoxide (5). When the cation is well solvated, the charge is spread over a large volume and such dispersal of charge

Table 1. Solvents in Which Homogeneous Alkylations of Phenoxide Salts Result in Oxygen Alkylation (4)

Solvent	Salt	Alkylating Agent	% Oxygen Alkylation
t-Butyl Alcohol	Sodium Phenoxide	Allyl Bromide	100
Diethyl Ether	Sodium t-Octyl-phenoxide	Allyl Bromide	99
Dimethylformamide	Sodium Phenoxide	Allyl Chloride	100
	Sodium Phenoxide	Allyl Bromide	100
	Sodium Phenoxide	Benzyl Chloride	100
	Potassium Phenoxide	Allyl Chloride	100
Dioxane	Sodium Phenoxide	Allyl Chloride	100
		Allyl Bromide	93
		Benzyl Chloride	100
Ethanol	Sodium Phenoxide	Allyl Chloride	100
Ethylene Glycol Dimethyl Ether	Sodium Phenoxide	Allyl Chloride	99
		Allyl Bromide	100
		Benzyl Chloride	100
		Benzyl Bromide	99
	Potassium Phenoxide	Allyl Bromide	100
	Sodium p-t-Octyl-phenoxide	Allyl Bromide	98
	Potassium p-t-Octyl-phenoxide	Benzyl Bromide	97
Methanol	Sodium Phenoxide	Allyl Chloride	100
		Allyl Bromide	96
		Benzyl Chloride	100
	Potassium Phenoxide	Benzyl Chloride	100
1-Propanol	Sodium Phenoxide	Allyl Bromide	93
		Benzyl Chloride	100
Tetraethylene Glycol Dimethyl Ether	Sodium Phenoxide	Allyl Bromide	94
		Benzyl Bromide	96
Tetrahydrofuran	Sodium Phenoxide	Allyl Chloride	96
		Allyl Bromide	94
		Benzyl Chloride	100
	Lithium Phenoxide	Allyl Bromide	92
Toluene	Potassium p-t-Octyl-phenoxide	Allyl Chloride	97
		Benzyl Chloride	97

Table 2. Solvents in Which Alkylation of Phenolic Salts Results in Both Carbon and Oxygen Alkylation (4)

Solvent	Salt	Alkylating Agent	Alkylation % O	% C
Water	Sodium Phenoxide	Allyl Chloride	49	51
		Allyl Bromide	51	38
		Benzyl Chloride	65	24
Phenol	Sodium Phenoxide	Allyl Chloride	72	18
		Allyl Bromide	23	77
		Benzyl Chloride	22	69
2,2,3,3-Tetrafluoropropanol-1	Sodium Phenoxide	Allyl Chloride	58	37
2,2,2-Trifluoroethanol	Sodium Phenoxide	Allyl Bromide	37	42
		Benzyl Chloride	62	26

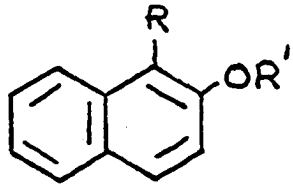
Table 3. Reaction of Benzyl Bromide with Sodium β-Naphthoxide (5)

Solvent	Dielectric Constant	% Oxygen Alkylation	% Carbon Alkylation
Dimethylformamide	37	97	0
Dimethyl Sulfoxide	45	95	0
Ethylene Glycol Diethyl Ether	7	70	22
Tetrahydrofuran	7	60	36
Methanol	33	57	34
Ethanol	24	52	28
2,2,2-Trifluoroethanol	27	7	85
Water	80	10	84

will minimize any coulombic restraint to ether formation. In general, it is agreed that ethylene glycol dimethyl ether is superior to tetrahydrofuran in solvating sodium ions. Both of these solvents have almost identical dielectric constants and the fact that alkylation of sodium β -naphthoxide with benzyl bromide in ethylene glycol dimethyl ether gives more oxygen alkylation than in tetrahydrofuran (Table 3) emphasizes this effect.

Alkylations of Sodium 1-Alkyl-2-naphthoxide

In 1960 Wenkert *et al.* (10) reported the use of alkylations of phenol salts in organic synthesis. Treatment of the sodio

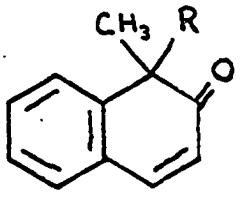


LXX

a, R = R' = H
b, R = H; R' = CH_3
c, R = CH_3; R' = H
d, R = $(CH_2)_3CH_3$; R' = H
e, R = $(CH_2)_3COCH_3$; R' = H
f, R = R' = CH_3
g, R = CH_3; R' = $(CH_2)_3CH_3$
h, R = $(CH_2)_3CH_3$; R' = CH_3
i, R = $(CH_2)_3COCH_3$; R' = CH_3
j, R = $(CH_2)_2CH(OH)CH_3$; R' = H
k, R = $(CH_2)_2CH(OH)CH_3$; R' = CH_3

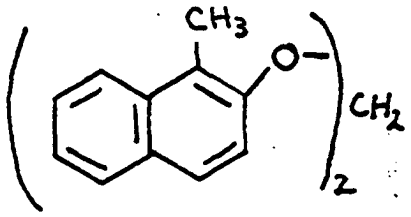
salt of 1-methyl-2-naphthol (LXXa) with refluxing methyl iodide gave 88% of C-methyl product LXXIa and only 4% of the ether

LXXf. Refluxing the same sodio salt with n-butyl bromide gave



LXXI

a, R = CH_3
b, R = $(CH_2)_3CH_3$
c, R = CH_2Cl
d, R = CH_2I
e, R = CH_2Cl_2
f, R = $(CH_2)_2COCH_3$
g, R = $(CH_2)_2CH(OH)CH_3$



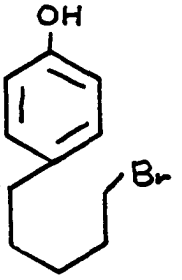
LXXII

a 50% yield of the ketone LXXIb along with 29% of the ether LXXg. Treatment of the sodio salt of naphthol LXXc with methylene chloride in a sealed tube at 100° produced predominately ketone LXXIc as well as some ether LXXII. Refluxing the same sodio salt with methylene iodide produced mostly ketone LXXId as well as ether LXXII, while treatment of the same salt with refluxing chloroform led to high yields of ketone LXXIe. Finally treatment of the sodio salt of naphthol LXXe with refluxing methyl iodide yielded some naphthalenone LXXIf, ether LXXi and the fragmentation products 1-methyl-2-naphthol (LXXc) and its ether LXXf, whereas treatment of the phenolic alcohol LXXj under the same conditions yielded only the carbon (LXXIg) and oxygen (LXXk) alkylated products.

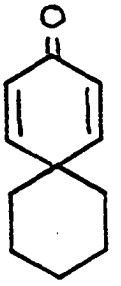
Intramolecular Alkylation of Phenol Salts

The first report of intramolecular alkylation of phenols

was that by Dreiding (11). When a solution of the potassium salt of phenol LXXIII in t-butanol was heated in a sealed tube

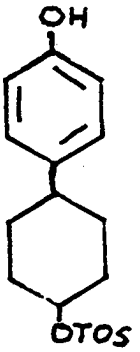


LXXIII

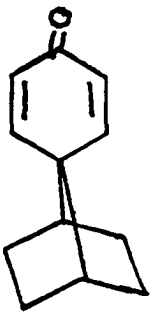


LXXIV

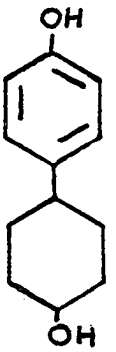
to 170°, the dienone LXXIV resulted in 88% yield. The same investigator with Barner and Schmid (12) treated the hexahydrobiphenyl LXXV under similar conditions and isolated the dienone LXXVI in 8% yield along with two other products identified as LXXVII and LXXVIII.



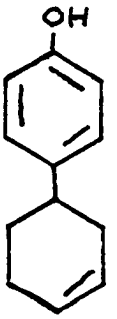
LXXV



LXXVI

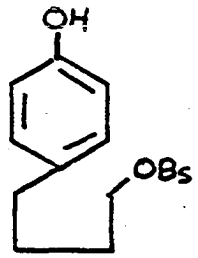


LXXVII

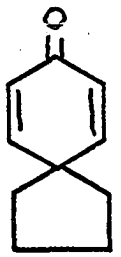


LXXVIII

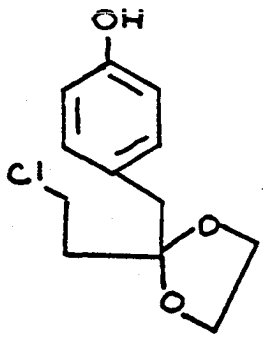
Winstein and Baird (13), in their study of displacement reactions with neighboring group participation, heated the potassium salt of phenol LXXIX in t-butyl alcohol and isolated the dienone LXXX in better than 50% yield from the reaction mixture.



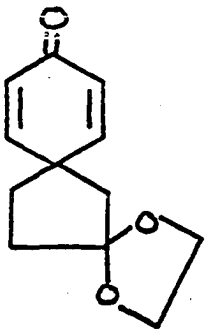
LXXIX



LXXX



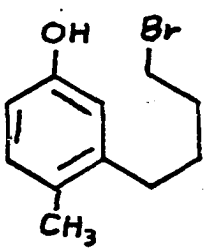
LXXXI



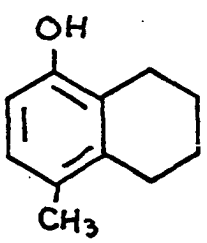
LXXXII

Dorling and Harley-Mason (14) observed a comparable product LXXXII on treatment of chlorophenol LXXXI with base.

The first instance of the utilization of this reaction for the synthesis of the bicyclo 4,4,0 decane system was reported by Newman and Mekler (15). On treatment of the bromophenol LXXXIII with sodium methoxide and methanol, tetrahydronaphthol LXXXIV resulted.



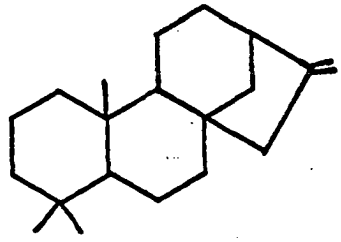
LXXXIII



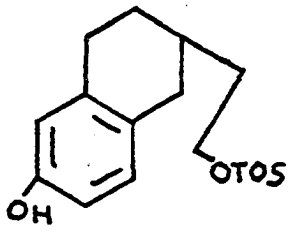
LXXXIV

The intramolecular alkylation reaction was utilized by two groups in their research directed towards the synthesis of natural products. Masamune (16), in his search for a method of synthesis of natural products containing the bicyclo[3,2,1] octane system, (e.g. the diterpene phyllocladene (LXXXV) treated the tosylate LXXVI with t-butoxide in t-butanol. The dienone

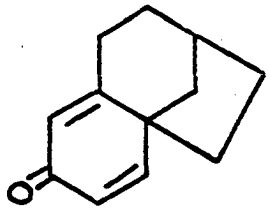
LXXXVII resulted in approximately 90% yield. Mandell et al. (17)



LXXXV

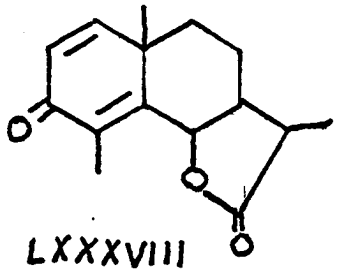


LXXXVI

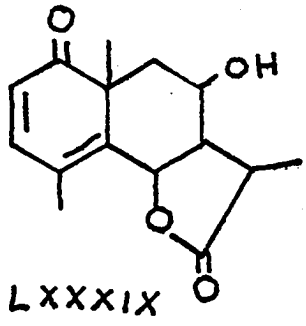


LXXXVII

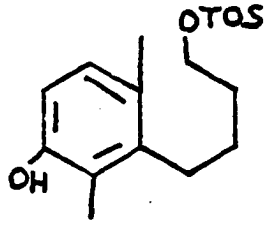
obtained dienones XCI and XCII of the santonin and ψ-santonin (LXXXIX) types by treatment of the tosylate XC with t-butoxide in t-butanol.



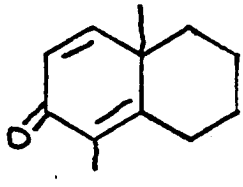
LXXXVIII



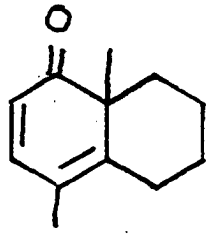
LXXXIX



XC



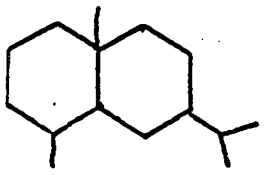
XCI



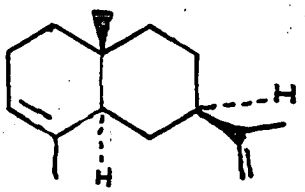
XCII

DISCUSSION

The group of naturally occurring compounds having the carbon skeleton XCIII are classified as eudesmane-type sesquiterpenes (e.g. XCIV). A large number of alcohols, ketones, acids, and



XCIII



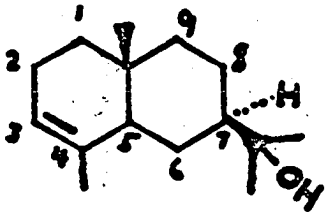
XCIV

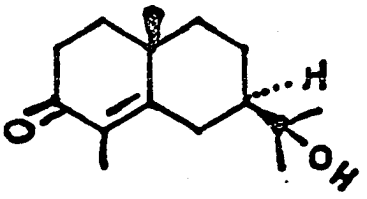
lactones of this general type occur in nature (cf. Fig. 18).

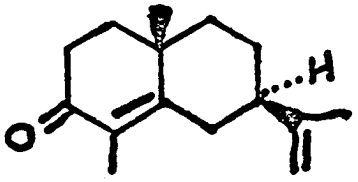
The intramolecular alkylation of meta-substituted phenol salts offers a possible method of synthesis of eudesmane-type intermediates. Since little was known about this type of cyclization reaction, several model compounds were chosen for study.

