1954

Studies in the oxindole series

Theodore Leslie Reid
Iowa State College

STUDIES IN THE OXINDOLE SERIES

by

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A Dissertation Submitted to the
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The Requirements for the Degree of
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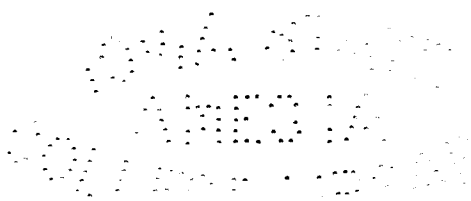

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ACKNOWLEDGEMENT

The author wishes to express his appreciation to Dr. Ernest Wenkert for the many stimulating discussions and for the helpful advice rendered during the course of these investigations. He also wishes to acknowledge the liberal assistance of his wife Minerva Reid in compiling this thesis.

DEDICATION

To the memory of

Leslie F. Reid

INTRODUCTION

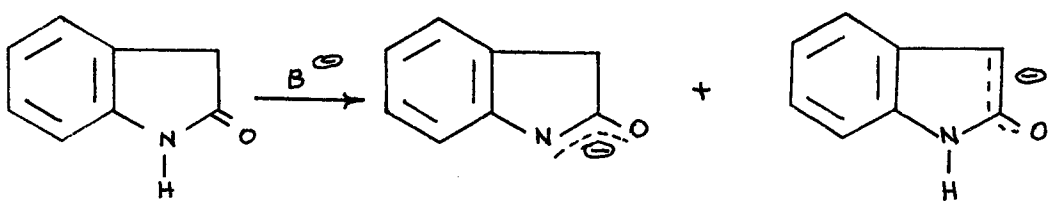
The literature on the alkylation of oxindoles is quite extensive and sometimes contradictory. One area which requires clarification is that of O-alkylation and C-alkylation of oxindole derivatives. The reinvestigation of the alkylation of oxindoles and further extension of some of these reactions is important for the purpose of the reinterpretation of possibly incorrect structures in this field. Furthermore, the recent reports indicating that several alkaloids, notably gelsemine, contain the oxindole moiety, necessitate a general survey of alkylations of simple oxindoles in order to assist in the elucidation of the structures of these compounds, and in the synthesis of their degradation products as well as the alkaloids themselves.

HISTORICAL

Alkylation

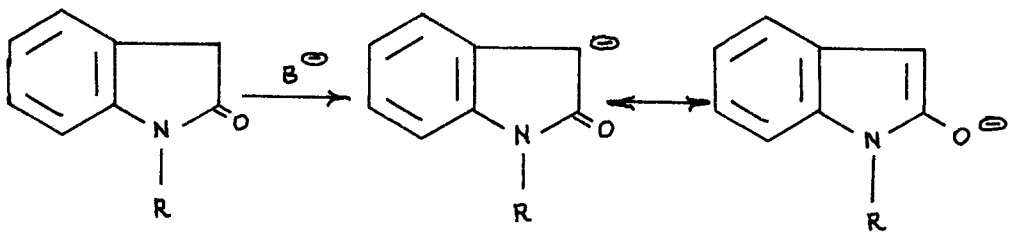
The alkylation of oxindole and its derivatives may be considered to take place by the attack of an anion, formed from the action of a base on the oxindole, on an alkyl halide. Whether C-alkylation, O-alkylation or N-alkylation occurs depends on the oxindole derivative used, the reactivity of the alkyl halide, and the experimental conditions.

The action of a base on oxindole (I) would produce anions which could best be represented by structures IIa and IIb. In such a case one could expect N-alkylation, O-alkylation or C-alkylation.



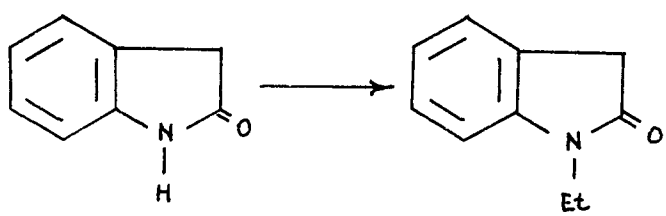
I IIa IIb

If an N-substituted oxindole (III) were used, the action of a base would produce an anion of which two main resonance contributors are IVa and IVb. In such a case one could expect C-alkylation or O-alkylation.



III IVa IVb

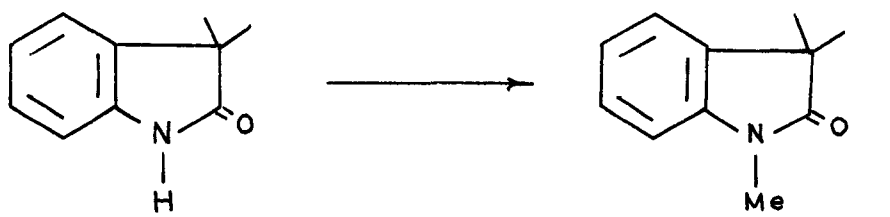
Baeyer and Comstock[1] report the first studies of alkylation in the oxindole series. From the reaction of oxindole (I) with ethyl iodide in sodium ethoxide solution, they isolated 1-ethyloxindole (V).



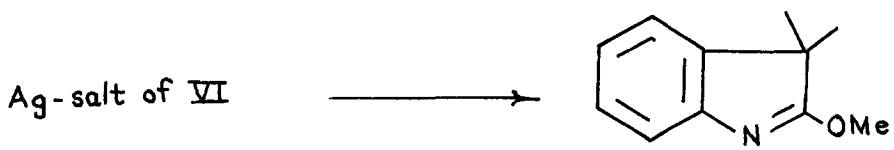
I V

[1]A. Baeyer and W. J. Comstock, Ber., 16, 1704-11 (1883).

Brunner[2] alkylated 3,3-dimethyloxindole (VI) with methyl iodide in sodium methoxide solution to yield 1,3,3-trimethyloxindole (VII). However, when the silver salt of VI was reacted with methyl iodide in ether, an O-alkylated compound, 2-methoxy-3,3-dimethylindolenine (VIII), was formed.



VI VII



VIII

The first instance of C-alkylation of oxindoles was reported by Brunner[3] who alkylated 3-methyloxindole (IX)

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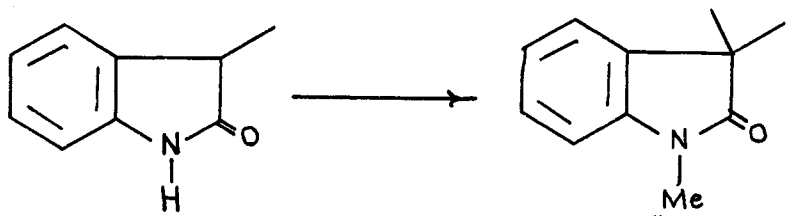
[2]K. Brunner, Monatsh., 18, 95-122 (1897).

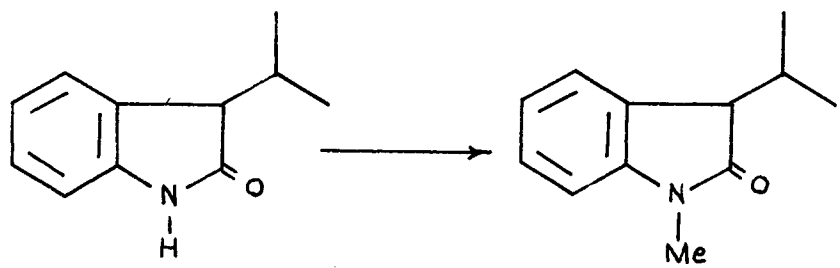
[3]K. Brunner, Monatsh., 18, 527-49 (1897).

by the action of methyl iodide in sodium methoxide to yield 1,3,3-trimethyloxindole (VII).



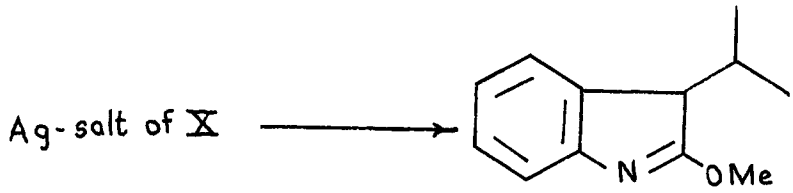
IX VII

Further alkylations were those of Schwarz[4] who prepared 1-methyl-3-isopropyloxindole (XI) by treating 3-isopropyloxindole (X) with methyl iodide in sodium methoxide solution. However, if the silver salt of X was reacted with methyl iodide in ether, Schwarz reported an O-alkylated product, 2-methoxy-3-isopropylindolenine (XII).



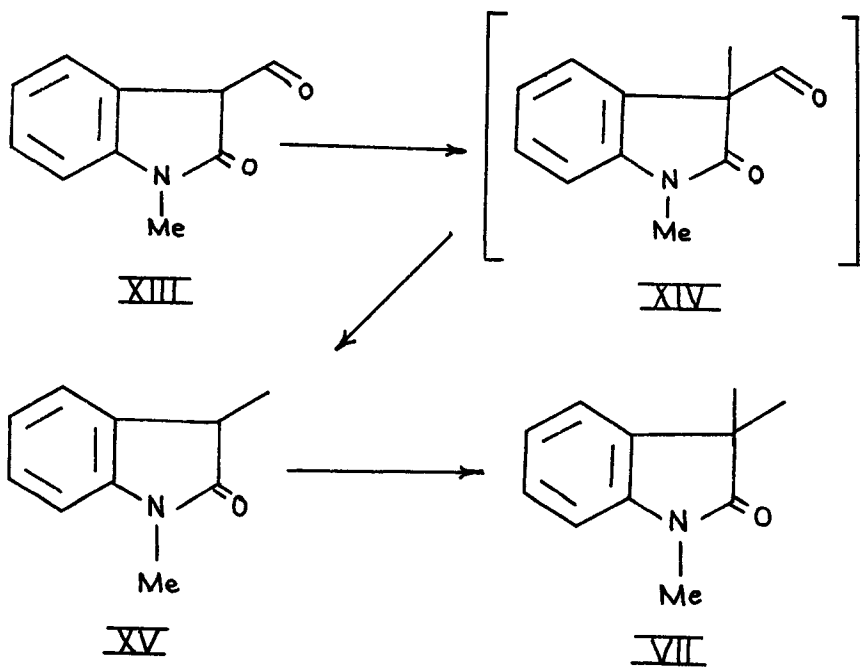
X XI

[4] H. Schwarz, Monatsh., 24, 568-78 (1903).



XII

Julian and co-workers[5] were able to carry out the alkylation of 1-methyl-3-formyloxindole (XIII) with methyl iodide to give either 1,3-dimethyloxindole (XV), or 1,3,3-trimethyloxindole (VII) depending on the amount of sodium methoxide used.



XIII XIV XV VII

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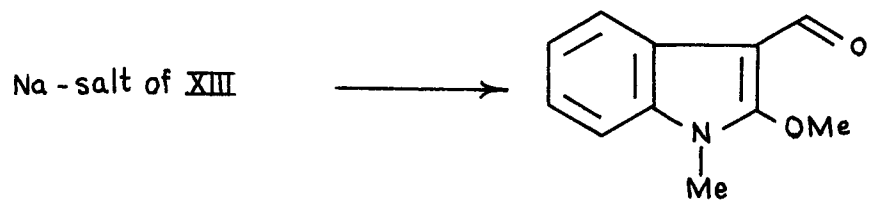
[5] P. L. Julian, J. Pikl and D. Boggess, J. Am. Chem. Soc., 56, 1797-801 (1934).

Julian and co-workers[5] were unable to isolate any of the C-alkylated aldehyde (XIV), which he postulated as an intermediate, and attributed this to the ease of hydrolysis of the compound.

In further alkylation studies of 1-methyl-3-formyloxindole (XIII), Julian and co-workers[5] reported that reaction of the sodium salt of 1-methyl-3-formyloxindole (XIII) with methyl iodide in acetone yielded an O-methyl derivative, 1-methyl-2-methoxy-3-formylindole (XVI).



XVI

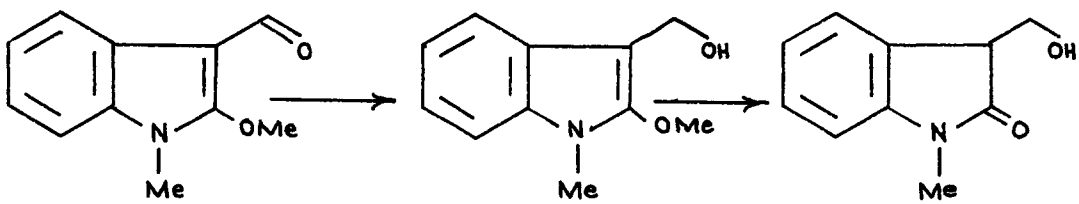
The structure assignment for XVI was based on the aldehyde-properties of the compound, such as the formation of a sodium bisulfite addition complex, and the methoxyl analysis.

The 2-ethoxy compound corresponding to XVI could be prepared in a similar fashion by using ethyl iodide (5). The

2-ethoxy derivative could also be prepared by refluxing XVI with ethanol[5].