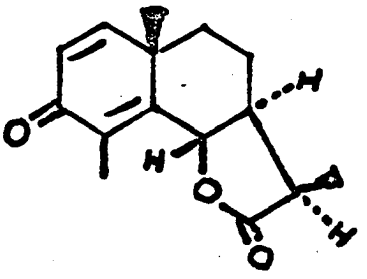
Bromophenol CIII was chosen as the first model. The procedure of Chuang and Huang (18) was followed to obtain keto acid C. Reduction of C to CI was accomplished catalytically over hydrogen and palladium on charcoal. This hydrogenation did not take place cleanly and the desired phenolic acid CI was obtained in 58% yield only after chromatography on silica gel. Reduction of CI with lithium aluminum hydride gave alcohol CII, which was converted to bromophenol CIII by refluxing hydrobromic acid in syn-tetrachloroethane according to the method of Newman and Mekler (15).

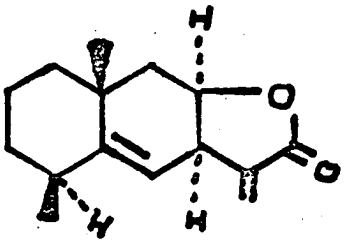
Fig. 18. Eudesmane Sesquiterpenes

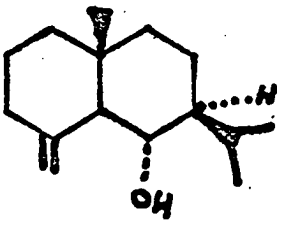

1
9
2
8
H
3
5
7
6
OH

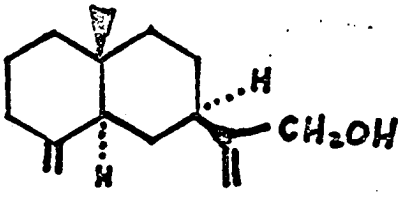

H
O
OH

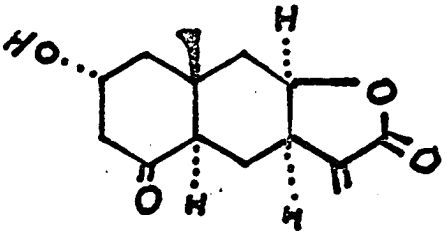

H
O


H
O
H
O
H
O


H
O
O
H
H


H
OH


H
CH₂OH
H

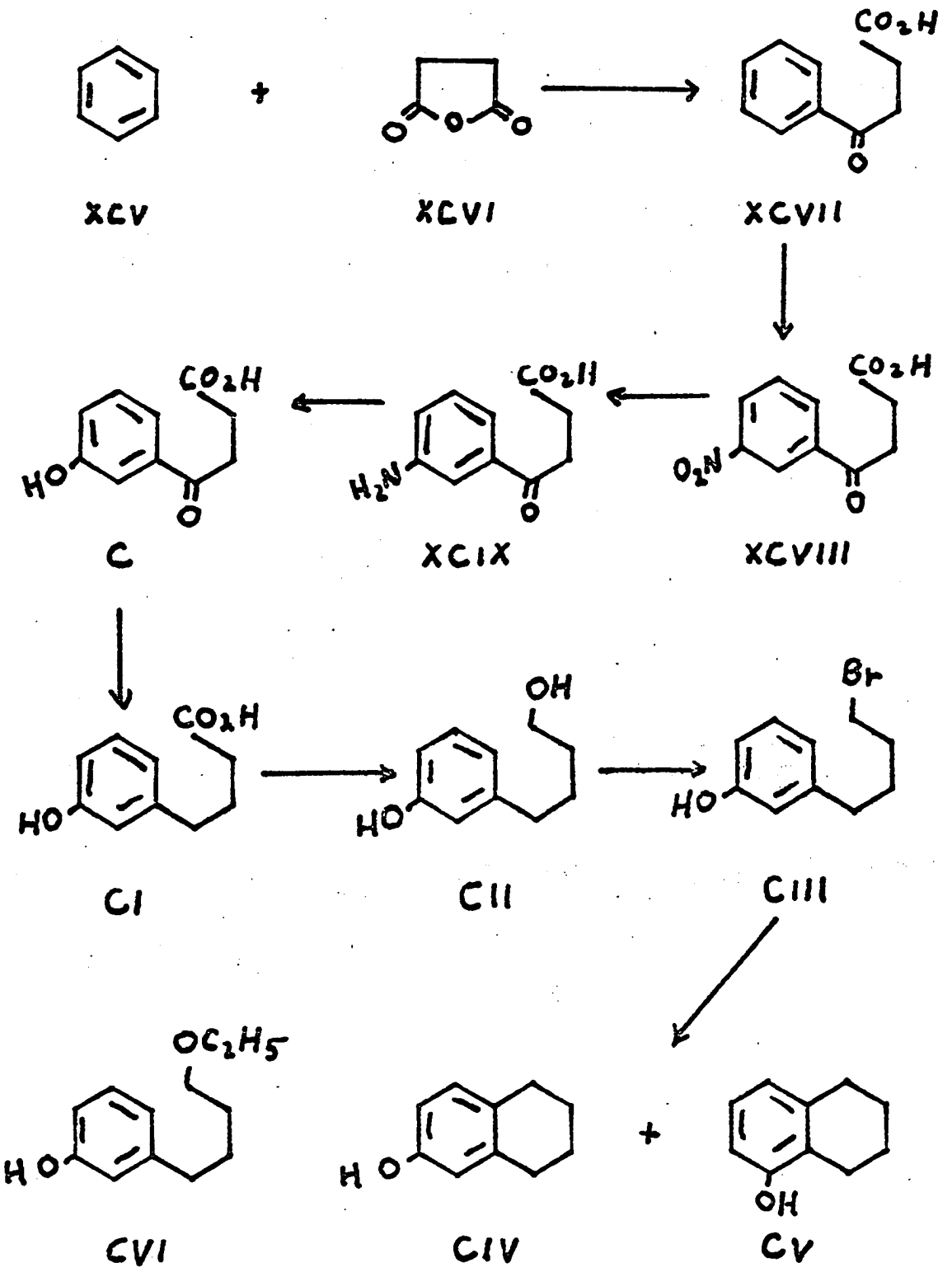

HO
H
O
O
O
H
H

The first cyclization of CIII was run in ethanol using a large excess of sodium ethoxide. Silica gel chromatography yielded 23% of a mixture of ar-tetrahydro- α and β -naphthol (CIV and CV). By means of fractional crystallization of the mixture pure ar-tetrahydro-α-naphthol (CV) and ar-tetrahydro-β-naphthol (CIV), identical with authentic samples, were obtained. A further product was an oil, 34%, which exhibited a strong absorption band in its infrared spectrum at 9.03μ. The compound was assigned the ether CVI structure.

The fact that the major product (CVI) in the cyclization reaction resulted from displacement of the bromide ion by ethoxide ion, rather than by the ortho or para ring carbon, appeared to be the consequence of the high concentration of ethoxide ions present. To test this proposal, the cyclization of CIII was run utilizing two moles of sodium ethoxide to one of the phenol. (One mole of base is required to form the salt of the starting phenol and the second to form the salt of the product.) Under these conditions of cyclization of CIII, no ether CVI was found. A partial separation of the products CIV and CV was obtained by chromatography on silica gel and a plot of the elution curve gave a quantitative estimation of the ratio of ortho to para cyclization products. The use of 2 moles of sodium ethoxide to one of phenol CIII gave a ratio of 1:1 CIV and CV.

Next, a study of solvent effects was undertaken. Approximately the same ratio of base to phenol as in the ethanol runs

Fig. 19. Reaction Scheme


XCV
XCVI
XCVII
XCVIII
XCIX
C
CI
CII
CIII
CIV
CV
CVI

was used for all other cyclizations.

The cyclization of CIII in t-butanol, using t-butoxide as the base, yielded 2:1 of CV and CIV. The use of sodium hydride in benzene gave approximately 2:1 of CV and CIV, while aqueous sodium hydroxide yielded 1:2 of CIV and CV. The attempted cyclization of CIII in acetone, using potassium carbonate as the base, resulted mostly in recovery of starting material.

Since many of the eudesmane-type sesquiterpenes have an oxygen substituted at C(8) (Fig. 18), it seemed desirable to have it already present in the synthetic intermediates. With this in mind, a second model compound CXIV was chosen. Cyclization of CXIV to either the ortho or para carbon would give product CXV containing a hydroxyl group at C(8).

Condensation of m-hydroxybenzaldehyde (CVII) with malonic acid gave the cinnamic acid CVIII which was hydrogenated to CIX in good yield. Acetylation of CIX with acetic anhydride and thionyl chloride treatment of CX in cyclohexane yielded impure acid chloride CXI. The latter with excess diazomethane gave diazoketone CXII which reacted with hydrobromic acid to give bromoketone CXIII. The impure bromoketone CXIII decomposed rapidly on standing while the pure compound remained stable for several weeks. Compound CXIII was converted to the bromohydrin CXIV by sodium borohydride reduction in methanol. When the reaction progress was followed by thin layer chromatography it could be shown that the reduction of CXIII was complete in five minutes. Thereafter the yield of CXIV decreased fairly rapidly

Fig. 20. Reaction Scheme

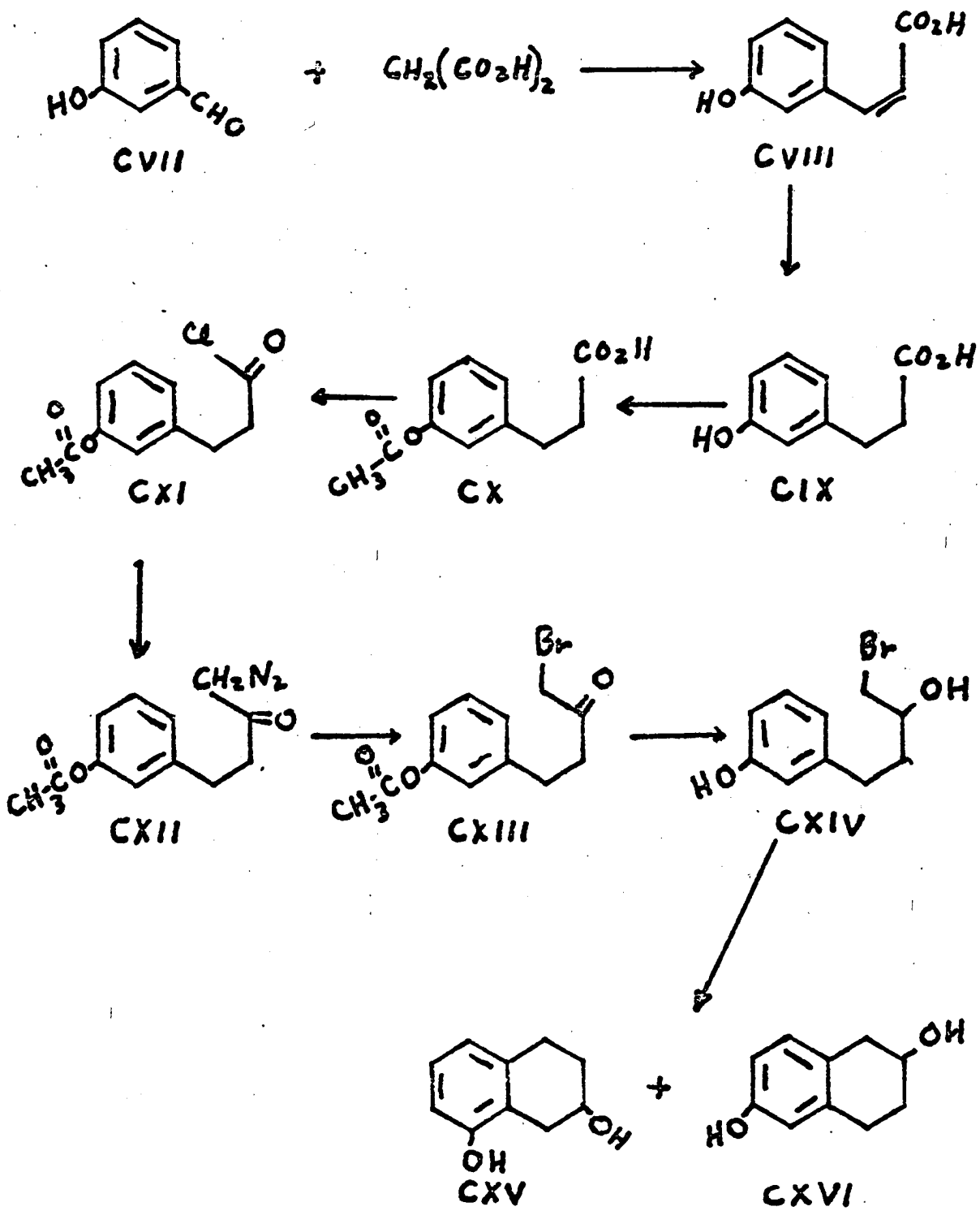
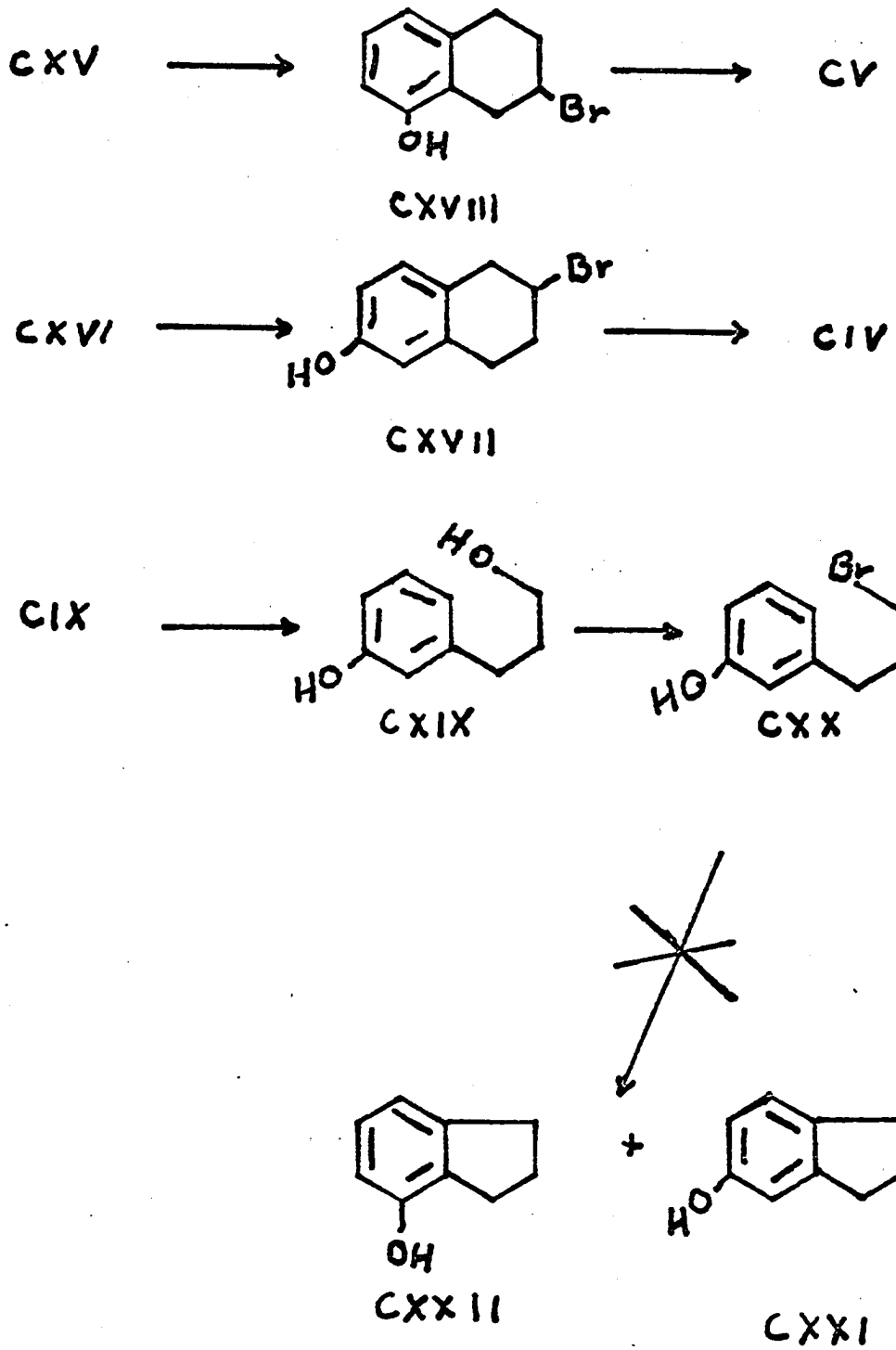

CVII
CVIII
CIX
CX
CXI
CXII
CXIII
CXIV
CXV
CXVI

Fig. 21. Reaction Scheme


CXV
Br
OH
CV
CXVIII
CXVI
Br
HO
CIV
CXVII
CIX
HO
HO
CXIX
Br
HO
CXX
OH
CXXII
+
HO
CXXI

until no L remained at the end of thirty minutes.

When bromohydrin CXIV was cyclized in t-butanol, using t-butoxide as the base, a mixture of naphthalenediols CXV and CXVI was formed. Partial separation of the naphthalene diols was achieved by chromatography on a thin layer silica gel-celite mixture and a plot of the elution curve gave the ortho-para ratio of reaction products.

In the same manner cyclizations of CXIV were carried out in aqueous sodium hydroxide and ethanolic sodium ethoxide. The same base-solvent effects though less pronounced on the ortho-para ratio were observed as in the case of CIII (Table 4). Cyclization of CXIV with t-butoxide in t-butanol gave more ortho cyclized product CXV, with sodium ethoxide in ethanol more or less equal amounts of ortho and para cyclized products CXV and CXVI, and with sodium hydroxide in water slightly more of the para cyclized product CXVI. The structures of the diols CXV CXV and CXVI were confirmed by converting them to CIV and CV via the bromo compounds CXVII and CXVIII, followed by hydrogenolysis.

At this point it was decided to investigate the cyclization reaction leading to a five membered ring. The bromophenol CXX was chosen for this purpose.

The acid CIX was obtained as previously described. Lithium aluminum hydride reduction of CIX gave the alcohol CXIX which was converted to the bromophenol CXX with hydrobromic acid by the procedure of Newman and Mekler (15).

The first cyclization of CXX was attempted in t-butanol, using t-butoxide as the base. Even after long reaction times, there was no evidence of the possible cyclization products CXXII and CXXI and most of the starting material was recovered.

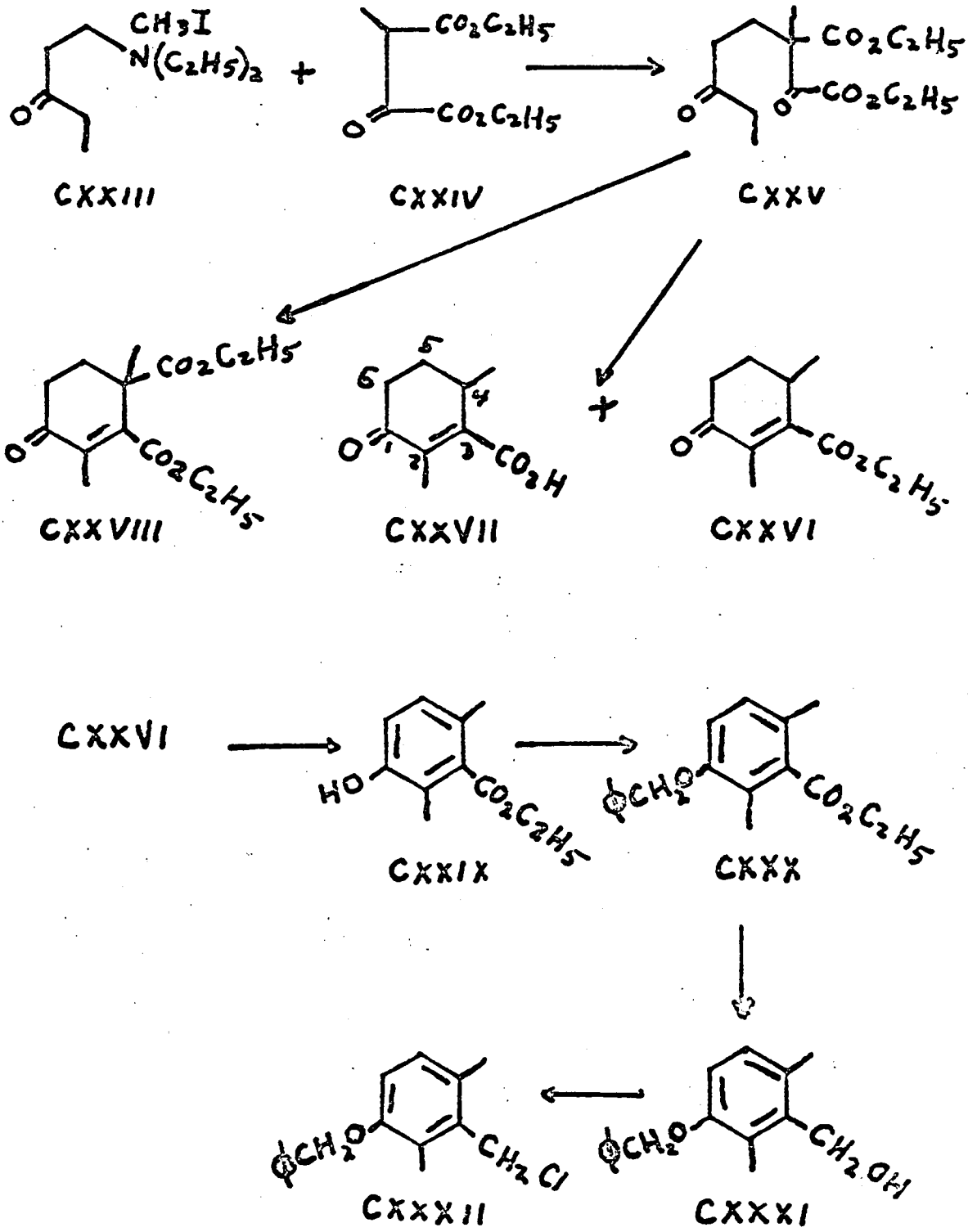
Attempted cyclization of CXX in water, using sodium hydroxide as the base, led to the displacement of the bromide ion by hydroxide ion, giving the alcohol CXIX. In this case also, no trace of cyclization products CXXII and CXXI was found. The lack of cyclization of CXX to form a product containing a five-membered ring may have a steric basis. The side chain of CXX may be too short for proper overlap of the bromine-bearing carbon and the π orbital of the benzene ring.

The bromophenol CXXXVII was chosen as a model precursor for the synthesis of the eudesmane skeleton.

Ethyl ethoxalylpropionate (CXXIV) was condensed with methiodide CXXIII giving diketone CXXV. Treatment of CXXV with refluxing hydrochloric and acetic acids gave a mixture of the cyclohexenone acid CXXVII and ester CXXVI. The diketone CXXV could also be cyclized to ester CXXVIII via p-toluenesulfonic acid in toluene. Ester CXXVIII could be converted to CXXVI and CXXVII under similar conditions.

The nuclear magnetic resonance spectrum of acid CXXVII, as well as its ester CXXVI (Fig. 32), proved interesting. Long range coupling between the C(4) hydrogen and the C(2) methyl hydrogen of CXXVII and CXXVI was observed. Both the C(2) methyl group of acid CXXVII and that of the ester CXXVI appeared as

Fig. 22. Reaction Scheme



CXXIII CXXIV CXXV

CXXVIII CXXVII CXXVI

CXXVI → CXXIX → CXXX

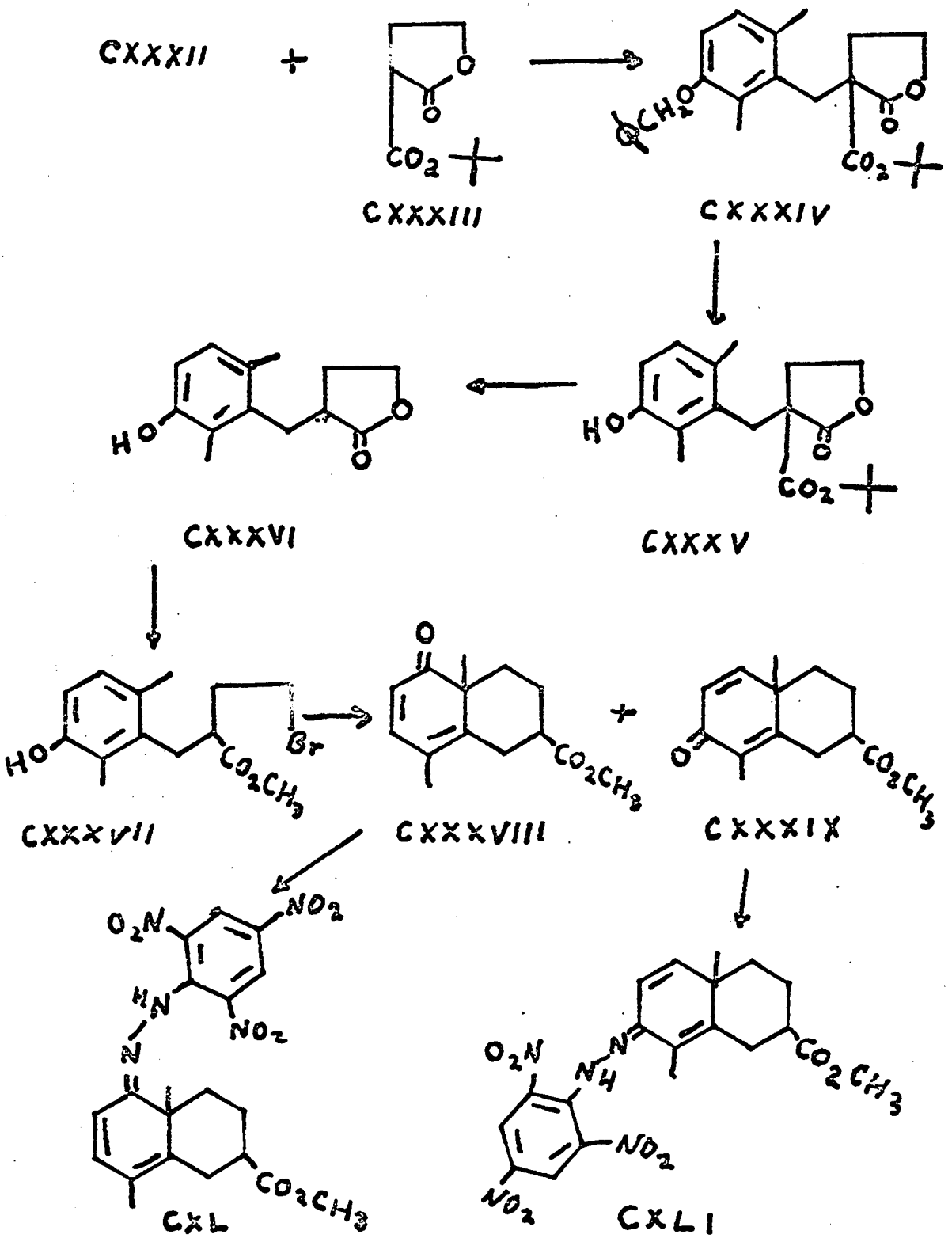
CXXXII ← CXXXI

doublets centered at 118 and 109 c.p.s. (J = 2 c.p.s.). As would be expected, the nuclear magnetic resonance spectrum of CXXVIII which has the hydrogen at C(4) replaced by a carbethoxy group, exhibits a singlet at 116 c.p.s. for the C(2) methyl group (Fig. 32). Several examples of this long range coupling between hydrogen atoms separated by three single and one double bond have appeared in the literature (19, 20, 21, 22).

The cyclohexenone ester CXXVI was aromatized to CXXIX by heating in the presence of palladium on charcoal. Alkylation of CXXIX with benzyl bromide gave the ether CXXX, which on reduction with lithium aluminum hydride, gave the alcohol CXXXI. Treatment of CXXXI with thionyl chloride afforded CXXXII, which on refluxing in toluene in the presence of the sodium salt of lactone CXXXIII gave the lactone ester CXXXIV. Hydrogenolysis of CXXXIV to CXXXV proceeded without difficulty and hydrolysis and decarboxylation of CXXXV was accomplished with p-toluene-sulfonic acid in toluene. The non-crystalline bromophenol CXXXVII was obtained from CXXXVI by treatment with anhydrous methanolic hydrobromic acid. Thin layer chromatography of crude CXXXVII showed a single spot. The product thus was used in the crude form for the next reaction.

The cyclization of CXXXVII was carried out with t-butoxide in t-butanol as described for CIII and CXIV. Chromatography of the crude product yielded dienone CXXXVIII and CXXXIX. The ultraviolet absorption maxima of CXXXVIII and CXXXIX agreed well with the values obtained by Mandel *et al.* (17) for

Fig. 23. Reaction Scheme


CXXXII
CXXXIII
CXXXIV
CXXXV
CXXXVI
CXXXVII
CXXXVIII
CXXXIX
CXL
CXLI

their dienones XCI and XCII. An approximate ratio of 3:1 CXXXVIII and CXXXIX was observed. This is in agreement with the ortho-para ratio found for the previous t-butoxide cyclizations (Table 4).