Attempts to make the 2-methoxy derivative of 3-formyloxindole (XVII) were unsuccessful[6].

Julian and co-workers[7] reported the catalytic reduction of XVI over palladium to yield 1-methyl-2-methoxyindole-3-carbinol (XVIII), which was readily hydrolyzed to 1-methyloxindole-3-carbinol (XIX).



XVI XVIII XIX

Direct alkylation was applied in the formation of 1,3-dimethyloxindolyl-3-acetonitrile (XX) from 1,3-dimethyloxindole (XV) and chloroacetonitrile[5].

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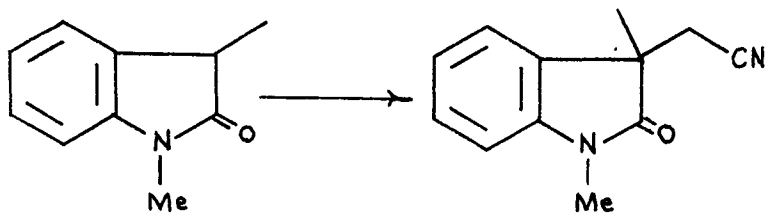
[6]P. L. Julian and H. C. Printy in R. C. Elderfield, "Heterocyclic Compounds," Volume III, John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, p. 154.

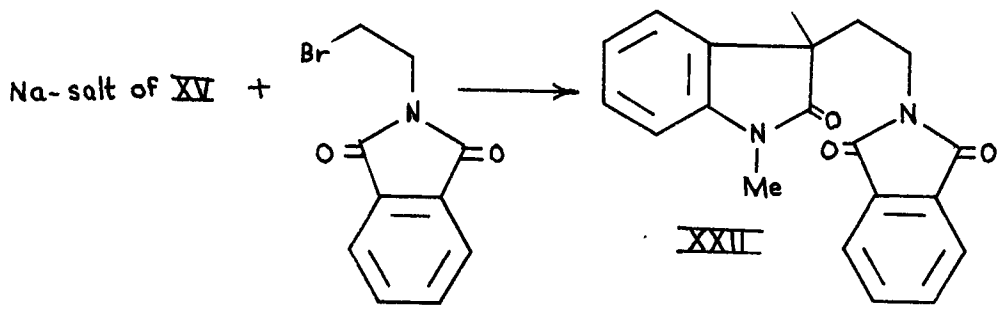
[7]P. L. Julian, J. Pikl and F. E. Wantz, J. Am. Chem. Soc., 57, 2026-9 (1935).



XV XX

The same procedure was successful in the alkylation of 1-methyloxindole (XXI) with chloroacetonitrile but was unsuccessful in the alkylation of oxindole (I) with chloroacetonitrile[8].

In another series of experiments, Julian and Pikl[9] extended the alkylation of 1,3-dimethyloxindole (XV) to the preparation of 1,3-dimethyl-3-β-phthalimidoethyloxindole (XXII). This was done by refluxing an ethereal suspension of the sodium salt of XV with phthalimidoethyl bromide.



XXII

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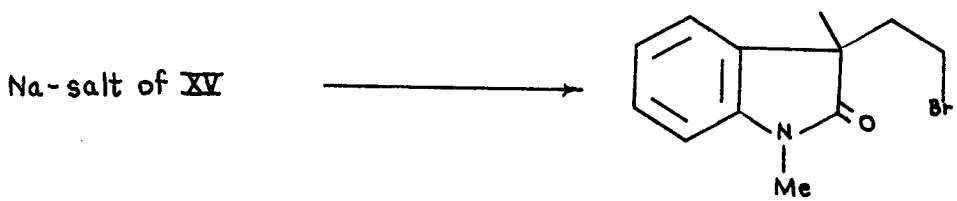
[8]P. L. Julian in R. C. Elderfield, "Heterocyclic Compounds," Volume III, John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, p. 171.

[9]P. L. Julian and J. Pikl, J. Am. Chem. Soc., 57, 539-44 (1935).

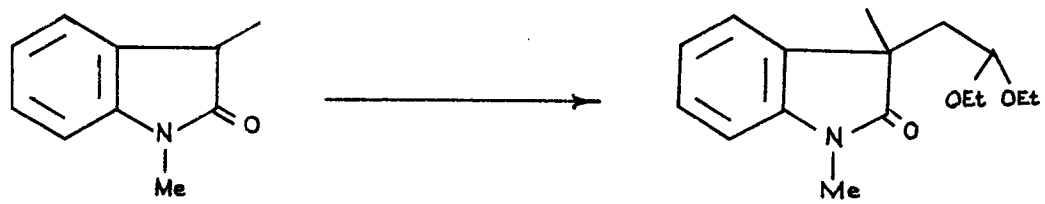
A further extension of the alkylation of 1,3-dimethyloxindole (XV) was carried out by Julian and Pikl[9] who prepared 1,3-dimethyl-3-β-bromoethyloxindole (XXIII) from the sodium salt of XV and ethylene bromide.



XXIII

By an analogous procedure using 1,3-dimethyl-5-ethoxyoxindole, Julian and Pikl[10] prepared the 5-ethoxy derivative of XXIII.

In connection with a proposed synthesis of oxytryptophan, Julian and co-workers[7] alkylated 1,3-dimethyloxindole (XV) with bromoacetal to yield 1,3-dimethyloxindolylacetal (XXIV).

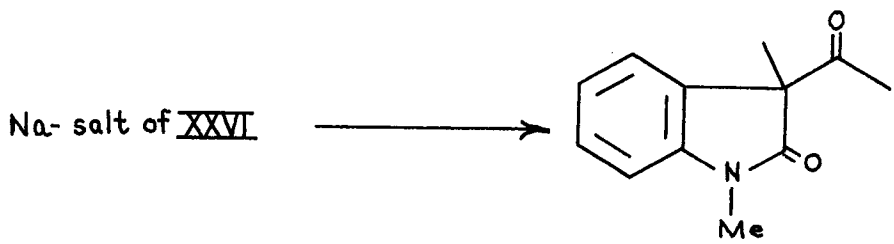


XV XXIV

[10] P. L. Julian and J. Pikl, J. Am. Chem. Soc., 57, 755-7 (1935).

However, attempted alkylations of oxindole (I) and 1-methyloxindole (XXI) with bromoacetal were unsuccessful[7] as was an attempted alkylation of 3-acetyloxindole (XXV) with bromoacetal[8].

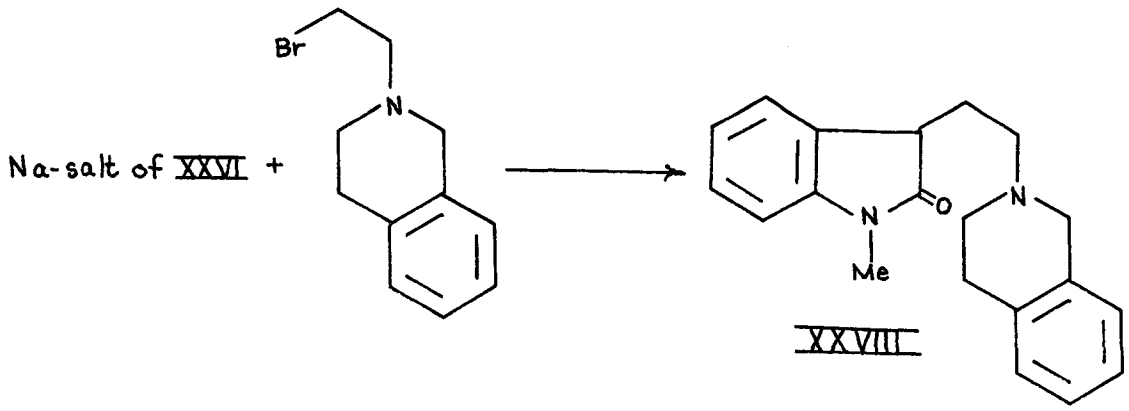
When Julian and co-workers[7] treated the sodium salt of 1-methyl-3-acetyloxindole (XXVI) with methyl iodide in acetone, a procedure which yielded an O-methyl derivative (XVI) with 1-methyl-3-formyloxindole (XIII), a C-alkyl derivative (XXVII) was obtained.



XXVII

This led to the utilization of this method to prepare several 1-methyl-3-monoalkyloxindoles, as the acetyl group of compounds such as XXVII could be readily removed by hydrolysis with sodium ethoxide.

Julian and co-workers[11] prepared 1-methyl-3-(2-N-tetrahydroisoquinolylethyl)-oxindole (XXVIII), from the sodium salt of 1-methyl-3-acetyloxindole (XXVI) and 1-bromo-2-N-tetrahydroisoquinolylethane in acetone.



The preparation of 1-methyl-3-(2-bromoethyl)-oxindole (XXX) by Julian and co-workers[11] involved the reaction, in acetone, of the sodium salt of 1-methyl-3-acetyloxindole (XXVI) with β-phenoxyethyl bromide to form, after hydrolysis, 1-methyl-3-(2-phenoxyethyl)-oxindole (XXIX). The phenoxy group of XXIX was then replaced by bromine, using HBr, to form XXX.

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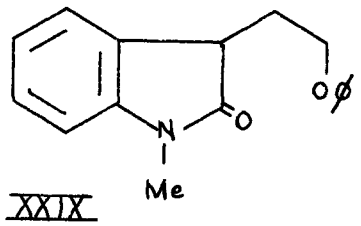
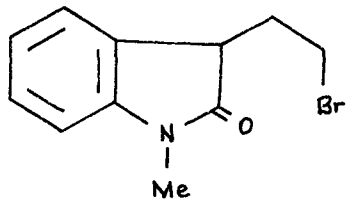
[11] P. L. Julian, A. Magnani, J. Pikl and W. J. Karpel, J. Am. Chem. Soc., 70, 174-9 (1948).

Na - salt of XXVI

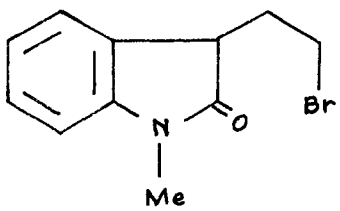


XXIX

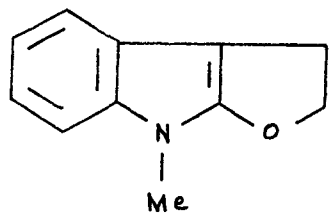


XXX

On treatment with sodium ethoxide, or tetrahydroisoquinoline in the cold, 1-methyl-3-(2-bromoethyl)-oxindole (XXX) formed 2,3-dihydro-8-methylfuro [2,3-b] indole (XXXI), which process is an example of intramolecular O-alkylation[11].

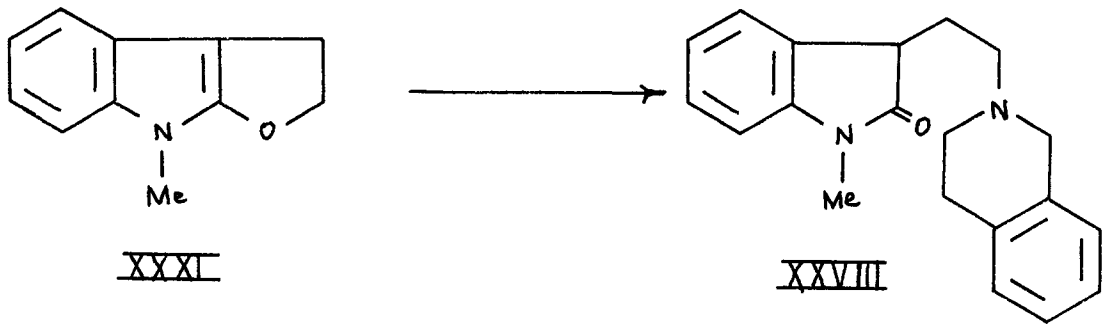


XXX



XXXI

Evidence for the structure assigned to XXXI was based on analyses, and the conversion of XXXI to XXVIII by treatment with tetrahydroisoquinoline hydrobromide.



XXXI XXVIII

In connection with investigations on the alkaloid yohimbine, Julian and Magnani[12] had occasion to carry out further alkylation of 1-methyl-3-acetyloxindole (XXVI), and reported the isolation of an O-alkylation compound. The product was obtained by treating the sodium salt of XXVI with 2-(β-chloroethyl)-1-isoquinolone, 2-(β-bromoethyl)-1-isoquinolone, or 2-(β-toluenesulfonoxyethyl)-1-isoquinolone to give XXXII, an O-alkylated compound.

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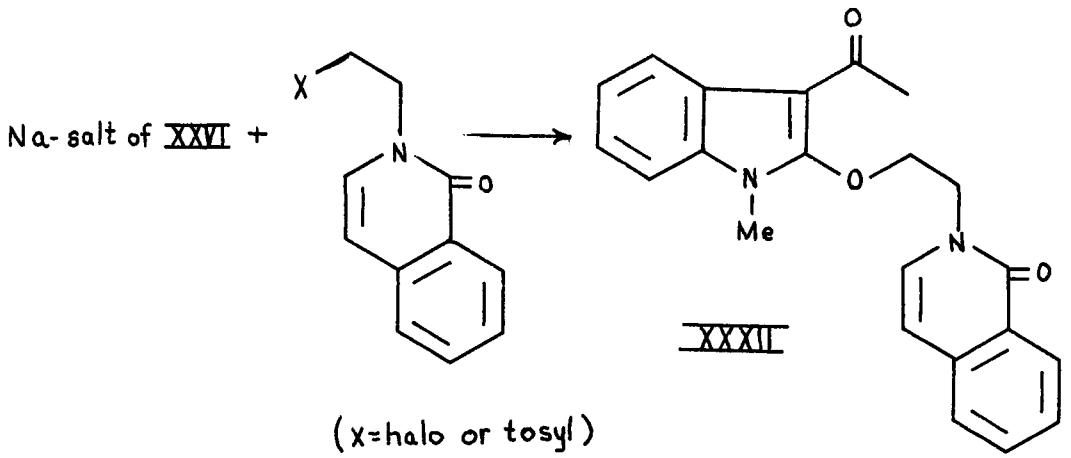
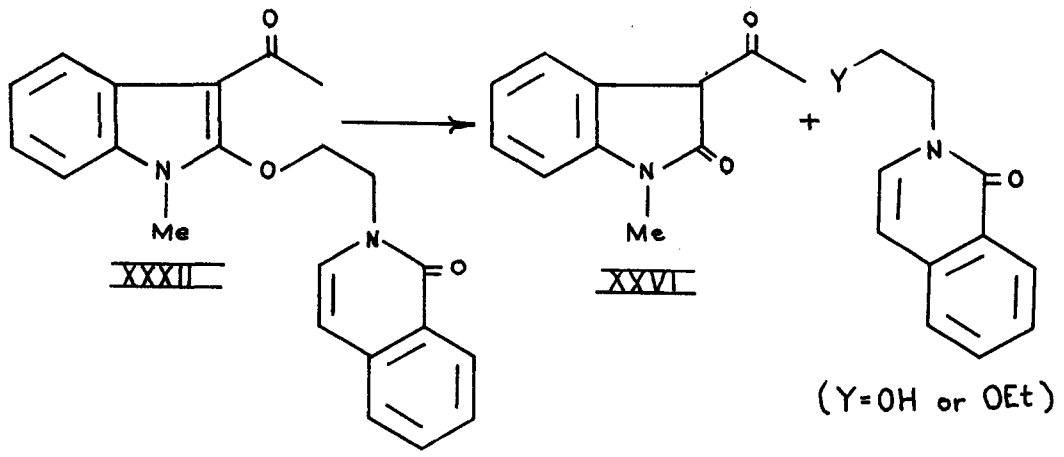
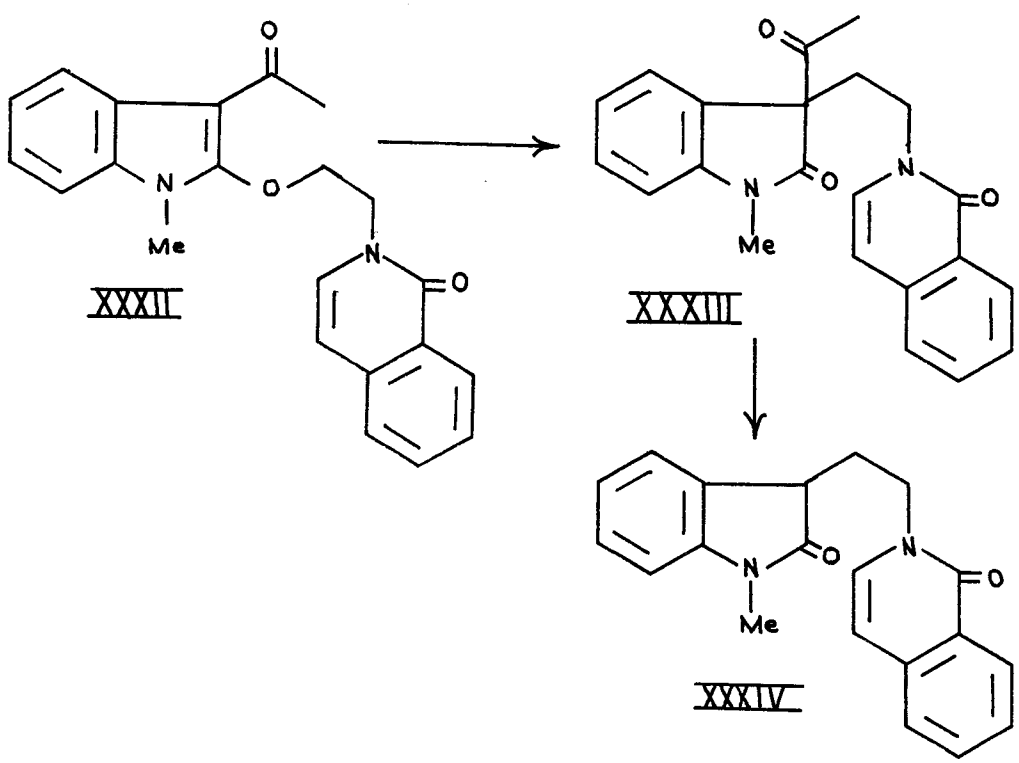
[12] P. L. Julian and A. Magnani, J. Am. Chem. Soc., 71, 3207-10 (1949).



The structure assigned to XXXII was based on analyses and on hydrolytic studies using sodium ethoxide, which yielded 2-(β-hydroxyethyl)-1-isoquinolone, 2-(β-ethoxyethyl)-1-isoquinolone and 1-methyl-3-acetyloxindole (XXVI).



The O-alkylated compound XXXII could be thermally rearranged to the C-alkyl compound XXXIII which could then be deacylated to yield 1-methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XXXIV).



Horning and Rutenberg[13] carried out some alkylations on 1-methyl-3-ethyloxindole (XXXV), in connection with the

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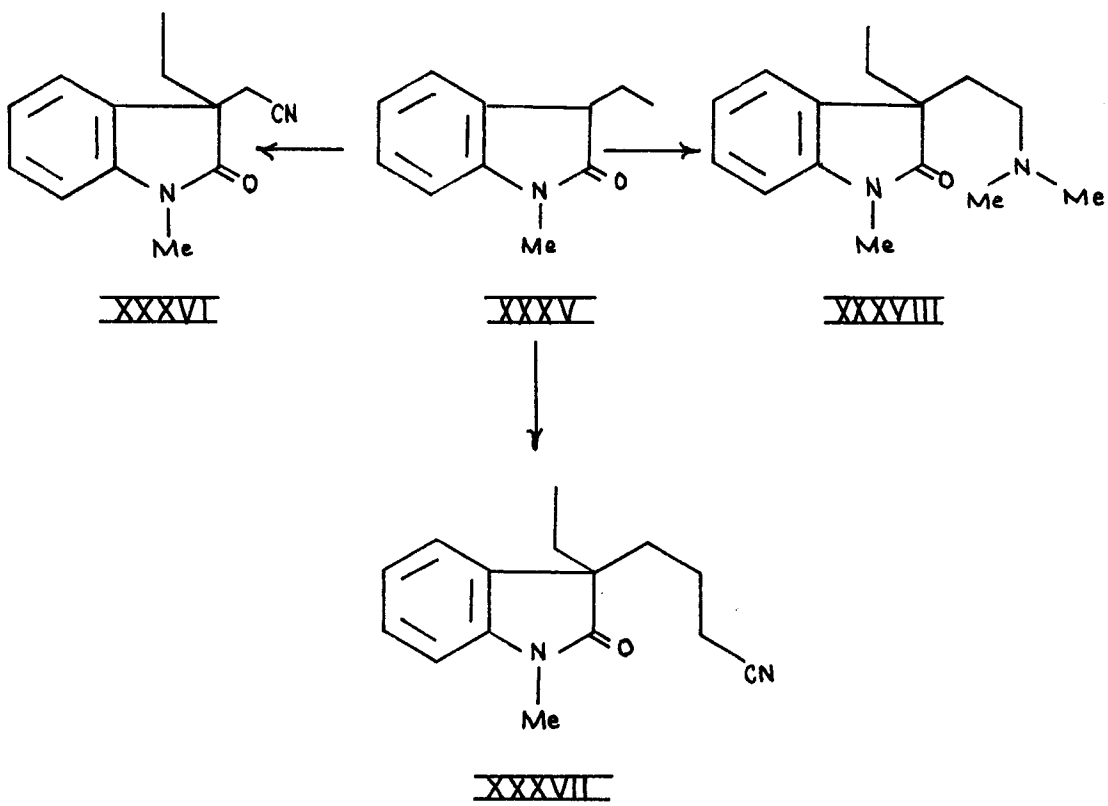
[13]E. C. Horning and M. W. Rutenberg, J. Am. Chem. Soc., 72, 3534-6 (1950).

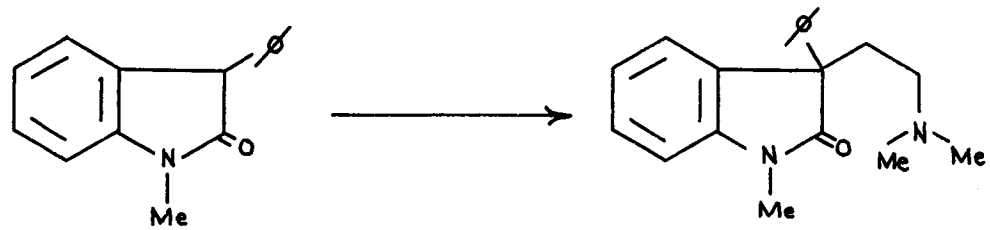
structure of morphine derivatives and synthetic analgesics. The various alkyl halides used were chloroacetonitrile, γ-chlorobutyronitrile, and β-dimethylaminoethyl chloride, yielding the respective oxindole derivatives; 1-methyl-3-ethyl-3-cyanomethyloxindole (XXXVI), 1-methyl-3-ethyl-3-(γ-cyanopropyl)-oxindole (XXXVII) and 1-methyl-3-ethyl-3-(β-dimethylaminoethyl)-oxindole (XXXVIII). In the case of chloroacetonitrile, sodium ethoxide in ethanol was used, whereas with the other two alkyl halides, sodamide in toluene was employed.



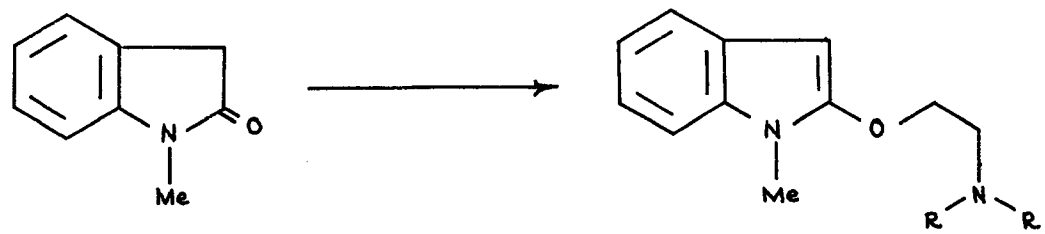
XXXVI XXXV XXXVIII

XXXVII

Palazzo and Rosnati[14] carried out several alkylations of 1-methyloxindoles using sodamide in toluene. 1-Methyl-3-phenyloxindole (XXXIX) reacted with β-dimethylaminoethyl chloride to form 1-methyl-3-phenyl-3-(β-dimethylaminoethyl)-oxindole (XL). However, under the same conditions, both dimethylaminoethyl chloride and diethylaminoethyl chloride reacted with 1-methyloxindole (XXI) to give the O-alkylated derivative (XLI).



XXXIX XL

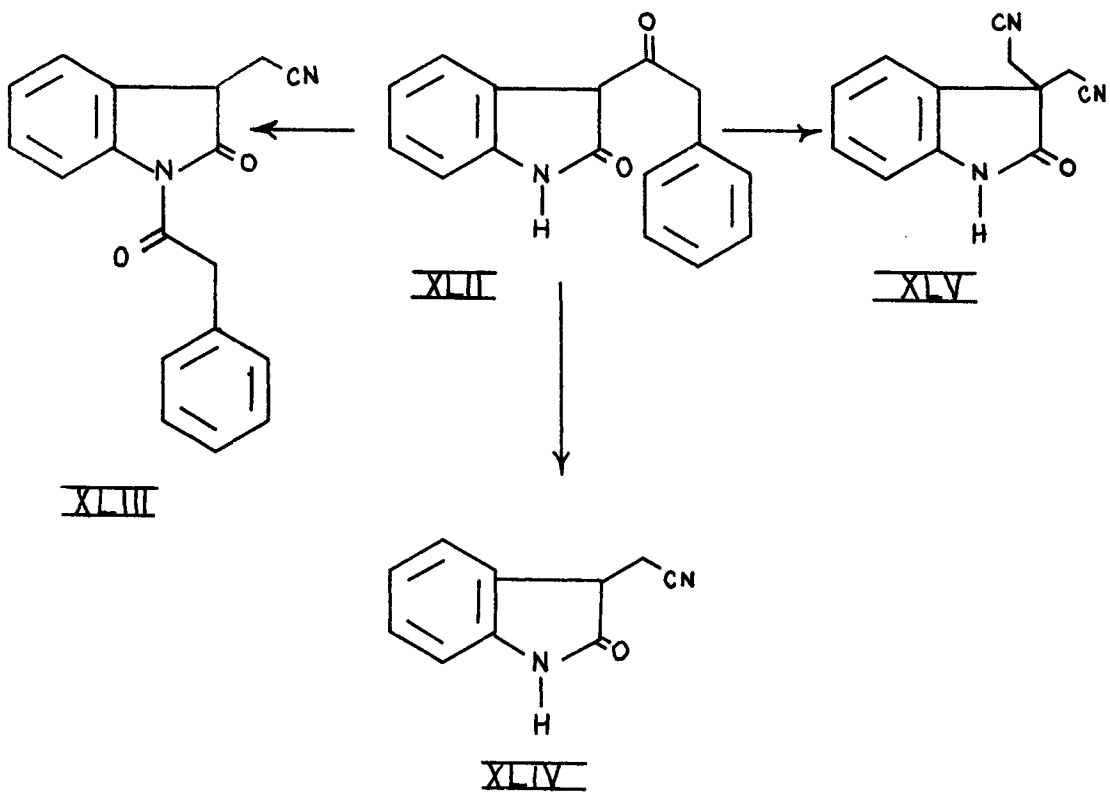


XXI XLI

(R=Me or Et)

[14] G. Palazzo and V. Rosnati, Gazz. chim. ital., 82, 584-94 (1952).