The dienones CXXXVIII and CXXXIX were obtained as oils and conversion to the 2,4-dinitrophenylhydrazones CXL and CXLI proceeded without difficulty.

The lack of any doublet peak in the infrared spectrum of starting bromophenol CXXXVII at 6-6.2μ characteristic of dienones, showed that no dienone was present at that stage. This shows conclusively that the dienones CXXXVIII and CXXXIX were formed only by base-catalyzed intramolecular alkylation.

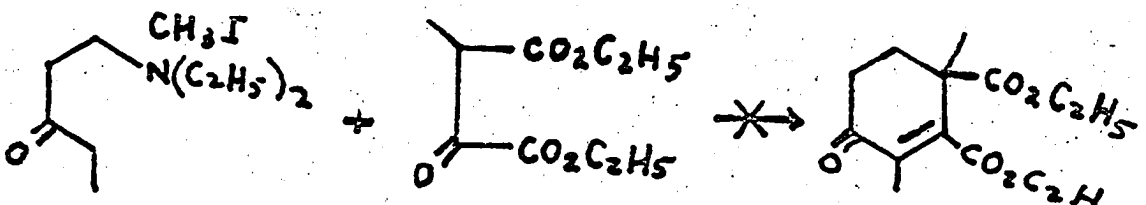
A summary of the base-solvent effects on the ortho-para ratio of cyclization products from phenols CIII, CXIV, and CXXXVII is shown in Table 4.

Table 4. Summary of Ratio of Ortho-Para Cyclization Products

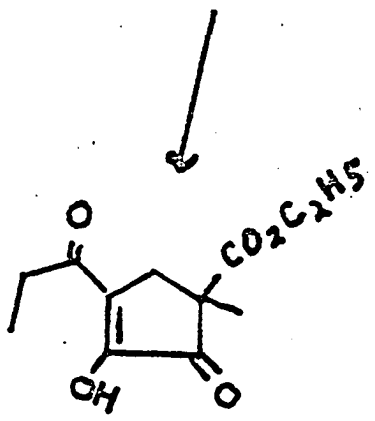
Solvent	Base	Phenol	Approximate o to p ratio
t-butanol	potassium t-butoxide	CIII	2:1
ethanol	sodium ethoxide	CIII	1:1
water	sodium hydroxide	CIII	1:2
benzene	sodium hydride	CIII	2:1
t-butanol	potassium t-butoxide	CXIV	1.2:1
ethanol	sodium ethoxide	CXIV	1:1.2
water	sodium hydroxide	CXIV	1:1.3
t-butanol	potassium t-butoxide	CXXXVII	3:1

The first attempt to prepare the cyclohexanone CXXVIII by a single step Michael condensation, ring closure, and dehydration

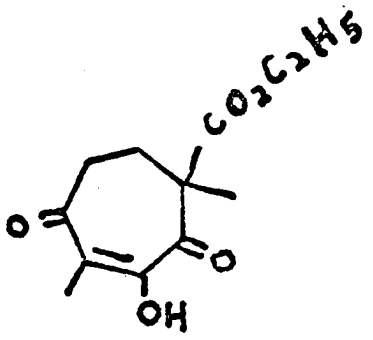
Fig. 24. Reaction Scheme



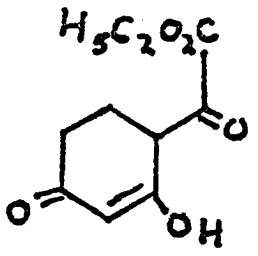
CXXIII CXXIV CXXVIII



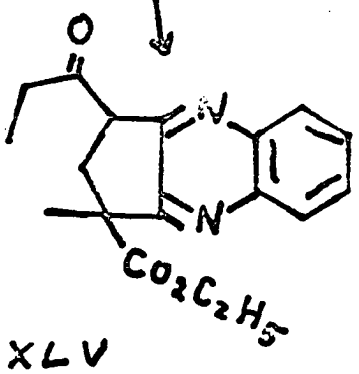
CXLII



CXLIII



CXLIV



CXLV

failed. Addition of sodium ethoxide to a mixture of methiodide CXXIII and ethyl ethoxalyl propionate CXXIV led to a product which gave a positive ferric chloride test and whose infrared spectrum (Fig. 28) exhibited strong hydroxyl absorption. It is reasonable to assume the diketone CXXV was the first product formed and cyclization of CXXV could conceivably take place at either of the carboethoxy groups, giving several β-diketones (CXLII, CXLIII, CXLIV) as possible products. The analytical data fit these postulated structures and such compounds would be expected to give a positive ferric chloride test. The nuclear magnetic resonance spectrum of the cyclized product (Fig. 32) exhibited two triplets at 71 and 74 c.p.s. (J = 7.3, 7.4 c.p.s.) and one singlet at 87.5 c.p.s. characteristic of methyl groups. This is in agreement with structure CXLII, since structures CXLIII and CXLIV should have two unsplit methyl group signals and one triplet. Also the C(4) methylene appeared as two doublets (152 and 174 c.p.s., J = 16.7) and the C(7) methylene group appeared as a quartet at 166 c.p.s. (J = 7.3 c.p.s.) respectively, as expected for LXXVII. Furthermore, the nuclear magnetic resonance spectrum (Fig. 32) of quinoxaline CXLV was almost identical with that of CXLII, except for the chemical shift of the C(3) methyl group. As its environment requires, it appeared at lower field at 97 c.p.s.

SPECTRA

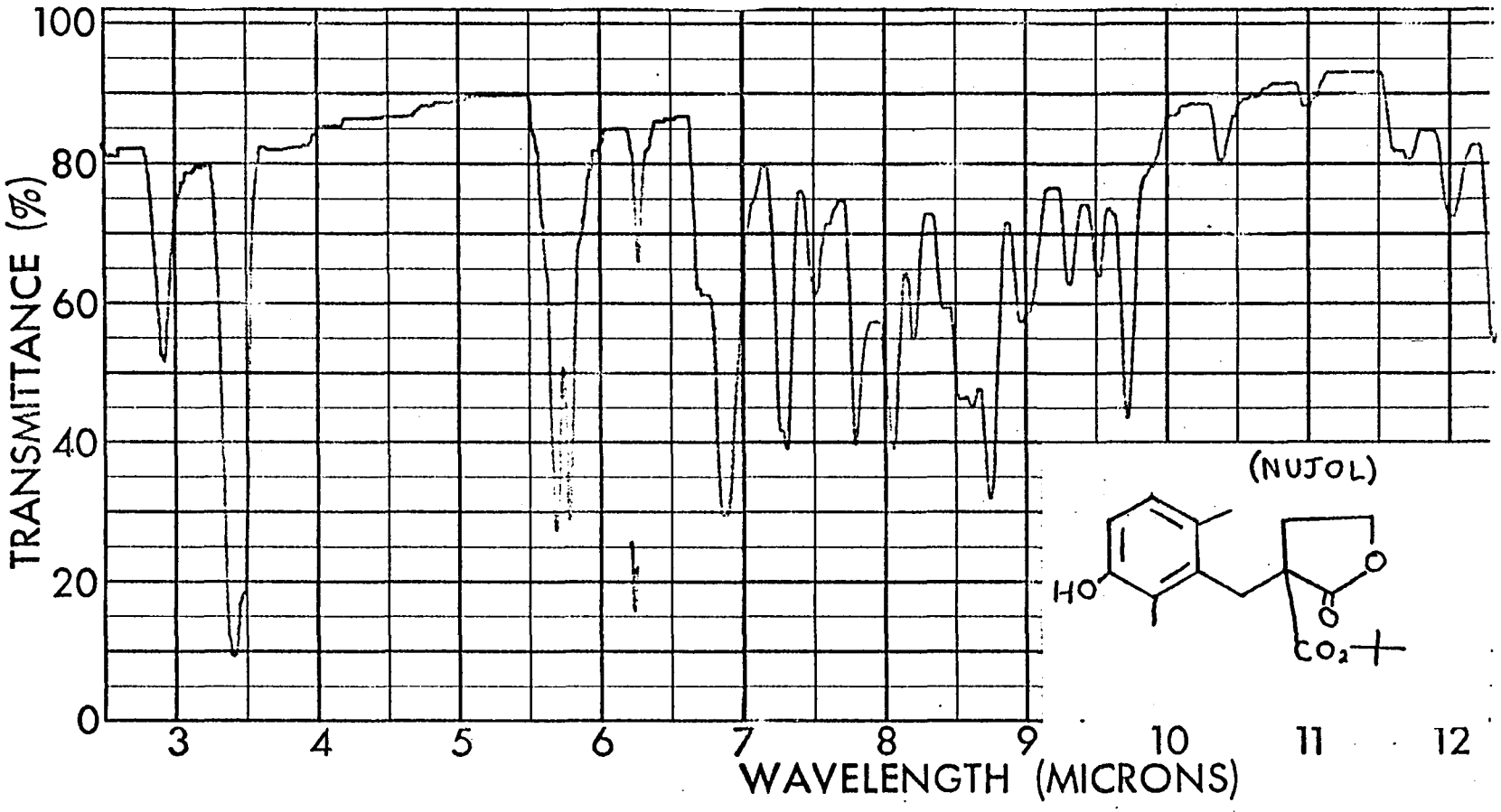


FIG. 25 INFRARED SPECTRUM

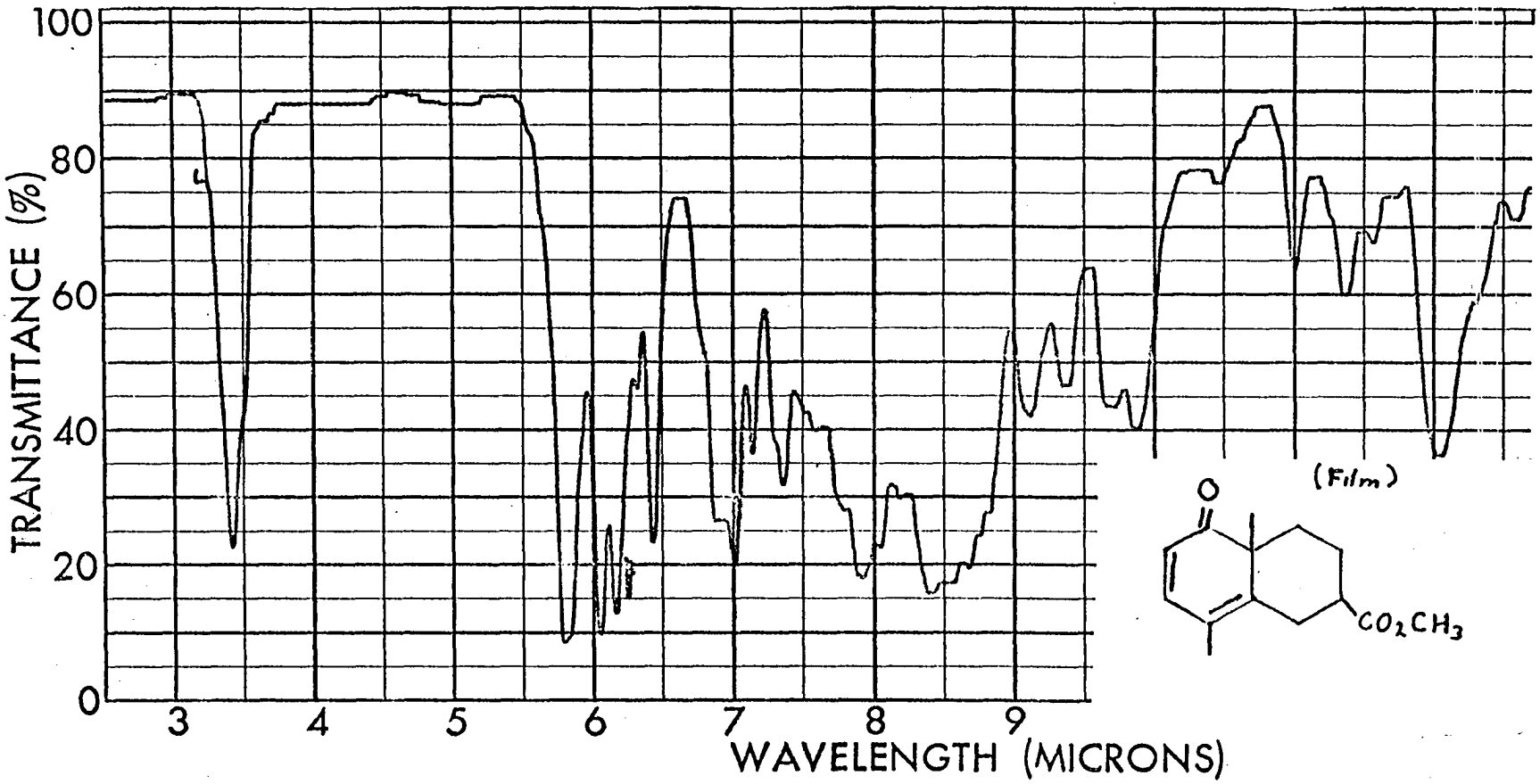


FIG. 26 INFRARED SPECTRUM

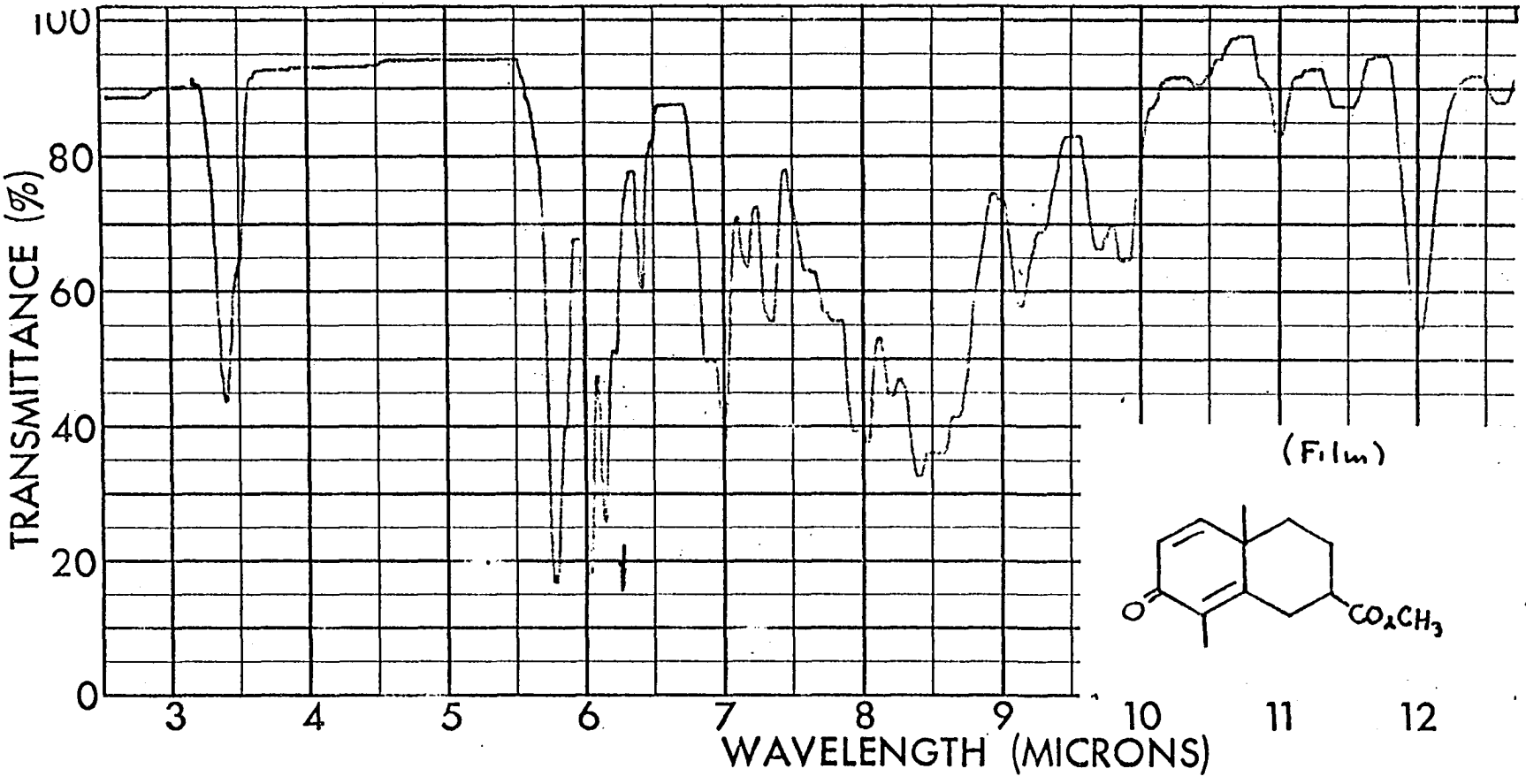


FIG. 27 INFRARED SPECTRUM

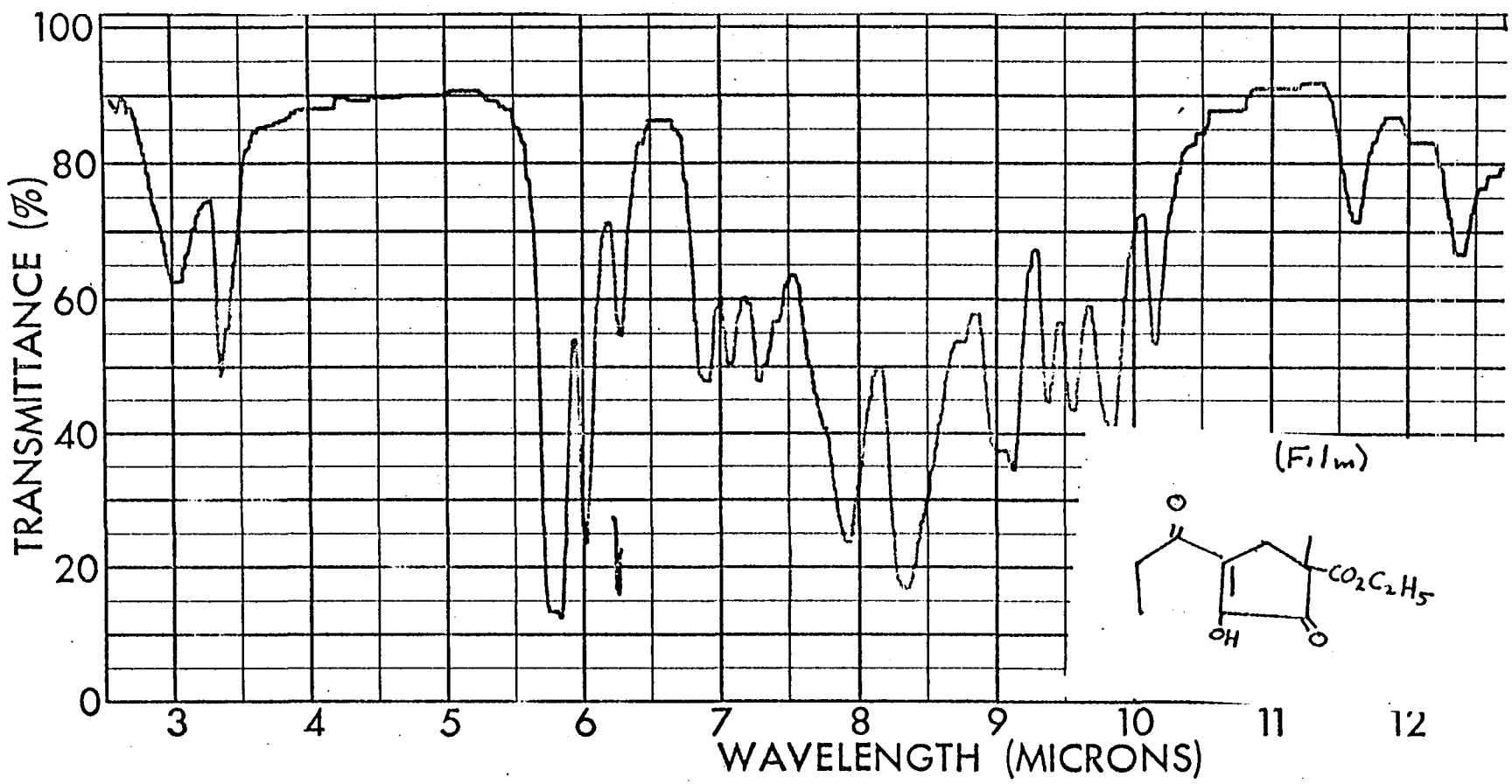


FIG. 28 INFRARED SPECTRUM

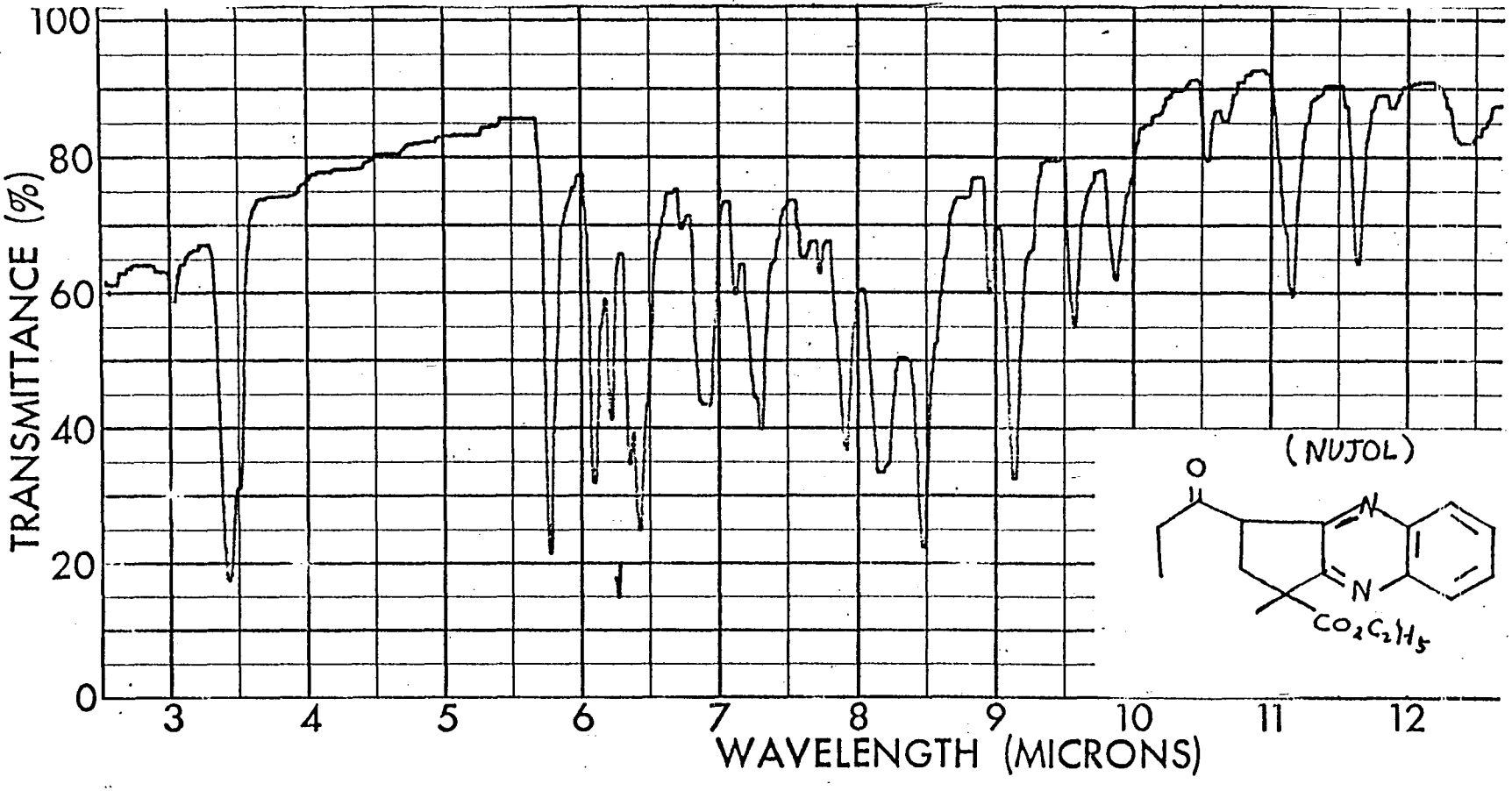


FIG. 29 INFRARED SPECTRUM

Fig. 30. Ultraviolet Spectra

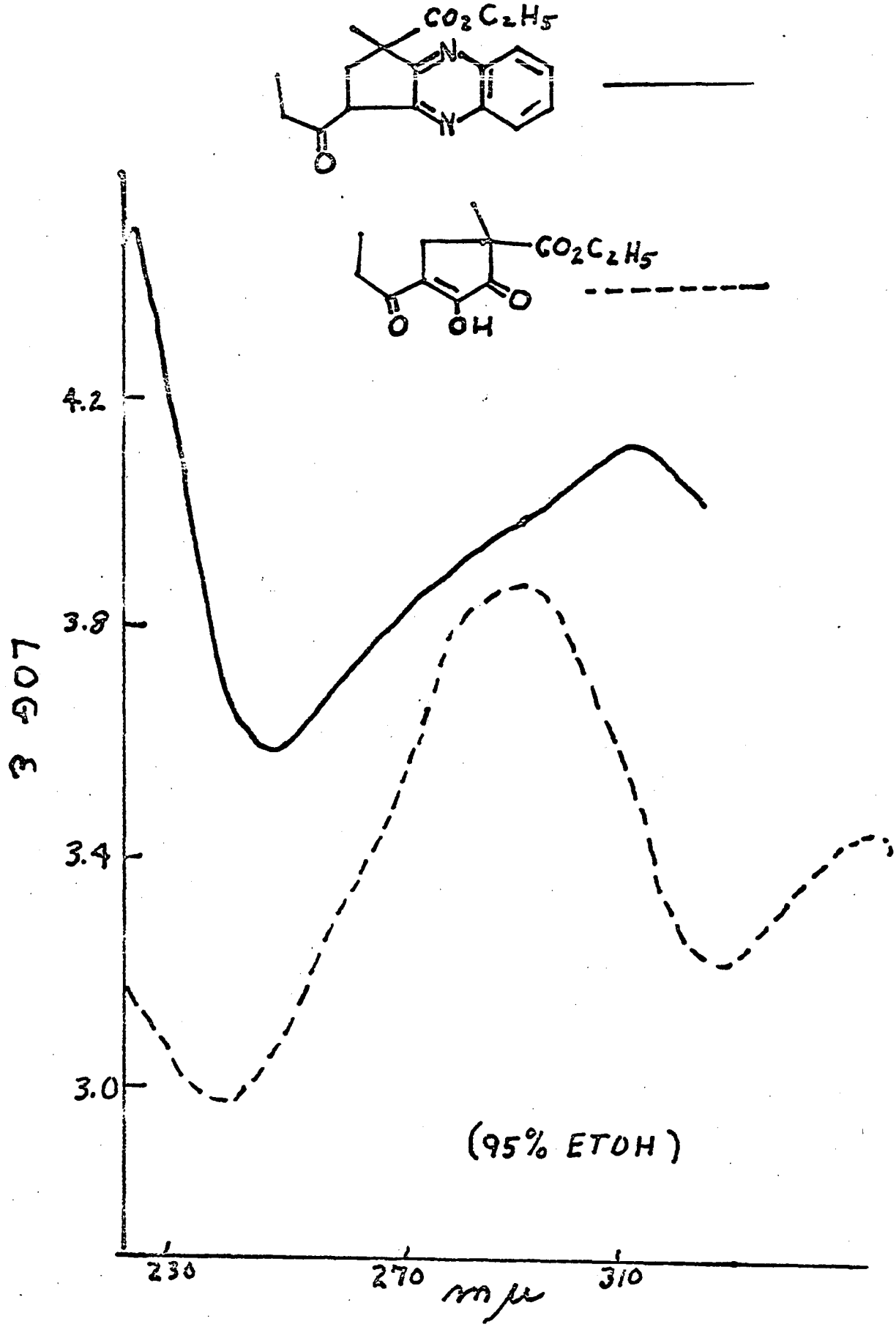

CO2C2H5
N
N
O
CO2C2H5
O
O
OH
4.2
3.8
3.4
3.0
3 907
(95% ETOH)
230
270
310
mμ

Fig. 31. Nuclear Magnetic Resonance Spectra

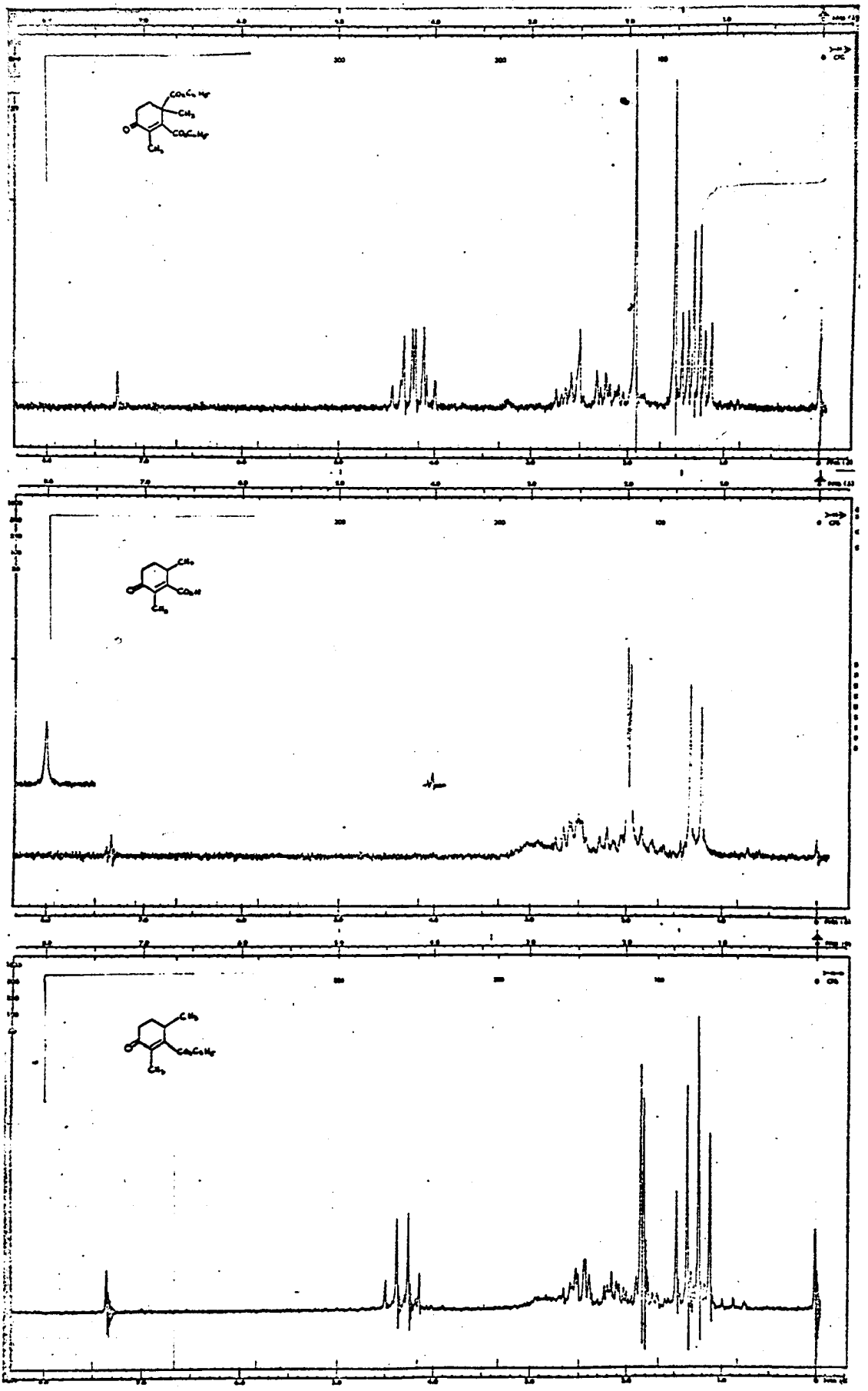
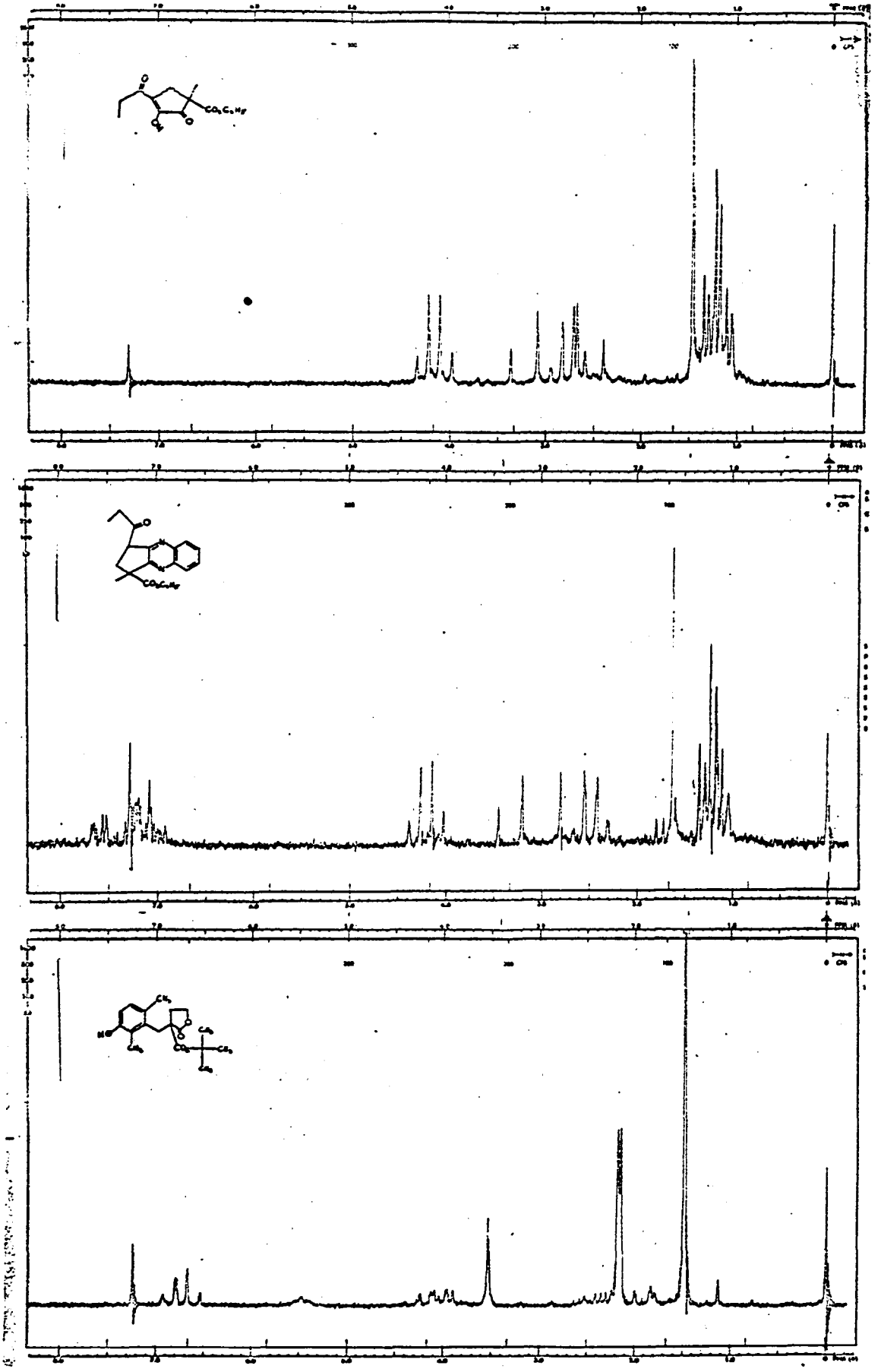


Fig. 32. Nuclear Magnetic Resonance Spectra



EXPERIMENTAL

The microanalyses were performed by Midwest Microlab, Indianapolis, Indiana; and Alfred Bernhardt of the Max Planck Institute, Mulheim (Ruhr), Germany.

The use of silica gel in the text refers to that supplied by G. F. Smith Chemical Co., Columbus, Ohio, and the thin layer silica was that supplied by Research Specialties Co., Richmond, California.

All melting and boiling points taken are uncorrected.

Ultraviolet spectra were measured in 95% ethanol solution with a Cary Model 14 spectrophotometer. All infrared spectra were taken on a Perkin-Elmer Model "Infracord" spectrophotometer. The nuclear magnetic resonance spectra were taken in deuterochloroform solution using a Varian Model A60.

β-Benzoylpropionic Acid (XCVII)

This compound, m.p. 110-113°, was prepared in 75% yield by the Friedel-Crafts reaction of succinic anhydride and benzene, according to the method of Summerville and Allen (23).

m-Hydroxy-β-benzoylpropionic Acid (C)

The synthesis employed was that of Chuang and Huang (18). β-Benzoylpropionic acid (XCVII) was nitrated. The resulting m-nitro-β-benzoylpropionic acid (XCVIII) in 47% yield, m.p.

158-161°, was reduced leading to m-amino-β-benzoylpropionic acid (XCIX), m.p. 130-131°, in 81% yield. The amine was diazotized and hydrolyzed giving m-hydroxy-β-benzoylpropionic acid (C) in 83.5% yield, m.p. 135-139° [Lit. value for nitro compound, m.p. 165-166°, amine, m.p. 130-131°, and phenol, m.p. 146-147° (18)].

γ-(m-Hydroxyphenyl)-butyric Acid (CI)

A solution of 2.85 g. (0.0147 mole) m-hydroxy-β-benzoyl-propionic acid (C) in 40 ml. of glacial acetic acid was hydrogenated over 0.30 g. of 10% palladium on charcoal at an initial pressure of 20 p.s.i. for 2 hours. The catalyst was filtered and the acetic acid removed in vacuo. The resulting oil solidified on cooling. Crystallization from benzene-cyclohexane yielded γ-(m-hydroxyphenyl)-butyric acid (CI), 1.45 g., m.p. 79-83°. On concentration of the mother liquor, an additional 0.20 g., m.p. 81-84°, was obtained (total yield of 58%). Repeated crystallization from benzene-cyclohexane gave a product melting at 84-86°.

Analysis

Calculated for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.79.

γ-(m-Hydroxyphenyl)-butanol (CII)

To a slurry of 0.45 g. (0.012 mole) of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran was added 1.0 g.

(0.0055 mole) of γ-(m-hydroxyphenyl)-butyric acid (CI) which had been dissolved in 25 ml. of anhydrous tetrahydrofuran. The mixture was refluxed for 4 hours, cooled and decomposed with acid. A crude yield of 1.0 g. of the alcohol was obtained which was used for further reactions. A small amount was distilled, b.p. 190-195°/1.5 mm.

Analysis

Calculated for $C_{10}H_{12}O_2$: C, 72.26; H, 8.49. Found: C, 72.05; H, 8.82.

γ-(m-Hydroxyphenyl)-butyl Bromide (CIII)

This compound was prepared by the method of Newman and Mekler (15). A mixture of 6 ml. of 48% hydrobromic acid, 6 ml. of syn-tetrachloroethane and 0.50 g. (0.0030 mole) γ-(m-hydroxyphenyl)-butanol (CII) was refluxed vigorously for 2 hours. The solution was cooled, extracted with ether, and the residue obtained after evaporation of the ether was distilled twice. The fraction boiling at 120-125°/1.5 mm. was collected. The yield of twice-distilled product was 0.45 g. (65%).