Wenkert[15] has carried out alkylations of 3-phenylacetyloxindole (XLII) with chloroacetonitrile using sodium carbonate in acetone. Depending on the reaction time and the quantity of chloracetonitrile used, the following products were obtained; 1-phenylacetyloxindolyl-3-acetonitrile (XLIII), oxindolyl-3-acetonitrile (XLIV), and 3,3-dicyanomethyloxindole (XLV).



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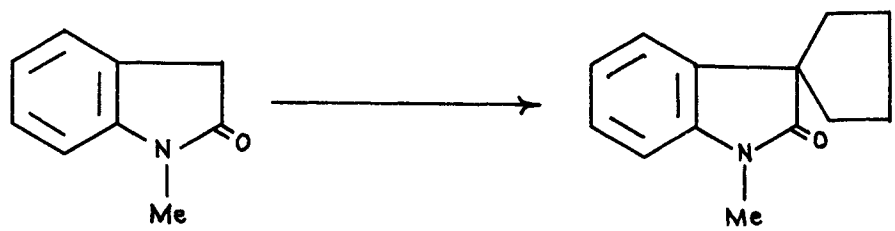
[15]E. Wenkert, Doctoral Dissertation, Harvard University, 1951.

Recently, Witkop and Patrick[16] and Wenkert and Merten[17] have dialkylated 1-methyloxindole (XXI) with tetramethylene dibromide to form 1-methyl-3,3-tetramethyleneoxindole (XLVI).



XXI XLVI

Witkop and Patrick[16], in connection with reactions involving gelsemine and dihydrogelsemine, both of which have been considered as 3,3-disubstituted oxindoles (XLVII), prepared the N-methyl derivatives (XLVIII) of these compounds by refluxing their potassium salts with methyl iodide in benzene.

XLVIII

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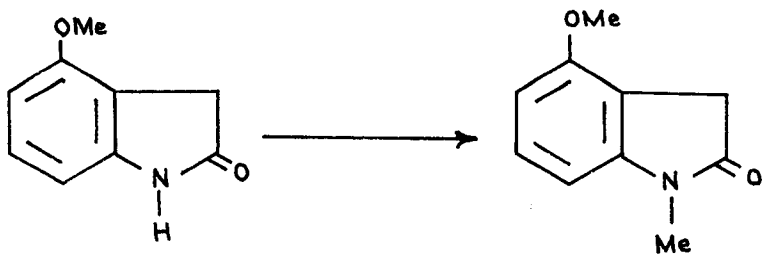
[16]B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 75, 2572-6 (1953).

[17]E. Wenkert and H. Merten, unpublished studies.

The conversion of an oxindole to the corresponding 1-methyloxindole derivative has been reported by Cook and co-workers[18]. Reaction of 4-methoxyoxindole (XLIX) with methyl iodide in sodium methoxide gave 1-methyl-4-methoxyoxindole (L).



XLIX L

A summary of the literature on the alkylation of oxindole and its derivatives with alkyl halides, is given in Table 1. This table covers the literature thoroughly through 1953, and includes data on temperatures, reaction times, product yields where possible and appropriate references.

Another procedure to form 1-methyloxindoles is by reacting a solution of the oxindole compound in excess base with excess dimethyl sulfate. This procedure has been applied to gelsemine (XLVII) by Wenkert[16] to give N-methylgelsemine

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[18] J. W. Cook, J. D. Loudon and P. McCloskey, J. Chem. Soc., 1952, 3904-12.

Table 1. Summary of Alkylations of Oxindole and Oxindole Derivatives

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
Oxindole	excess ethyl iodide	sodium ethoxide		ethanol	reflux.	2 hrs.	1-ethyl-oxindole		1
3,3-di-methyl-	methyl iodide	sodium methoxide		methanol	100-120[a]	16 hrs.	1,3,3-tri-methyl-oxindole		2
Gelsemine	methyl iodide	potassium salt of A[b]	1:1:1	benzene	reflux.	2 hrs.	N-methyl-gelsemine	25	16
Dihydro-gelsemine	methyl iodide	potassium salt of A[b]	1.3:1:1	benzene	reflux.	over-night	N-methyl-dihydro-gelsemine	80	16
3-isopro-pyl-	methyl iodide	sodium methoxide	8.5:1:3.8	methanol	110-120[a]	16 hrs.	1-methyl-3-isopropyl-oxindole		4

[a] sealed tube.

[b] prepared from potassium metal and the oxindole derivative.

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
4-methoxy-	methyl iodide	sodium methoxide	1:1:1	methanol	40-45	6 hrs.	1-methyl-4-methoxy-oxindole	19	18
3-methyl-	methyl iodide	sodium methoxide		methanol	110-120[a]	11 hrs.	1,3,3-trimethyl-oxindole		3
1-methyl-3-formyl-	methyl iodide	sodium methoxide	2:1:1.1	methanol	reflux.	3 hrs.	1,3-dimethyl-oxindole	100	5
1-methyl-3-formyl-	methyl iodide	sodium methoxide	2:1:2.2	methanol	reflux.	3 hrs.	1,3,3-trimethyl-oxindole		5
1,3-dimethyl-	methyl iodide	sodium methoxide	2.2:1:1.7	methanol	reflux.	3 hrs.	1,3,3-trimethyl-oxindole	84	5
1,3-dimethyl-	chloro-aceto-nitrile	sodium ethoxide	1.8:1:1.2	ethanol	60	3 hrs.	1,3-dimethyl-oxindolyl-3-aceto-nitrile	90	5

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield	Ref.
1,3-dimethyl-	phthalimidoethyl bromide	sodium salt of A[c]	.8:1:1	diethyl ether	reflux.	overnight	1,3-dimethyl-3-(β-phthalimidoethyl-oxindole	73	9
1,3-dimethyl-	ethylene bromide	sodium salt of A[c]	8.7:1:1	diethyl ether	reflux.	overnight	1,3-dimethyl-3-(β-bromoethyl)-oxindole	61	9
1,3-dimethyl-5-ethoxy-	ethylene bromide	sodium salt of A[c]		diethyl ether	reflux.	overnight	1,3-dimethyl-5-ethoxy-3-(β-bromoethyl)-oxindole		10
1,3-dimethyl-	bromoacetal	sodium ethoxide	1:1:1.1	ethanol	reflux.	1 hr.	1,3-dimethyl-3-oxindolyl acetal	69	7

[c]prepared from sodium metal and the oxindole derivative.

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield	Ref.
1-methyl-3-acetyl-	methyl iodide	sodium salt of A[d]		acetone			1,3-dimethyl-3-acetyl-oxindole		7
1-methyl-3-acetyl-	1-bromo-2-(N-tetrahydroisoquinolyl)-ethane	sodium salt of A[d]	.9:1:1	acetone[f]	100[a]	24 hrs.	1-methyl-3-(β-N-tetrahydroisoquinolyl-ethyl)-oxindole	27	11
1-methyl-3-acetyl-	1-bromo-2-(N-tetrahydroisoquinolyl)-ethane	sodium salt of A[d]		acetone[f]	140-150[a]	24 hrs.	1-methyl-3-(β-N-tetrahydroisoquinolyl-ethyl)-oxindole	27	11

[d]prepared from sodium ethoxide and the oxindole derivative.

[e]prepared from alcoholic silver nitrate and the oxindole derivative.

[f]containing sodium iodide.

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
1-methyl-3-acetyl-	1-bromo-2-(N-tetrahydroisoquinolyl)-ethane	sodium salt of A[d]		dioxane[f]	80-90	11 hrs.	1-methyl-3-(β-N-tetrahydroisoquinolyl-ethyl)-oxindole	27	11
1-methyl-	tetramethylene bromide	sodium ethoxide	1:1:2	ethanol	reflux.	1 hr.	1-methyl-3,3-tetramethylene-oxindole	60-70	16, 17
3-phenylacetyl-	chloroacetonitrile	sodium carbonate		acetone	reflux.	4-6 hrs.	1-phenylacetyl-3-cyanomethyl-oxindole		15
3-phenylacetyl-	chloroacetonitrile	sodium carbonate		acetone	reflux.	17 hrs.	3-cyanomethyl-oxindole		15
3-phenylacetyl-	excess chloroacetonitrile	sodium carbonate		acetone	reflux.	48 hrs.	3,3-dicyanomethyl oxindole		15

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
1-methyl-3-phenyl-	β-dimethylaminoethyl chloride	sodamide	1.3:1:1.3	toluene			1-methyl-3-phenyl-3-(β-dimethylaminoethyl)-oxindole		14
1-methyl-	chloroacetonitrile	sodium methoxide		methanol			1-methyl-3-oxindolylacetonitrile	60	8
1-methyl-3-acetyl-	β-phenoxyethyl bromide	sodium salt of A[d]	5:1:1	acetone[f]	150-160[g]	15 hrs.	1-methyl-3-(β-phenoxyethyl)-oxindole	56	11
1-methyl-3-ethyl-	chloroacetonitrile	sodium ethoxide	2:1:1.1	ethanol			1-methyl-3-ethyl-3-oxindolylacetonitrile		13

[g]reflux, with oil bath temp. = 150-160°.

Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
1-methyl-3-ethyl-	β-dimethylaminoethyl chloride	sodamide	1.9:1:1.4	toluene			1-methyl-3-ethyl-3-(β-dimethylaminoethyl)-oxindole		13
1-methyl-3-ethyl-	γ-chloropropionitrile	sodamide	2.1:1:1.2	toluene			1-methyl-3-ethyl-3-(γ-cyanopropyl)-oxindole		13
3,3-dimethyl-	excess methyl iodide	silver salt of A[e]		diethyl ether	60[a]	10 hrs.	2-methoxy-3,3-dimethylindolenine		2
3-isopropyl-	excess methyl iodide	silver salt of A[e]		diethyl ether	70[a]	12 hrs.	2-methoxy-3-isopropylindolenine		4
1-methyl-	β-dimethylaminoethyl chloride	sodamide	1.7:1:1.2	toluene			1-methyl-2-(β-dimethylaminoethoxy)-indole	41	14

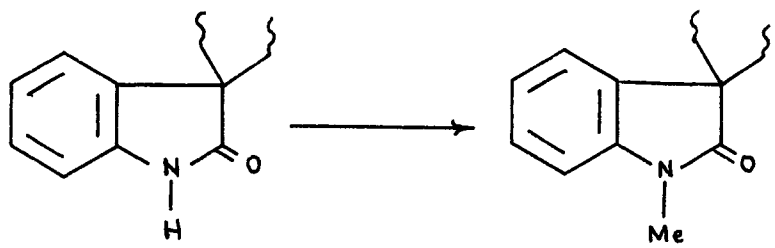
Table 1 (Continued)

Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
1-methyl-3-formyl-	methyl iodide	sodium salt of A[d]	3.1:1:1	acetone	reflux.	5 hrs.	1-methyl-2-methoxy-3-formyl-indole	22	5
1-methyl-3(β-bromoethyl)-	1-methyl-3(β-bromoethyl)-oxindole	sodium ethoxide		ethanol	room temp.	10-15 min.	2,3-dihydro-8-methylfuro [2,3-b]-indole	100	11
1-methyl-3(β-bromoethyl)-	1-methyl-3(β-bromoethyl)-oxindole	tetrahydroisoquinoline		benzene	room temp.	10-15 min.	2,3-dihydro-8-methylfuro [2,3-b]-indole	100	11
1-methyl-3-acetyl-	2-(β-chloroethyl)-1-isoquinolone	sodium salt of A[d]	.5:1:1	dioxane[f]	100	17 hrs.	1-methyl-2-[2-N-(1-oxo-1,2-dihydroisoquinolyl-ethoxy)]-3-acetyl-indole	25	12

Table 1 (Continued)

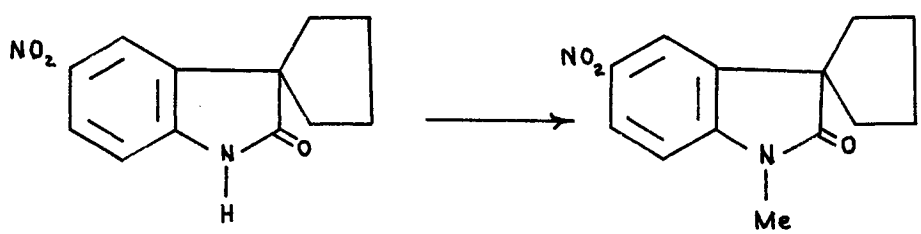
Oxindole and Deriv. A	Alkyl Halide B	Base C	Mole Ratio of B:A:C	Solvent	Temp. °C	Time	Product	Yield %	Ref.
1-methyl-3-acetyl-	2-(β-bromoethyl)-1-isoquinolone	sodium salt of A[d]	.4:1:1	dioxane[f]	100	5 hrs.	1-methyl-2-[2-N-(1-oxo-1,2-dihydroisoquinolylethoxy)]-3-acetylindole	22	12
1-methyl-3-acetyl-	2-(β-p-toluenesulfonoxyethyl)-1-isoquinolone	sodium salt of A[d]	.7:1:1	acetone	reflux.	1 hr.	1-methyl-2-[2-N-(1-oxo-1,2-dihydroisoquinolylethoxy)]-3-acetylindole	55	12

(XLVIII) and to 3,3-tetramethylene-5-nitrodxindole (LI) by Witkop and Patrick[16], to give



XLVII XLVIII

1-methyl-3,3-tetramethylene-5-nitrodxindole (LII).