Cyclization of γ-(m-Hydroxyphenyl)-butyl Bromide (CIII)

With sodium ethoxide in ethanol

To a solution of 2.0 g. (0.087 mole) of sodium dissolved in 100 ml. of absolute ethanol was added 0.45 g. (0.0020 mole) of

γ-(m-hydroxyphenyl)-butyl bromide (CIII) and the resulting solution refluxed for 4 hours. The ethanol was removed in vacuo, 100 ml. of water was added and the solution was acidified with dilute hydrochloric acid. The aqueous solution was extracted with ether and the crude product, obtained after evaporation of the ether, was chromatographed on silica gel. Elution with benzene yielded 0.090 g. (23%) of an oil which after fractional crystallization yielded ar-tetrahydro-α-naphthol (CV), m.p. 64-66°, and ar-tetrahydro-β-naphthol (CIV), m.p. 61-62° Lit. value for α-isomer, m.p. 61.5-62° (24), and for β-isomer, m.p. 68.5-69° (25) . The mixed melting point of each of the above tetrahydronaphthols showed no depression and their infrared spectra were identical.

Further elution with 10% acetone-90% benzene yielded 0.15 g. (38%) of crude ethyl γ-(m-hydroxyphenyl)-butyl ether (CVI), b.p. 120°/1.5 mm.

Analysis

Calculated for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.83; H, 9.08.

In another experiment a solution of 0.826 g. (0.000380 mole of γ-(m-hydroxyphenyl)-butyl bromide (CIII) in 85 ml. absolute ethanol and 0.0180 g. (0.000730 mole) of sodium, dissolved in 1.5 ml. absolute ethanol, was refluxed for 4 hours under nitrogen and the reaction was worked up as above. The crude product was chromatographed on 10 g. of silica and eluted

with 50% benzene-50% cyclohexane. The first fractions consisted of crystalline ar-tetrahydro-α-naphthol (0.009 g.), the center fractions consisted of a mixture of the ar-tetrahydro- α and β-naphthols (0.011 g.) and the later fractions contained ar-tetrahydro-β-naphthol (0.018 g.). Based on a plot of the elution curve, approximately one mole of the α isomer was formed with each mole of the β isomer.

With aqueous sodium hydroxide

To a mixture of 70 ml. of water and 0.073 g. (0.00032 mole) of γ-(m-hydroxyphenyl)-butyl bromide (CIII) was added a solution of 0.040 g. (0.0010 mole) of sodium hydroxide in 2 ml. of water and the resulting solution refluxed under nitrogen for 4 hours. The mixture was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The crude product, after evaporation of the ether, was chromatographed on silica gel. Elution with 50% cyclohexane-50% benzene first gave fractions of crystalline ar-tetrahydro-α-naphthol (0.012 g.), then fractions containing a mixture of ar-tetrahydro-α- and β-naphthols (0.004 g.) and finally fractions containing crystalline ar-tetrahydro-β-naphthol (0.017 g.). The combined yield was 0.632 g. (67%). A plot of the elution curve showed approximately 1 mole of the α isomer formed to two moles of the β isomer.

With potassium t-butoxide in t-butyl alcohol

To a solution of 0.069 g. (0.00030 mole) of γ-(m-hydroxyphenyl)-butyl bromide (CIII) in 70 ml. of anhydrous t-butyl

alcohol was added a solution of 0.025 g. (0.00640 mole) of potassium dissolved in 4 ml. of t-butyl alcohol. The solution was refluxed under nitrogen for 4 hours. Work-up as usual, chromatography of the residue on silica and elution with 50% cyclohexane-50% benzene gave crystalline ar-tetrahydro-α-naphthol (0.024 g.), an oil (0.005 g.) consisting of a mixture of the ar-tetrahydro-α- and β-naphthols, and finally crystalline ar-tetrahydro-β-naphthol (0.007 g.). The total yield was 0.036 g. (81%). The product ratio was 2:1 of α and β isomers.

With potassium t-butoxide in anhydrous benzene

A solution of 0.170 g. (0.000740 mole) of γ-(m-hydroxyphenyl)-butyl bromide (CIII) in 100 ml. anhydrousbenzene was added to 0.153 g. (0.00148 mole) of crystalline potassium t-butyl alcohol and evaporation of the solvent in vacuo under anhydrous conditions. The resulting reaction mixture was refluxed under nitrogen for 10.5 hours and worked up as described in previous cyclizations. After silica gel chromatography there was obtained 0.024 g. of ar-tetrahydro-α-naphthol, 0.005 g. of a mixture of α and β isomers and 0.013 g. ar-tetrahydro-β-naphthol. The total yield was 0.041 g. (38%). The product ratio was 2:1 of the α and β isomers.

With sodium hydride in benzene

To a slurry of 0.048 g. (0.00021 mole) of γ-(m-hydroxyphenyl)-butyl bromide (CIII) in 40 ml. of anhydrous benzene was added 0.025 g. of 50% sodium hydride suspension in mineral oil,

and the resulting mixture was refluxed under nitrogen for 29 hours. Normal work-up and silica gel chromatography yielded 0.007 g. of ar-tetrahydro-α-naphthol, 0.002 g. of a mixture of the α and β isomers and 0.0028 g. of ar-tetrahydro-β-naphthol. The total yield was 0.012 g. (38%) and the product ration 2:1 of α and β isomers.

Attempted cyclization using potassium carbonate in anhydrous acetone

To a solution of 0.069 g. (0.0029 mole) of γ-(m-hydroxyphenyl)-butyl bromide (CIII) in 70 ml. anhydrous acetone (treated with potassium permanganate and distilled over anhydrous potassium carbonate) was added 0.085 g. (0.00061 mole) of potassium carbonate and the mixture was worked up as described above. Chromatography yielded only a trace of ar-tetrahydro-α-naphthol and mostly unchanged starting material.

m-Hydroxycinnamic Acid (CVIII)

m-Hydroxycinnamic acid was prepared in 70% yield, m.p. 191-193°, by the method of Koo et al. (26). Lit. value, m.p. 191° (27).

β-(m-Hydroxyphenyl)-propionic Acid (CIX)

When 6.5 g. (0.036 mole) of m-hydroxycinnamic acid (CVIII) was hydrogenated in glacial acetic acid over 0.6 g. of 10%

palladium on carbon at an initial pressure of 20 p.s.i., there resulted after evaporation of the acetic acid and crystallization of the residue from acetone-cyclohexane, 4.0 g. (63%) of β-(m-hydroxyphenyl)-propionic acid (CIX), m.p. 100-103° [Lit. value, m.p. 111° (28)].

β-(m-Hydroxyphenyl)-propyl Alcohol (CXIX)

A solution of 5.0 g. (0.030 mole) of β-(m-hydroxyphenyl)-propionic acid (CIX) in 50 ml. of anhydrous ether was added to a slurry of 2.5 g. (0.066 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether and the resulting mixture refluxed for 7 hours. The reaction mixture was decomposed with acid and the ethereal solution of crude product was extracted with sodium bicarbonate solution. The extract was then dried with anhydrous sodium sulfate and evaporated producing 2.6 g. (57%) of the β-(m-hydroxyphenyl)-propyl alcohol (CXIX). After several crystallizations from benzene, the alcohol had a melting point of 53.5-55°.

Analysis

Calculated for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.96; H, 8.03.

When the sodium bicarbonate extract was acidified with dilute hydrochloric acid, there was found 2.0 g. (40%) unchanged starting material.

β-(m-Hydroxyphenyl)-propyl Bromide (CXX)

This compound was prepared from the corresponding alcohol by the procedure described for the preparation of γ-(m-hydroxyphenyl)-butyl bromide (CIII). The bromide was obtained in 72% yield, b.p. 115-118°/1.5 mm.

Attempted Cyclization of β-(m-Hydroxyphenyl)-propyl Bromide (CXX)

With aqueous sodium hydroxide

A solution of 0.038 g. (0.00096 mole) of sodium hydroxide in 5 ml. of water was added to a mixture of 0.013 g. (0.000480 mole) of β-(m-hydroxyphenyl)-propyl bromide (CXX) and 95 ml. of water. The resulting reaction mixture was refluxed for 4 hours under nitrogen, acidified with dilute hydrochloric acid and extracted with ether. After evaporation of the ether, there was obtained 0.050 g. (82%) of crude β-(m-hydroxyphenyl)-propyl alcohol (CXIX), m.p. 50-54°. The infrared spectrum of the product was identical with that of an authentic sample. No trace of cyclized product was found.

With potassium t-butoxide in t-butanol

To a solution of 0.086 g. (0.00041 mole) of β-(m-hydroxyphenyl)-propyl bromide (CXX) in 70 ml. of anhydrous t-butyl alcohol there was added a solution of potassium t-butoxide, formed from 0.032 g. (0.0082 mole) potassium and 5 ml. anhydrous

t-butyl alcohol. The mixture was refluxed 24 hours under nitrogen and worked up in a manner already described. Elution of the crude product from silica gel with 50% benzene-50% cyclohexane gave mainly unchanged starting bromo compound, 0.041 g. (77%). No trace of cyclized product was found.

β-(m-Acetoxyphenyl)-propionic Acid (CX)

To a suspension of 5.0 g. (0.03 mole) of β-(m-hydroxyphenyl)-propionic acid (CIX) in 15 ml. of acetic anhydride there was added 2 drops of concentrated sulfuric acid. The solid dissolved immediately with warming. After 10 minutes the reaction mixture was poured into an ice-water mixture. Extraction and evaporation of the ether gave a residue which was chromatographed on silica gel. Elution with 5% acetone-95% benzene gave 3.0 g. (48%) of β-(m-acetoxyphenyl)-propionic acid (CX), m.p. 51.5-53° after crystallization from ligroin-ether.

Analysis

Calculated for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.22; H, 5.60.

β-(m-Acetoxyphenyl)-propionyl Chloride (CXI)

Refluxing a mixture of 1.09 g. (0.0046 mole) of β-(m-acetoxyphenyl)-propionic acid (CX), 6 ml. of thionyl chloride, and 25 ml. of cyclohexane for 2 hours and evaporation of the

solvent yielded 1.1 g. of the crude acid chloride which was not purified further but used directly in the next reaction.

1-Bromo-4-(m-acetoxyphenyl)-2-butanone (CXIII)

To a cooled solution of diazomethane from 9.0 g. of N-methyl-N-nitrosourea in 100 ml. of anhydrous ether there was added dropwise 1.1 g. of crude β-(m-acetoxyphenyl)-propionyl chloride (CXI) in 50 ml. of anhydrous ether. The solution was stirred vigorously and the temperature of the reaction kept below 5° during the addition. The mixture was allowed to stand at room temperature overnight. A solution of 48% hydrobromic acid was added dropwise and the reaction mixture stirred vigorously until the evolution of nitrogen ceased. The ethereal layer was washed with water, dried and evaporated to give a crude yellow oil. Elution from silica gel with 1% ether-99% benzene yielded 0.70 g. of 1-bromo-4-(m-acetoxyphenyl)-2-butanone (58% based on β-(m-acetoxyphenyl)-propionic acid). After several crystallizations the compound melted at 41-41.5°.

Analysis

Calculated for $C_{12}H_{13}BrO_3$: C, 50.54; H, 4.59. Found: C, 50.60; H, 4.75.

1-Bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV)

A solution of 1-bromo-4-(m-acetoxyphenyl)-2-butanone (CXIII), formed from 0.032 g. (0.0082 mole) potassium and 5 ml. anhydrous

0.40 g. (0.0014 mole), in 15 ml. of methanol was treated with 0.25 g. (0.0053 mole) of sodium borohydride. The mixture was stirred for 5 minutes while the temperature was kept at 30°. The reaction mixture was decomposed with dilute sulfuric acid and extracted with ether. The residue from evaporation of the ether was chromatographed on silica gel. Elution with 5% acetone-95% benzene yielded 0.29 g. (83%) of 1-bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV). Crystallization from benzene-cyclohexane gave a product melting at 79.5-81°.

Analysis

Calculated for $C_{10}H_{13}BrO_2$: C, 48.96; H, 5.34. Found: C, 49.45; H, 5.34.

Cyclization of 1-Bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV)

With potassium t-butoxide in t-butanol

To a solution of 0.16 g. (0.00064 mole) of 1-bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV) in 75 ml. of anhydrous t-butyl alcohol there was added 5 ml. of t-butyl alcohol containing 0.060 g. (0.0015 mole) of dissolved potassium. On addition of the t-butoxide solution a precipitate formed immediately. The resulting reaction mixture was refluxed for 60 hours under nitrogen. Work-up, as described in the previous cyclization, gave a crude product which was chromatographed on 10 g. of a mixture of 50% thin layer silica-50% celite. Elution

with 10% ethyl acetate-90% chloroform yielded 2,6-dihydroxyl-1,2,3,4-tetrahydronaphthalene (CXIV), 0.017 g., which melted at 138-140° after crystallization from benzene-cyclohexane [Lit. value, m.p. 140-144° (29)].

Further elution of the column with the same solvent system gave 0.023 g. of a mixture of CXVI and CXV and finally the latter compound itself. It melted at 147-151° after crystallization from benzene-cyclohexane.

Analysis

Calculated for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.26.

Yields corresponded approximately to 0.030 g. (28%) of 2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI) and 0.040 g. (38%) of 2,8-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXV).

With sodium hydroxide in water

To a suspension of 0.079 g. (0.0031 mole) of 1-bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV) was added 0.035 g. (0.00087 mole) of sodium hydroxide dissolved in 3.5 ml. of water. The resulting solution was refluxed for 2 hours under nitrogen, then acidified with dilute hydrochloric acid and extracted with ether. The residue was chromatographed as above. Yields amounted to 0.020 g. (38%) of 2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI) and 0.025 g. (48%) of 2,8-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXV).

With sodium ethoxide in absolute ethanol

To a solution of 0.064 g. (0.00026 mole) of 1-bromo-2-hydroxy-4-(m-hydroxyphenyl)-butane (CXIV) in 50 ml. of anhydrous ethanol was added 3 ml. of absolute ethanol containing 0.020 g. (0.00087 mole) of dissolved sodium. The resulting solution was refluxed under nitrogen for 2 hours. After acidification, extraction, and chromatography of the residue as described above, there was obtained (based on a plot of the elution curve) 0.019 g. (44%) of 2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI) and 0.014 g. (33%) of 2,8-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXV).

Conversion of 2,6-Dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI) to ar-Tetrahydro-β-naphthol (CIV)

A solution of 0.025 g. (0.00015 mole) of 2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI), 5 ml. glacial acetic acid and 0.5 ml. of 48% hydrobromic acid was refluxed for 1 hour. The reaction was cooled and extracted with ether. The crude 2-hydroxy-6-bromo-1,2,3,4-tetrahydronaphthalene (CXVII) was hydrogenated for 12 hours at a pressure of 40 p.s.i. over 0.040 g. of 5% palladium on charcoal and 0.050 g. sodium bicarbonate. After filtration and evaporation the oil was chromatographed on silica. Tetrahydro-β-naphthol, 0.005 g. (22%), m.p. 64-66° Lit. value, m.p. 68.5-69° (25), was eluted with 50% benzene-50% cyclohexane. The mixed melting point of the product with

an authentic sample was undepressed.

Conversion of 2,8-Dihydroxy-1,2,3,4-tetrahydronaphthalene (CXV) to ar-Tetrahydro-α-naphthol (CV)

This conversion to tetrahydro-α-naphthol (CV) in 15% yield, m.p. 61-62° [Lit. value, m.p. 61.5-62° (24)], was carried out in the same manner as the conversion of its isomer. The mixed melting point of the product with an authentic sample showed no depression.

1-Diethylamino-3-pentanone Methiodide (CXXIII)

Methyl iodide, 36 g., was added in portions to a vigorously shaken 36 g. (0.218 mole) of 1-diethylamino-3-pentanone (30). The oily methiodide was allowed to stand at room temperature for 1 hour. The mixture was decanted and the product washed with anhydrous ether.

Ethyl 2,6-Dioxo-3-carbethoxy-3-methyloctanoate (CXXV)

The procedure followed was that suggested by Prelog *et al.* (31).

The sodium salt of ethyl α-ethoxalylpropionate (CXXIV) (32) was prepared by adding the ester, 25.6 g. (0.128 mole), dropwise to a solution of sodium, 2.8 g. (0.12 mole), in 100

ml. of absolute alcohol. To insure complete salt formation, the resulting solution was refluxed for 5 minutes. To the stirred solution of sodio ethyl ethoxalylpropionate, maintained at a temperature of 0°, was added dropwise a solution of the above 1-diethylamino-3-pentanone methiodide (CXXIII) in 200 ml. of absolute ethanol. The solution was allowed to stand at room temperature for 12 hours and then was refluxed for 1 hour. It was poured into 500 ml. of water and extracted with 100 ml. portions of ether. Evaporation of the extract and distillation of the residue gave 20 g. (58%) of ethyl 2,6-dioxo-3-carbethoxy-3-methyloctanoate (CXXV), b.p. 125-129°/0.2 mm.

Infrared spectrum

(Film) C=O, 5.75(s)μ.

Analysis

Calculated for $C_{14}H_{22}O_6$: C, 58.73; H, 7.73. Found: C, 58.91; H, 7.69.

3-Methyl-3-carbethoxy-5-propionylcyclopentane-1,2-dione (CXLII)

A solution of sodium ethoxide, prepared from 1.1 g. (0.049 mole) of sodium dissolved in 30 ml. of absolute ethanol, was added dropwise with stirring to a solution of 6.4 g. (0.032 mole) of ethyl ethoxalylpropionate (CXXIV) and 1-diethylamino-3-pentanone methiodide (CXXIII), prepared from 5.0 g. (0.032 mole)

of 1-diethylamino-3-pentanone and 5.0 g. of methyl iodide, in 30 ml. of anhydrous benzene cooled in an ice bath. The reaction mixture was allowed to warm to room temperature over a 4 hour period, was refluxed for 0.5 hours, cooled, acidified with dilute sulfuric acid and extracted with ether. The ethereal solution was washed with water, dried with anhydrous sodium sulfate, and evaporated. Distillation of the residue yielded 2.5 g. (31%) of CXLII boiling at 132-135°/0.5 mm. It gave a strong positive ferric chloride test.