LI LII

Diazomethane has been employed to prepare O-methylated oxindole derivatives. Whereas Horner[19] reported that

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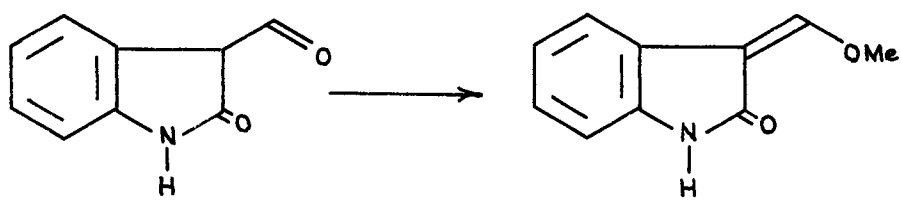
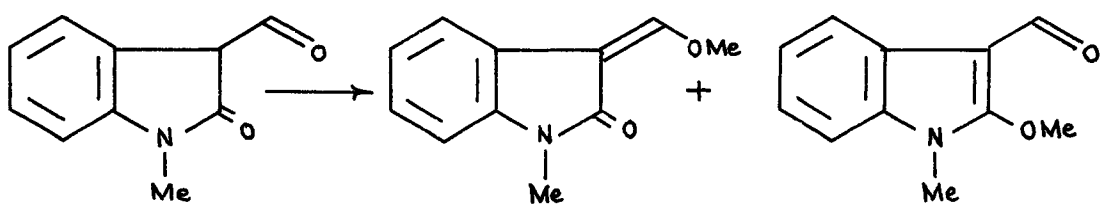
[19]L. Horner, Ann., 548, 117-46 (1941).

treatment of 3-formyloxindole (XVII) with diazomethane yields 3-methoxymethyleneoxindole (LIII), Julian[6] found that diazomethane reacted with 1-methyl-3-formyloxindole (XIII) to form 1-methyl-2-methoxy-3-formylindole (XVI), and also 1-methyl-3-methoxymethyleneoxindole (LIV), by analogy with Horner's compound (LIII).



XVII LIII

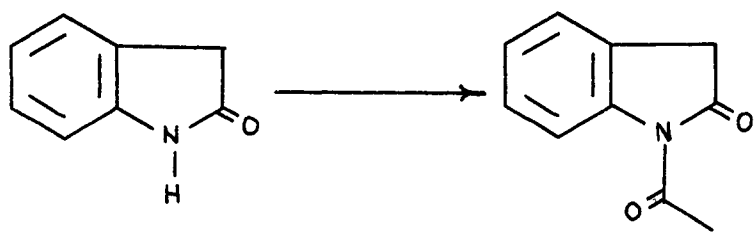


XIII LIV XVI

Acylation

Acylation of oxindole derivatives can occur by the attack of anions, formed from the interaction of oxindoles with bases, on acyl halides, esters, or anhydrides. As mentioned previously, the products would be N-acylated, O-acylated or C-acylated compounds, depending on experimental conditions and the nature of the reactants.

Suida[20] prepared 1-acetyloxindole (LV) by reaction of oxindole (I) and acetic anhydride.

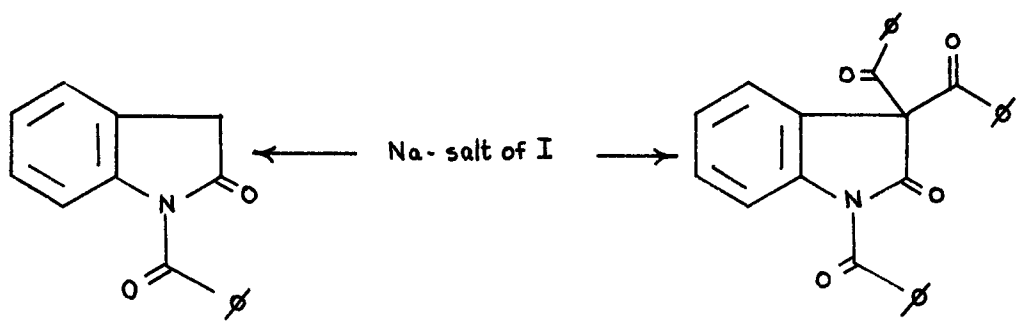


I IV

[20] W. Suida, Ber., 12, 1326-8 (1879).

Other oxindole derivatives similarly yield 1-acetyl derivatives[2,3,4,21,22,23].

Heller and Heine[24] reacted the sodium salt of oxindole (I) with benzoyl chloride to give 1-benzoyloxindole (LVI). With an excess of benzoyl chloride, a tribenzoyl derivative (LVII) was formed.



LVI LVII

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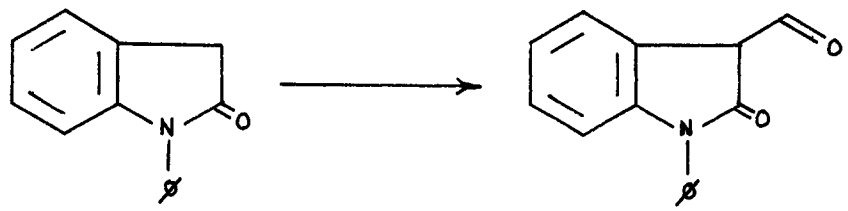
[21] G. Mazzara and A. Borgo, Gazz. chim. ital., 35, II, 320-6, 563-9 (1905).

[22] A. Reissert and J. Scherck, Ber., 31, 387-97 (1898).

[23] G. Wahl, Monatsh., 38, 525-35 (1917).

[24] G. Heller and H. Heine, Ber., 49, 2775-8 (1916).

Stollé and co-workers[25] showed that 1- henyloxindole (LVIII) could be condensed with ethyl formate in the presence of sodium to yield 1-phenyl-3-formyloxindole (LIX).



LVIII LIX

Julian and co-workers[5] expanded this reaction to include not only formylation with ethyl formate, but general acylation with a variety of esters[7,11]. The general procedure consisted of reacting the ester with 1-methyloxindole (XXI) in the presence of a slight excess of sodium ethoxide to produce 1-methyl-3-acyloxindoles (LX).

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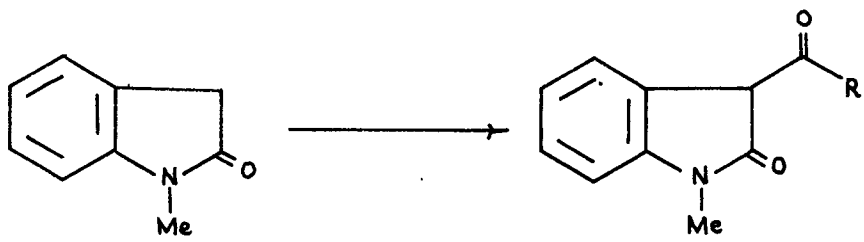
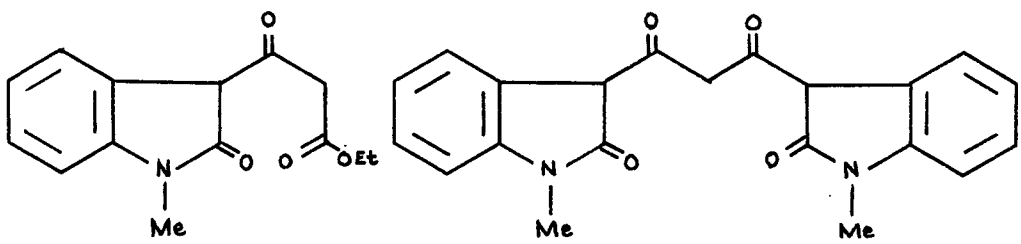
[25]R. Stollé, H. Hecht and W. Becker, J. prakt. Chem., 135, 345-60 (1932).



XXI LX

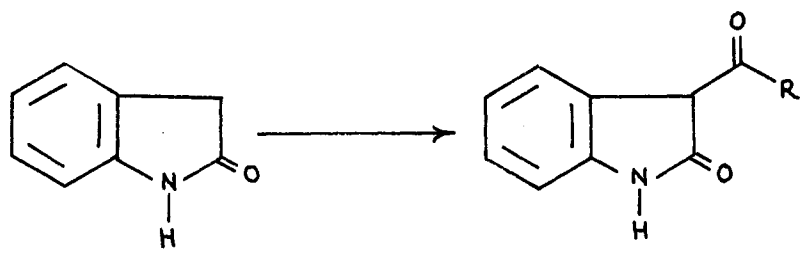
Esters employed by Julian and co-workers were ethyl formate[5], ethyl propionate[6], ethyl acetate, ethyl dimethylaminoacetate, ethyl malonate[7] and ethyl tetrahydroisoquinolylacetate[11]. In the case where the ester was ethyl malonate, either LXI or LXII could be obtained depending on the conditions.



LXI LXII

The acylation of 1-methyloxindole (XXI) was also studied by Porter and co-workers[26], who prepared the 3-acyl derivative using ethyl oxalate.

Horner[19] applied the same reaction to oxindole (I) and prepared 3-acyl derivatives (LXIII) from ethyl acetate, ethyl oxalate, ethyl malonate, ethyl glycolate and ethyl glycolate methyl ether.



I LXIII

However, Horner[19] was unable to prepare 3-acyl derivatives of oxindole from ethyl phthalimidomalonate, ethyl isonitrosomalonate, ethyl isonitrosocyanoacetate, and ethyl tartrate. From the acylation of oxindole with ethyl malonate, in contrast to Julian's work on 1-methyloxindole (XXI),

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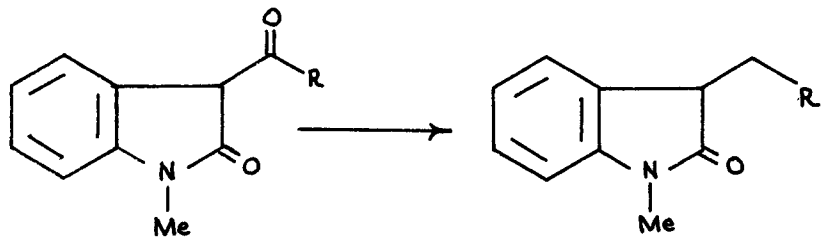
[26]J. C. Porter, R. Robinson and M. Wyler, J. Chem. Soc., 1941, 620-24.

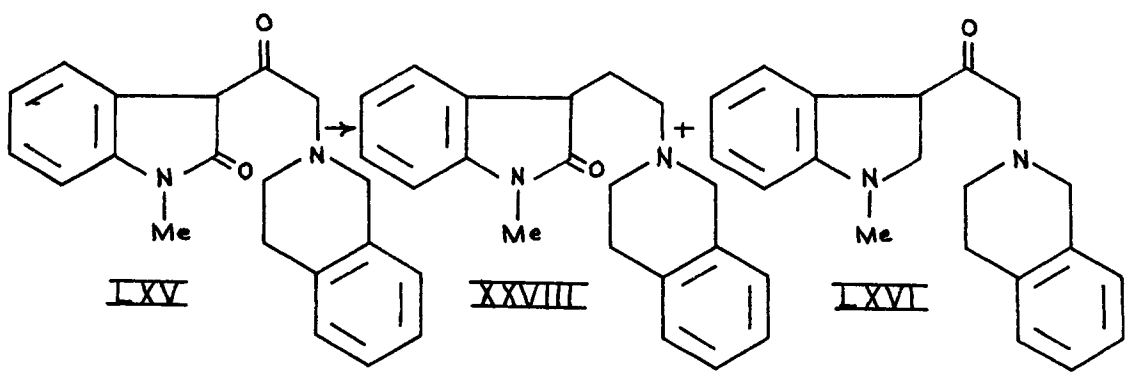
Horner was unable to obtain the desmethyl product analogous to LXI, but obtained only the desmethyl analog of LXII.

The catalytic reduction of 1-methyl-3-acyloxindoles (LX) has been reported by Julian and co-workers[7] to give the corresponding 1-methyl-3-alkyloxindoles (LXIV).



LX LXIV

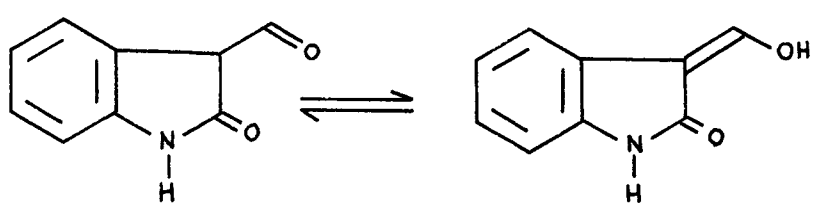
It is interesting to note however that in the reduction of 1-methyl-3-(β-N-tetrahydroisoquinolylacetyl)-oxindole (LXV), two products were obtained; the alkyl oxindole (XXVIII), and the acyl indoline (LXVI)[11].



LXV XXVIII LXVI

Horner[19] reported that 3-acyl oxindoles (LXIII) were not catalytically reduced to 3-alkyl oxindoles. However, Julian[11] found no difference in the reduction of LXV, and the corresponding desmethyl derivative, although in the latter case, no products were isolated.

Grǻnacher and Mahal[27] considered 3-formyloxindole (XVII) to exist principally in the enol form (LXVII).



XVII LXVII

The enolbenzoate (LXVIII)[19,27,28], enolbenzenesulfonate (LXIX) and enolacetate (LXX)[19,28] of LXVII are known, as well as the enolbenzoate (LXVIII)[28], and enolacetate (LXX)[28] of 1-methyl-3-hydroxymethyleneoxindole (LXXI)(enol form of XIII).

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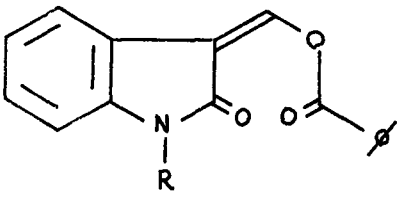
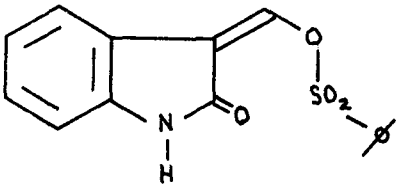
[27]C. Grǻnacher and A. Mahal, Helv. Chim. Acta., 6, 467-82 (1923).

[28]H. Fischer and K. Smeykal, Ber., 56, 2368-78 (1923).

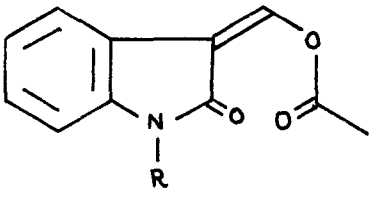


LXVIII

(R=H or Me)



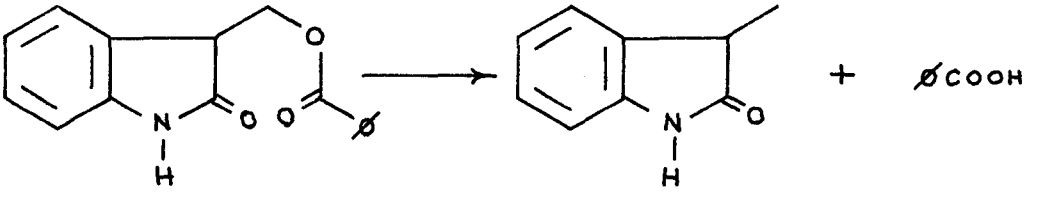
LXIX



LXX

(R=H or Me)

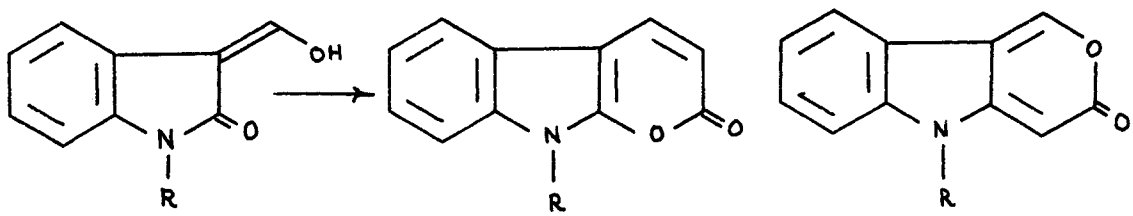
A proof of the structure of LXVIII was given by Horner[19], who showed that on catalytic hydrogenation, LXVIII was converted to 3-methyloxindole and benzoic acid.



LXVIII IX

Condensation of oxindole aldehydes

Fischer and Smeykal[28] in attempted Perkin condensations of LXVII and LXXI obtained products which they consider to be LXXII, but which Horner[19], on reinvestigation, believed to be LXXIII.



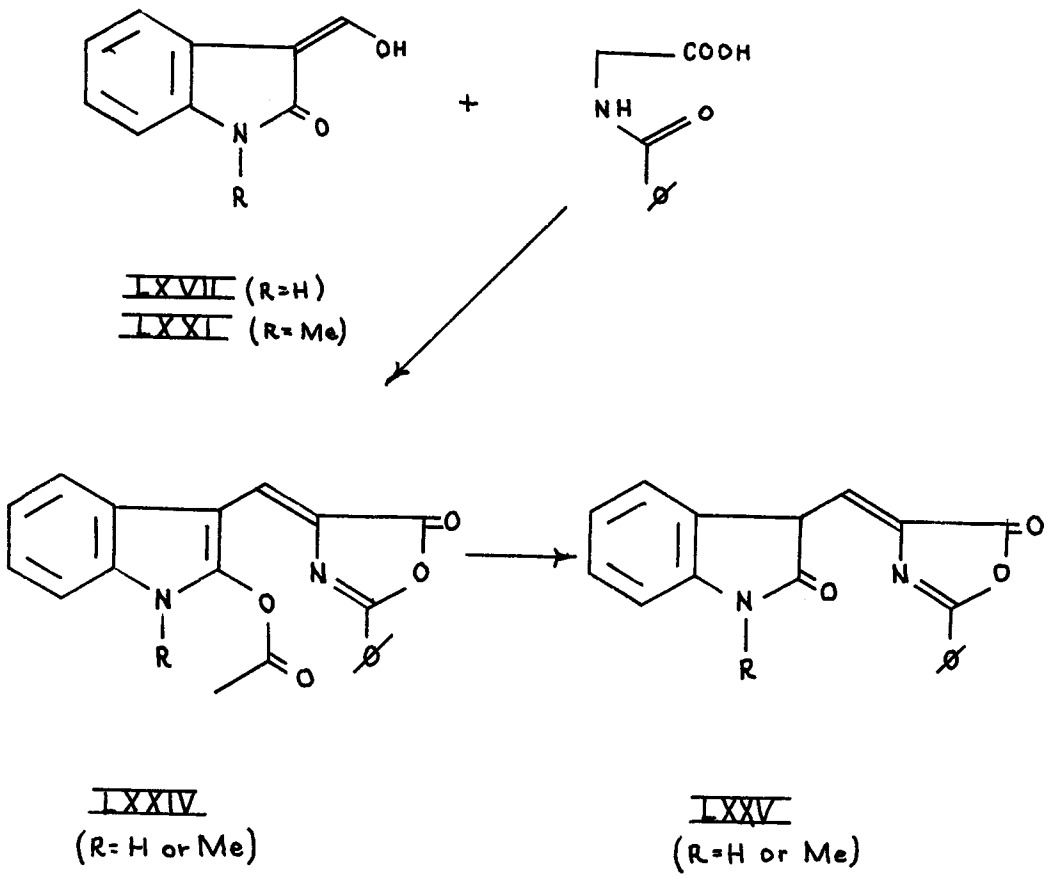
LXVII (R=H)
LXXI (R=Me)

LXXII
(R=H or Me)

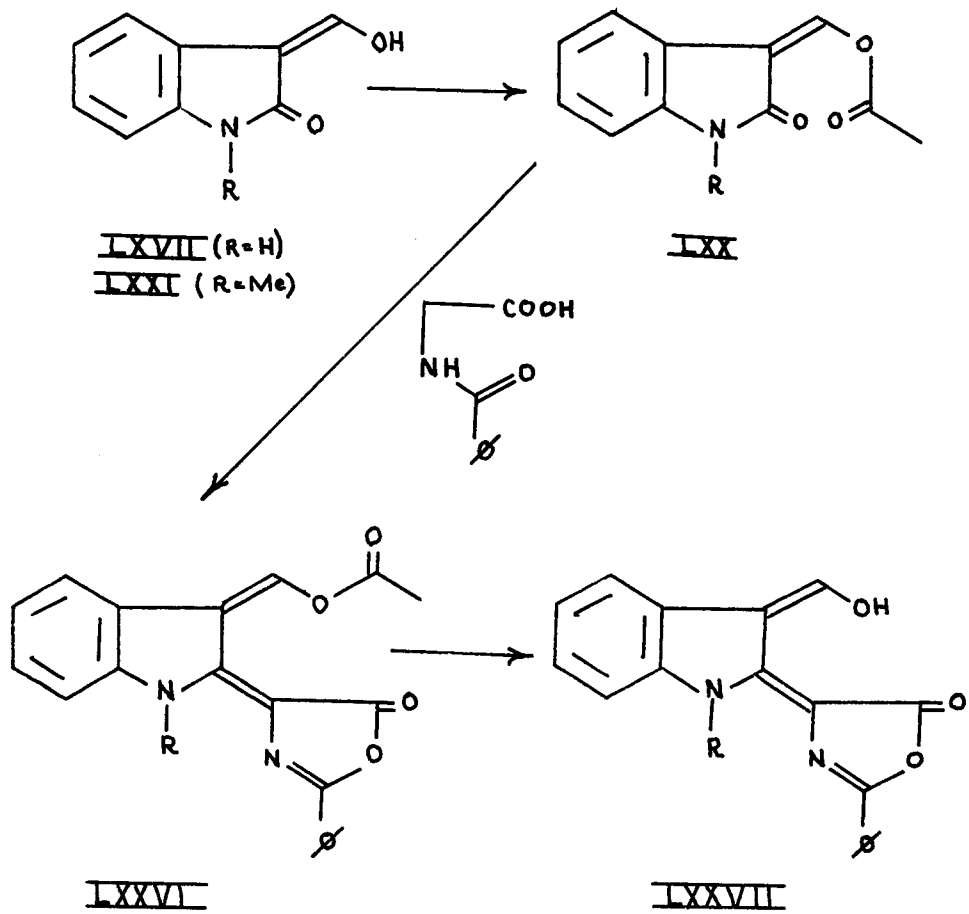
LXXIII
(R=H or Me)

Attempted condensations of 3-hydroxymethyleneoxindole (LXVII) with rhodanine[28] were unsuccessful, a fact ascribed to enolic character of LXVII.

However, Fischer and Smeykal[28] were able to condense either LXVII or LXXI with hippuric acid in the presence of sodium acetate in acetic anhydride, to give an acetyl azlactone (LXXIV) which could be hydrolyzed to the azlactone (LXXV).



Inasmuch as the azlactone could not be hydrolyzed to the expected acrylic acid, and after reinvestigation of the reaction, Horner[19] postulated the formation of the enolacetate (LXX), followed by condensation at the 2-position to give an acetyl azlactone (LXXVI) which could then be hydrolyzed to the azlactone (LXXVII).



The condensation of 3-hydroxymethyleneoxindole with hydantoin[29] in the presence of acetic anhydride formed an N-acetyl condensation product (LXXVIII), which could then be hydrolyzed to the deacylated compound LXXIX.