Infrared spectrum

See Fig. 28.

Ultraviolet spectrum

See Fig. 30.

Nuclear magnetic resonance spectrum

See Fig. 32.

Analysis

Calculated for $C_{12}H_{16}O_5$: C, 59.99; H, 6.72. Found: C, 60.01; H, 7.00.

The quinoxaline CXLV, prepared by heating equal weights of CXLII and o-phenylenediamine in ethanol-acetic acid on the steam bath for 5 minutes and then pouring the reaction mixture into water, was crystallized from cyclohexane. It had a m.p. 127-129°.

Infrared spectrum

See Fig. 29.

Ultraviolet spectrum

See Fig. 30.

Nuclear magnetic resonance spectrum

See Fig. 32.

Analysis

Calculated for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.79; H, 6.37; N, 8.19.

2,4-Dimethyl-3-carboxy-2-cyclohexen-1-one (CXXVII)

The procedure used was that suggested by Prelog et al. (31).

A solution of 20 g. (0.068 mole) of ethyl 2,6-dioxo-3-carbethoxy-3-methyloctanoate (CXXV) in 125 ml. of acetic acid and 90 ml. of concentrated hydrochloric acid was refluxed for 24 hours. Evaporation of the solvent in vacuo yielded a residual oil which solidified on standing. The residue was taken up in ether and the ethereal solution extracted with sodium bicarbonate solution. Evaporation of the ether and distillation of the residual oil yielded 2.5 g. (19%) of 2,4-dimethyl-3-carbethoxy-2-cyclohexen-1-one (CXXVI), b.p. 92-94°/0.3 mm.

Infrared spectrum

(CCl_4) C=O, 5.83(s)μ, 5.93(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 240 mμ (log ε 4.0).

Nuclear magnetic resonance spectrum

See Fig. 31.

The sodium bicarbonate extract was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the extract and crystallization of the residue from benzene-cyclohexane yielded 6.6 g. (59%) of 2,4-dimethyl-3-carboxy-2-cyclohexen-1-one (CXXVII), m.p. 131-133°.

Infrared spectrum

(Nujol) C=O, 5.95(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 244 mμ (log ε 4.02).

Nuclear magnetic resonance spectrum

See Fig. 31.

Analysis

Calculated for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.87; H, 7.26.

The methyl ester was prepared by adding an ethereal solution of diazomethane to the acid. It was used in crude form for further reactions.

2,4-Dimethyl-3,4-dicarbethoxy-2-cyclohexen-1-one

(CXXVIII)

A solution of 20 g. (0.068 mole) of ethyl 2,6-dioxo-3-carbethoxy-3-methyloctanoate (CXXV) was refluxed for 5 hours with 11.6 g. (0.068 mole) of p-toluenesulfonic acid in 100 ml. of anhydrous benzene in the presence of a water separator. The solution was cooled, washed with water, dried and evaporated in vacuo. Distillation of the residual dark brown oil yielded 10 g. (54%) of 2,4-dimethyl-3,4-dicarbethoxy-2-cyclohexen-1-one (CXXVIII), b.p. 136-138°/0.8 mm.

Infrared spectrum

(Liquid film) C=O, 5.81(s)μ, 5.95(s)μ.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 240 mμ (log ϵ 4.0).

Nuclear magnetic resonance spectrum

See Fig. 31.

Analysis

Calculated for $C_{14}H_{20}O_5$: C, 62.66; H, 7.51. Found: C, 62.27; H, 7.61.

The above product could be converted also to 2,4-dimethyl-3-carboxy-2-cyclohexen-1-one (CXXVII) and its ester by refluxing with acetic and hydrochloric acids under the conditions described above.

Ethyl 2,6-Dimethyl-3-hydroxybenzoate (CXXIX)

The procedure used was that suggested by Clemo and McQuillin (33).

A mixture of 0.40 g. of 30% palladium on carbon and 1.0 g. (0.0051 mole) of 2,4-dimethyl-3-carbethoxy-2-cyclohexen-1-one (CXXVI) was heated under nitrogen in a Wood's metal bath at 230-240° for 45 minutes. The cooled mixture was taken up in ether, the catalyst filtered and the solution evaporated. There was obtained 0.90 g. of crude ethyl 2,6-dimethyl-3-hydroxybenzoate (CXXIX).

Infrared spectrum

(Film) OH, 2.9(m)μ; C=O, 5.8(s)μ; C=C, 6.28(s)μ.

2,6-Dimethyl-3-benzyloxybenzyl Alcohol (CXXXI)

A mixture of 0.90 g. (0.0046 mole) of crude ethyl 2,6-dimethyl-3-hydroxybenzoate (CXXIX), 25 ml. of anhydrous acetone, 2 ml. of benzyl chloride, and 15 g. of anhydrous potassium carbonate was filtered and the acetone was evaporated to give crude ethyl 2,6-dimethyl-3-benzyloxybenzoate (CXXX). The crude product was treated with 0.70 g. (0.020 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether for 6 hours. Normal work-up gave a partially crystalline residue. Chromatography of the crude product on silica gel and elution with 100:1 acetone-benzene yielded 0.65 g. (52%, based on 2,4-

dimethyl-3-carbethoxy-2-cyclohexen-1-one) of 2,6-dimethyl-3-benzyloxybenzyl alcohol (CXXXI) which melted at 79-80° after several crystallizations from cyclohexane.

Infrared spectrum

(Nujol) OH, 3.02(w)μ; C=C, 6.31(w)μ.

Analysis

Calculated for $C_{16}H_{18}O_2$: C, 79.31; H, 7.48. Found: C, 79.29; H, 7.51.

2,6-Dimethyl-3-benzyloxybenzyl Chloride (CXXXII)

Thionyl chloride, 5 ml., was added dropwise to a stirred solution of 5 g. (0.020 mole) of crude 2,6-dimethyl-3-benzyl oxybenzyl alcohol (CXXXI) in 50 ml. of anhydrous ether cooled in an ice bath. The reaction mixture was allowed to stand for 6 hours in the refrigerator and then was poured into an ice-water mixture. The ether layer was separated, washed with water and sodium bicarbonate solution, dried with anhydrous sodium sulfate and evaporated. The residue solidified on cooling and yielded 4.5 g. (85%) of 2,6-dimethyl-3-benzyloxy-benzyl chloride (CXXXII), m.p. 63-64° after crystallization from ligroin.

Analysis

Calculated for $C_{16}H_{17}ClO$: C, 73.69; H, 6.57. Found: C, 74.12; H, 6.74.

α-Carbo-t-butoxy-γ-butyrolactone (CXXXIII)

The procedure used was that suggested by Traube and Lehman (34).

A suspension of the potassium salt of di-t-butyl malonate was prepared by adding 12 g. (0.056 mole) of di-t-butyl malonate (35) to a solution of 2.3 g. (0.59 mole) of potassium dissolved in 40 ml. of anhydrous t-butyl alcohol. The mixture was refluxed 15 minutes, cooled to room temperature, 2.5 g. (0.057 mole) of ethylene oxide was added in one portion and the reaction mixture was shaken by hand for 10 minutes until it solidified. The reaction mixture was allowed to stand at room temperature overnight. The solid was dissolved in dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with sodium bicarbonate, dried over potassium carbonate and the orange oil, obtained after evaporation of the ether, was distilled, giving 6.6 g. (61%) of α-carbo-t-butoxy-γ-butyrolactone (CXXXIII), b.p. 102-103°/0.5 mm.

Infrared spectrum

(Film) C=O, 5.65(s)μ, 5.85(s)μ.

Analysis

Calculated for $C_9H_{14}O_4$: C, 58.05; H, 7.59. Found: C, 57.69; H, 7.37.

α-Carbo-t-butoxy-α-(2,6-dimethyl-3-benzyloxybenzyl)-butyrolactone (CXXXIV)

To a suspension of 0.42 g. (0.017 mole) of sodium hydride in 40 ml. of anhydrous toluene was added 3.0 g. (0.016 mole) of α-carbo-t-butoxy-γ-butyrolactone CXXXIII at such a rate that the hydrogen evolution did not become too vigorous. 2,6-Dimethyl-3-benzyloxybenzyl chloride (CXXXII), 4.3 g. (0.017 mole), was added in one portion and the mixture refluxed for 24 hours. Water was added to the cooled mixture and the toluene layer dried with sodium sulfate and evaporated in vacuo. An oily product partially solidified on cooling. It was heated with 15 ml. of ligroin, cooled and the crystals filtered, giving 5.2 g. (72%) of α-carbo-t-butoxy-α-(2,6-dimethyl-3-benzyloxybenzyl)-γ-butyrolactone (CXXXIV), m.p. 115-120°. After several crystallizations from ligroin a product melting at 121-123° was obtained.

Infrared spectrum

(Nujol) C=O, 5.68(s)μ, 5.78(s)μ; C=C, 6.3(m)μ.

Analysis

Calculated for $C_{25}H_{32}O_5$: C, 73.14; H, 7.31. Found: C, 73.39; H, 7.44.

α-Carbo-t-butoxy-α-(2,6-dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXV)

When 1.0 g. (0.024 mole) of α-carbo-t-butoxy-α-(2,6-dimethyl-3-benzyloxybenzyl)-γ-butyrolactone (CXXXIV), dissolved in 50 ml. of acetone and 50 ml. ethanol, was hydrogenated in a Parr apparatus at an initial pressure of 30 p.s.i., hydrogen uptake was complete in one hour. The catalyst was filtered and the solvent evaporated in vacuo yielding 0.70 g. (88%) of α-carbo-t-butoxy-α-(2,6-dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXV), m.p. 130-135°. After several crystallizations from cyclohexane the compound melted at 144-146°.

Infrared spectrum

See Fig. 25.

Nuclear magnetic resonance spectrum

See Fig. 32.

Analysis

Calculated for $C_{18}H_{26}O_5$: C, 67.48; H, 7.55. Found: C, 67.31; H, 7.62.

α-(2,6-Dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXVI)

A solution of 0.70 g. (0.0022 mole) of crude α-carbo-t-butoxy-α-(2,6-dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXV)

in 25 ml. of toluene was refluxed with 0.050 g. (0.00029 mole) of p-toluenesulfonic acid for 24 hours. Water was added and the toluene layer separated and dried with sodium sulfate. Evaporation of the toluene in vacuo yielded an oily solid from which, after one crystallization from ethanol-water, 0.450 g. (83%) of α-(2,6-dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXVI), m.p. 160-165°, was obtained. Several crystallizations from ethanol-water raised the melting point to 181-183°.

Infrared spectrum

(Nujol) OH, 3.05(m)μ; C=O, 5.78(s)μ; C=C, 6.3(w)μ.

Analysis

Calculated for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.39; H, 7.35.

2,4-Dimethyl-3-(β-carbomethoxy-δ-bromobutyl)-phenol (CXXXVII)

A solution of 0.60 g. (0.0027 mole) of α-(2,6-dimethyl-3-hydroxybenzyl)-γ-butyrolactone (CXXXVI) in 30 ml. of absolute methanol, was saturated at 0° with anhydrous hydrogen bromide and allowed to stand in the refrigerator for 6 hours. The reaction mixture was poured into an ice-water mixture and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution, dried and evaporated giving 0.65 g. (76%) of crude 2,4-dimethyl-3-(β-carbomethoxy-δ-bromobutyl)-phenol

(CXXXVII) as an oil. It decomposed slowly on standing.

Infrared spectrum

($CHCl_3$) C=O, 5.8(s)μ.

Cyclization of 2,4-Dimethyl-3-(β-carbomethoxy-δ-bromobutyl)-phenol (CXXXVII)

To a solution of 0.500 g. (0.00158 mole) of crude 2,4-dimethyl-3-(β-carbomethoxy-δ-bromobutyl)-phenol (CXXXVII) in 100 ml. of anhydrous t-butyl alcohol there was added 4 ml. of anhydrous t-butyl alcohol containing 0.075 g. (0.00101 mole) of dissolved potassium. The mixture was refluxed for 24 hours under nitrogen. Water was added and the mixture was extracted with ether. Evaporation of the solvent yielded 0.200 g. of a bright yellow oil which was chromatographed on 10 g. of silica gel. Elution with 1:1 chloroform-cyclohexane produced 0.058 g. (16%) 5,6,7,8-tetrahydro-4,8a-dimethyl-6-carbomethoxy-1(4aH)-naphthalenone (CXXXVIII) as a yellow oil.

Infrared spectrum

See Fig. 26.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 328 mμ (log ε 3.54).

The dinitrophenylhydrazone CXL crystallized from methanol-chloroform.

Analysis

Calculated for $C_{20}H_{26}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.90; H, 5.56; N, 13.69.

Continued elution with 1:1 chloroform-cyclohexane gave 0.043 g. (11.6%) of amixture of the two dienones followed by 0.025 g. (6.7%) of 5,6,7,8-tetrahydro-1,4a-dimethyl-7-carbomethoxy-2(4aH)-naphthalenone (CXXXIX) as a yellow oil.

Infrared spectrum

See Fig. 27.

Ultraviolet spectrum

(95% Ethanol) λ_{max} 238 mμ (log ϵ 3.84), $\lambda_{shoulder}$ 265 mμ (log ϵ 3.68).

The 2,4-dinitrophenylhydrazone CXLI was crystallized from chloroform-methanol producing blood red crystals, m.p. 215-218°.

Analysis

Calculated for $C_{20}H_{26}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.89; H, 5.71; N, 13.51.

SUMMARY

The base-catalyzed cyclization of m-substituted phenols to bicyclo[4,4,0]decane systems was investigated.

Cyclization of γ-(m-hydroxyphenyl)-butyl bromide (CIII) gave ar-tetrahydro-α-naphthol (CV) and ar-tetrahydro-β-naphthol (CIV).

Cyclization of 1-bromo-2-hydroxy-4-(m-hydroxyphenyl)-butyl bromide (CXIV) gave a mixture of 2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXVI) and 2,8-dihydroxy-1,2,3,4-tetrahydronaphthalene (CXV).

Cyclization of 2,4-dimethyl-3-(β-carbomethoxy-δ-bromobutyl)-phenol (CXXXVII) gave 5,6,7,8-tetrahydro-4,8a-dimethyl-6-carbomethoxy-1(8aH)-naphthalenone (CXXXVIII) and 5,6,7,8-tetrahydro-1,4a-dimethyl-7-carbomethoxy-2(4aH)-naphthalenone (CXXXIX).

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