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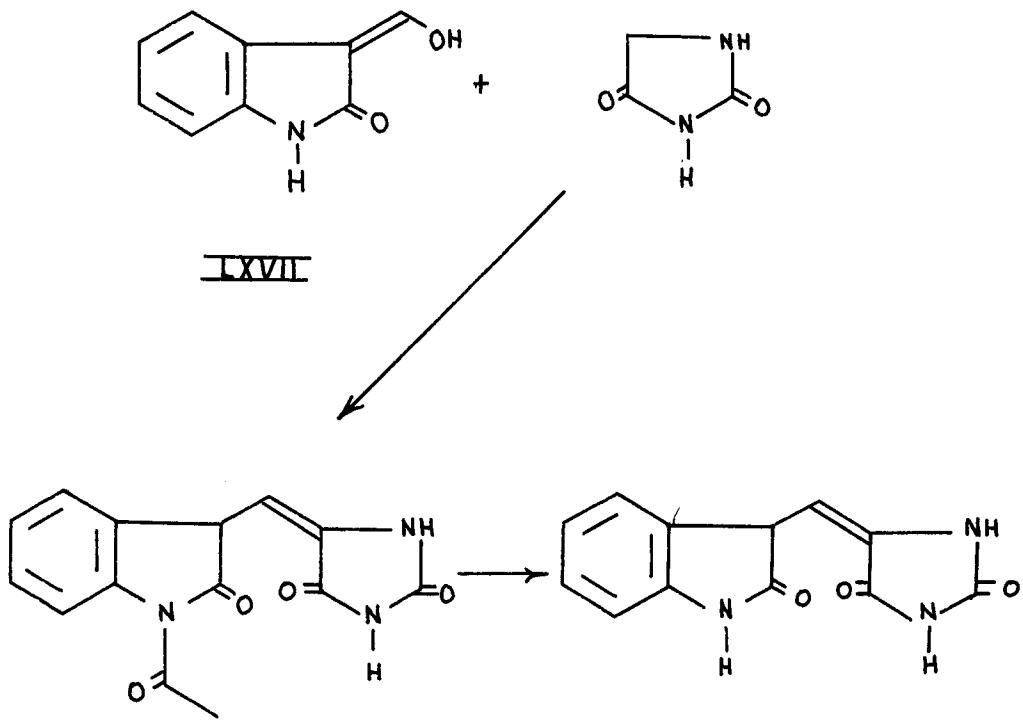
[29] Z. Iwao, T. Katumura and M. Kotaki, J. Chem. Soc. Japan, 60, 454-6 (1939).



LXVII

LXXVIII

LXXIX

Oxindole alkaloids

Recently, several alkaloids from various plant species have been considered to be oxindole derivatives. Of these, one of the first was gelsemine, derived from Gelsemium sempervirens Ait. The evidence for this conclusion came from degradation studies on gelsemine, in which 3-methyl-oxindole (IX) was isolated from a zinc dust distillation of

gelsemine hydrochloride[30]; and also from spectral studies by Kates and Marion[31] who showed that the ultraviolet absorption spectra of gelsemine and 3,3-dimethyloxindole (VI) were superimposable, while comparison of the infrared absorption spectra showed excellent correlation for imino, carbonyl and benzene ring absorption.

Schwarz and Marion[32] in further investigations on alkaloids derived from the gelsemium species, isolated two minor alkaloids of the group, gelsedine and gelsevirine which, on the basis of comparisons of ultraviolet and infrared spectra, were considered to be 1,3-disubstituted and 1,3,3-trisubstituted oxindole derivatives respectively.

A comparison of the ultraviolet spectra of gelsemine; and formosanine, rhyncophylline and mitraphylline derived from various mitragyna species was made by Raymond-Hamet[33]. On the basis of similarities in the spectra, it was proposed that these mitragyna alkaloids had similar structural characteristics to gelsemine.

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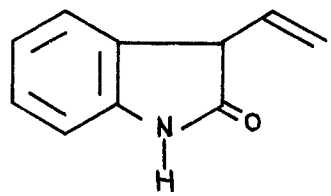
[30]R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, Helv. Chim. Acta, 34, 1139-53 (1951).

[31]M. Kates and L. Marion, Can. J. Chem., 29, 37-45 (1951).

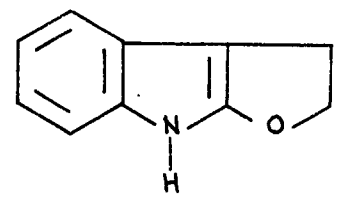
[32]H. Schwarz and L. Marion, Can. J. Chem., 31, 958-75 (1953).

[33]Raymond-Hamet, Compt. rend., 230, 1405-7 (1950).

Degradation studies on rhyncophylline[34], mitraphylline[35], and uncarine-A from Uncaria kawakimii Hayata[36] yielded a $C_{10}H_9ON$ compound. Barger and co-workers[34] obtained the compound by a calcium oxide distillation of rhyncophylline and thought it to be methylcarbostyril, whereas Cook and co-workers[35] isolated a $C_{10}H_9ON$ compound from a zinc dust distillation of mitraphylline hydrochloride, which was considered to be identical with the product derived from rhyncophylline[34], but was thought to be 3-vinyloxindole (LXXX)[35]. The product isolated by Kondo and Nozoye[36] by the palladium distillation of uncarine-A or the degradative distillation of uncarine-A methiodide was thought to have the dihydrofuroindole structure (LXXXI).



LXXX



LXXXI

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[34] G. Barger, E. Dyer and L. J. Sargent, J. Org. Chem., 4, 418-27 (1939).

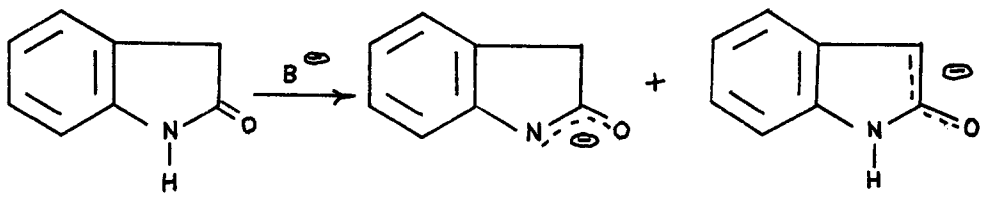
[35] J. W. Cook, R. M. Gailey and J. D. Loudon, Chemistry and Industry, 1953, 640.

[36] H. Kondo, T. Nozoye and M. Tomita, Annual Rept. ITSUU Lab., 1, 30-6 (1950).

The structure LXXX[35] was assigned on the basis of analyses, ultraviolet absorption spectra, and the catalytic hydrogenation of LXXX to 3-ethyloxindole, while LXXXI[36] was assigned on the negative evidence of unreactivity toward ozone, thus eliminating LXXX, and on analyses.

DISCUSSION

The action of bases on oxindole may lead to the formation of anions as represented by the following equation.



This affords the opportunity of N-alkylation, O-alkylation or C-alkylation on reaction with alkyl halides.

In general[1,2,4], however, with perhaps two exceptions[3,4], it has been shown that when the possibility of N-alkylation exists, it is the preferred reaction. Therefore, whenever C-alkylation was attempted[5,7,8,9,10], or if C-alkylation versus O-alkylation was to be studied[5,11,12], N-alkylated oxindoles have been used.

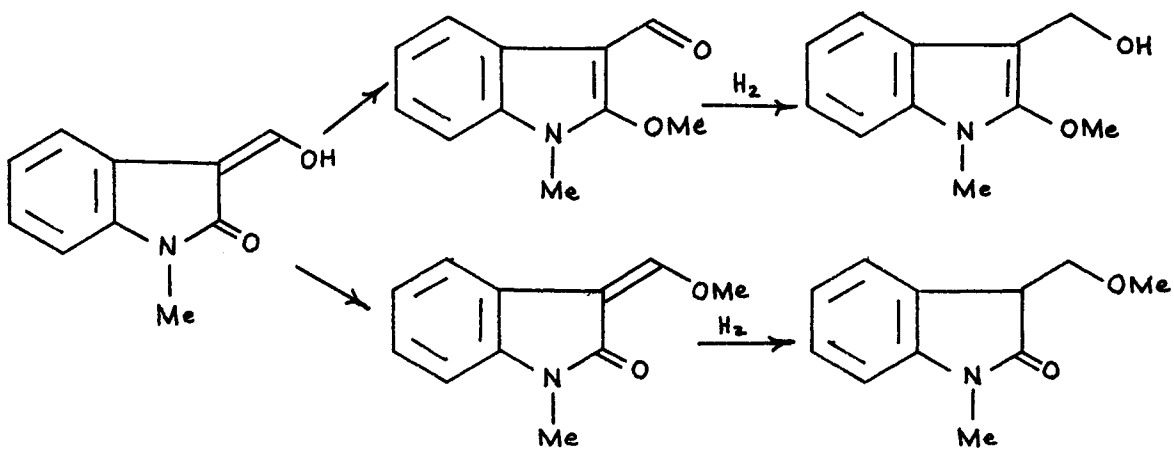
Instances in the oxindole series in which O-alkylation is reported to occur in preference to C-alkylation are quite rare, and it became of interest to reinvestigate some of these for possible structural misinterpretations and also for use that could be made of an O-alkylated oxindole to

function as a "model" compound for infrared and ultraviolet absorption studies.

The O-alkylation of 1-methyl-3-formyloxindole by Julian and co-workers[7] to produce 1-methyl-2-methoxy-3-formylindole, although not an alkylation of a simple oxindole, seemed to justify re-examination for the following reasons. It seemed strange that alkylation of this β-dicarbonyl system should occur on the carbonyl group of the amide function rather than that of the formyl group*.

It was hoped that a structure could be unambiguously assigned by a consideration of the infrared and ultraviolet absorption spectra of the alkylation product and its reduction product, and also chemically, by ozonization studies.

Schematically the structural possibilities could be outlined as follows:



*It has been reported[27] that 3-formyloxindoles are highly enolic, existing as the hydroxymethylene tautomers.

It was found in fact that the ultraviolet absorption spectrum of the alkylation product and starting material were very similar; the maxima appearing at 265 mμ (log ∈ 4.45), 301 mμ (log ∈ 4.00), and 265 mμ (log ∈ 4.38), 308 mμ (log ∈ 4.10) respectively. The ultraviolet absorption spectrum of the reduction product was very similar to a simple oxindole, having a characteristic maximum at 252 mμ (log ∈ 3.98). Furthermore, the infrared absorption spectrum of the alkylation product was quite similar to that of a simple oxindole with the addition of an absorption peak at 6.03 μ, which could be attributed to the enol ether linkage, while the infrared absorption spectrum of the reduction product showed characteristic oxindole carbonyl absorption at 5.82 μ and was in fact superimposable on that of 1,3-dimethyloxindole. In chemical studies, it was shown that the ozonization of the alkylation product yielded 1-methylisatin. Infrared and ultraviolet spectra are shown in Figures 1, 2, 12 and 13* and these together with the chemical data obtained indicated the alkylation product to be 1-methyl-3-methoxymethylene-oxindole rather than 1-methyl-2-methoxy-3-formylindole.

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*These figures and all others mentioned subsequently appear in the Spectra section.

This would lead to the prediction that in other instances involving the reported O-alkylation of 3-acyloxindoles[12], reaction may have occurred at the ketone carbonyl rather than the amide carbonyl.

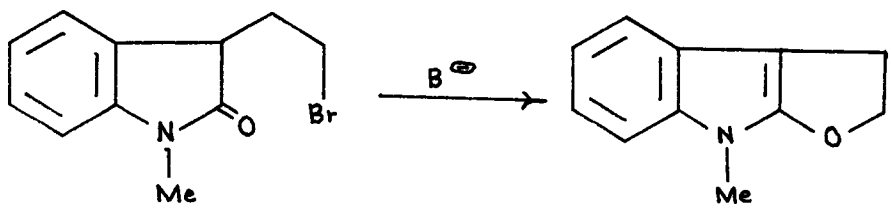
The reported O-alkylation of 1-methyloxindole with β-dimethylaminoethylchloride[14] warranted further study since the structural assignment seemed to be based on inconclusive evidence. The authors made a comparison of ultraviolet absorption spectra which showed considerable similarity to a simple oxindole, and compared the melting points of derivatives of their product with the corresponding C-alkylated product prepared by Julian[7]. However, the derivatives compared were not the same, being in one case the picrolonate[14], and in the other the picrate[7].

A careful repetition of this work yielded a product which gave an ultraviolet absorption spectrum completely in agreement with that of a simple oxindole, and an infrared absorption spectrum showing the characteristic oxindole carbonyl absorption at 5.82 μ. Furthermore, analyses of the picrate, and comparison with an authentic sample of the picrate of the C-alkylated product (prepared by Julian's method) indicated that the product was indeed C-alkylated.

Considerable difficulty was encountered in the preparation of this picrate due to the inability to obtain the

reported melting point[7]. Even after repeated recrystallizations it melted about eight degrees below the reported value. It was therefore necessary to obtain an authentic sample of the picrate*, which on comparison showed the same melting point, and gave no depression on mixed melting point determination. Infrared and ultraviolet absorption spectra are shown in Figures 3 and 14.

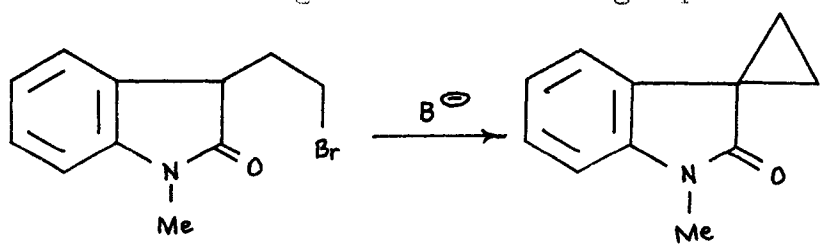
A further literature search for simple O-alkylated oxindoles *per se*, in an attempt to obtain a "model" compound for infrared and ultraviolet absorption spectra studies indicated that the reported intramolecular O-alkylation of 1-methyl-3-(β-bromoethyl)-oxindole to produce a dihydrofuro derivative[11] as outlined in the following equation would be worthy of repetition.



*An authentic sample was kindly supplied by Dr. P. L. Julian.

It is of interest to note that in the preparation of 1-methyl-3-(β-bromethyl)oxindole, contrary to published reports[7], that an N-alkylated oxindole unsubstituted in the 3-position cannot be alkylated directly, the direct C-alkylation of 1-methyloxindole could be used. The general procedure developed involved the prior formation of the anion from an equivalent amount of sodium hydride in benzene, followed by reaction with the appropriate alkyl halide*.

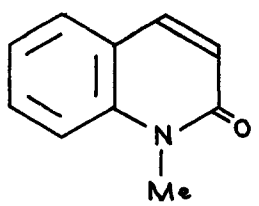
The further reaction of 1-methyl-3-(β-bromoethyl)-oxindole with sodium ethoxide solution yielded the supposed O-alkylation product. However, the ultraviolet absorption spectrum of this compound showed all the characteristics of a simple oxindole, while the infrared absorption spectrum contained the characteristic oxindole carbonyl band. Figures 4 and 15 show the infrared and ultraviolet absorption spectra comparisons which indicate, when coupled with analyses that the compound must be 1-methyl-3,3-dimethyleneoxindole, formed according to the following equation.



*See p. 67 for further discussion of this procedure.

The chemical evidence cited by Julian[11] to support the O-alkylated structure, such as conversion to starting material with concentrated hydrobromic acid, would apply equally well to the above C-alkylated structure.

This study led to some interesting predictions in the field of oxindole alkaloids. In view of the fact that three groups of investigators[34,35,36], had isolated a compound having an empirical formula $C_{10}H_9ON$ from degradation studies of the oxindole alkaloids rhyncophylline[34], mitraphylline[35] and uncarine-A[36], and that the reported melting points and other physical and chemical properties were in good agreement, it would not be too surprising if they were identical. However, conflicting structures had been assigned as follows,



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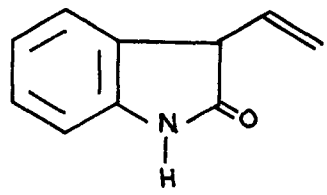

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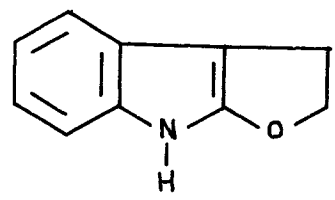

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although Cook[35] felt that his compound on the basis of reduction to 3-ethyloxindole and that of Barger[34] were identical and had the 3-vinyloxindole structure. Kondo[36] on the other

hand ruled out the 3-vinyloxindole structure on the basis of unreactivity toward ozone, which should also have ruled out the O-alkylated structure which he assigned. The other structural possibility neglected by these authors was the 3,3-dimethyleneoxindole structure, which had been synthesized by Markees and Burger[37] in connection with some antitubercular studies. Its melting point and ultraviolet absorption spectrum, run on an authentic sample*, were in good agreement with the degradation products and its ultraviolet spectrum was of course similar to that of 1-methyl-3,3-dimethyleneoxindole. It was predicted therefore, on the basis of these similarities and by comparison with 1-methyl-3,3-dimethyleneoxindole, that the degradation products from the oxindole alkaloids had the structure 3,3-dimethyleneoxindole. Figures 5 and 16 give infrared and ultraviolet absorption spectra comparisons. A melting point sample of Kondo's compound** showed no depression on mixed melting point determination with authentic 3,3-dimethyleneoxindole.

Since for biogenetic reasons oxindole alkaloids must possess a 3-ethanamino grouping, a possible mechanism for the formation of the degradation product would be the following.

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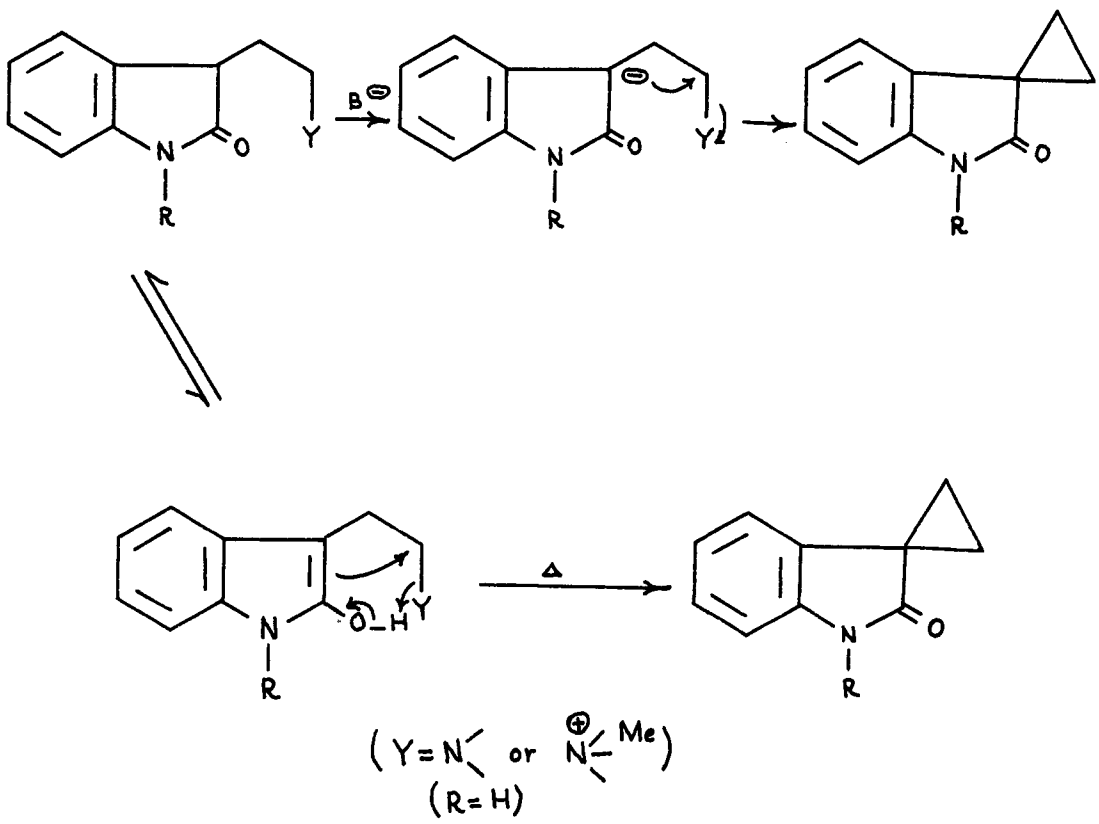
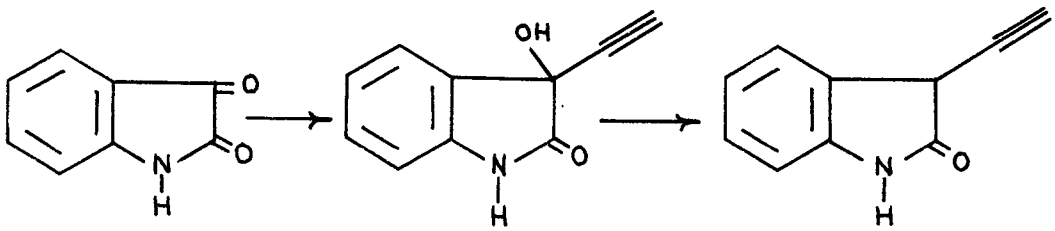
[37]D. G. Markees and A. Burger, J. Am. Chem. Soc., 71, 2031-5 (1949).

*A sample was kindly supplied by Professor Burger.

**A sample was kindly supplied by Dr. T. Nozoye of Dr. Kondo's group.



Some attempts were made to synthesize 3-vinyloxindole to compare its properties with those of 3,3-dimethyleneoxindole. The synthetic path proposed was to react lithium acetylide with isatin to form the corresponding dioxindole, and then by a reductive step (catalytically, chemically or both) produce 3-vinyloxindole.



Precedence for the reductive step can be found in various reports of conversion of dioxindoles to oxindoles[38,39,40,41], and of triple bonds to double bonds[42,43].

However, although 3-ethynyldioxindole was synthesized, various attempted catalytic reductions of other dioxindoles to oxindoles suggested that catalytic conditions stringent enough to remove the hydroxyl group by hydrogenolysis would certainly reduce a triple-bond to the singly-bonded system.

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[38] C. Marschalk, Ber., 45, 582-5 (1912).

[39] J. M. Gulland, R. Robinson, J. Scott and S. Thornley, J. Chem. Soc., 1929, 2924-41.

[40] P. L. Julian and H. C. Printy, J. Am. Chem. Soc., 71, 3206-7 (1949).

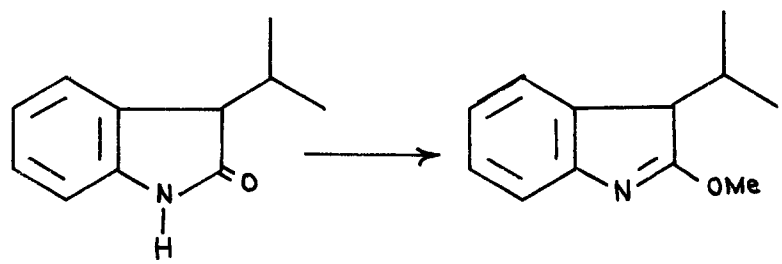
[41] B. Sakurai, Bull. Chem. Soc. Japan, 17, 269-74 (1942).

[42] K. N. Campbell and M. J. O'Connor, J. Am. Chem. Soc., 61, 2897-900 (1939).

[43] A. F. Thompson and S. B. Wyatt, J. Am. Chem. Soc., 62, 2555-6 (1940).

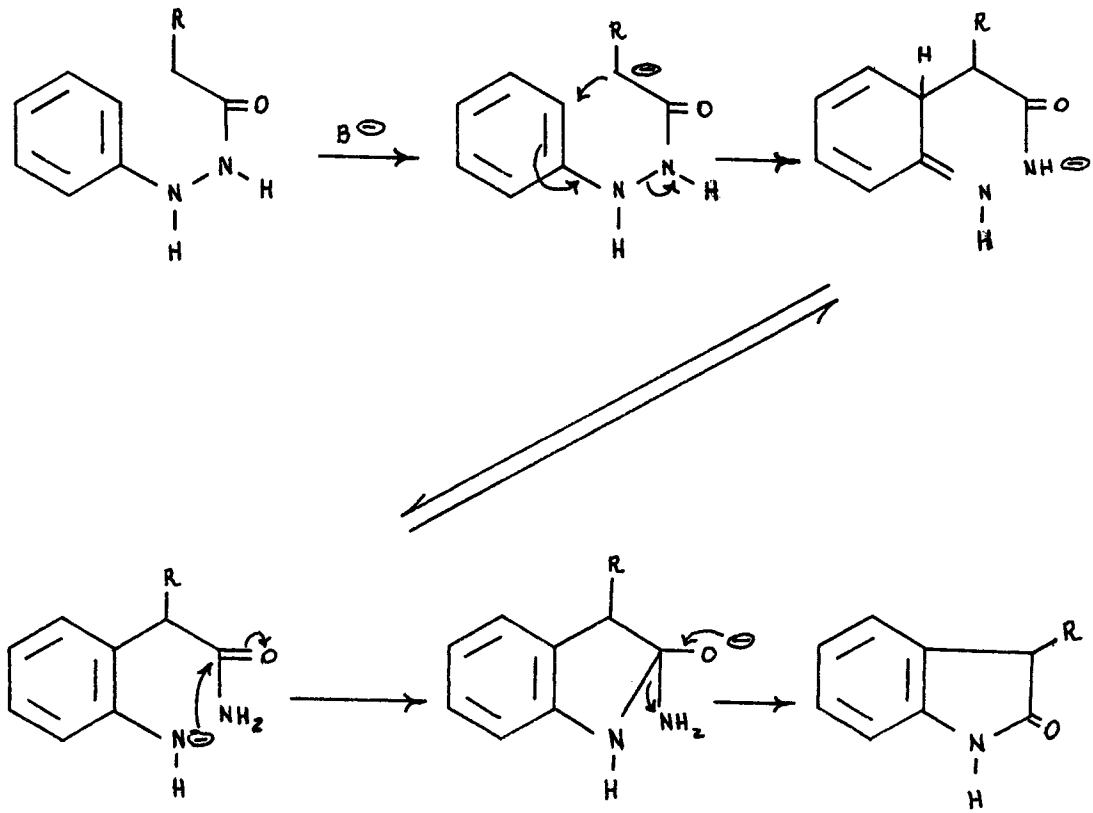
For example dioxindole was not catalytically reduced using palladium hydroxide on barium sulfate while with platinum oxide in glacial acetic acid and 3-isopropyldioxindole, amounts of hydrogen equivalent to two to three moles were absorbed, indicating a much deeper-seated reaction then simple hydrogenolysis. Furthermore, although mild catalytic conditions might be predicted to produce 3-vinyldioxindole from 3-ethynyldioxindole, further chemical reduction of the hydroxyl group would give as a final product 3-ethylideneoxindole. Infrared and ultraviolet absorption spectra are given in Figures 6 and 17.

One of the possible exceptions mentioned earlier to the criterion of N-alkylation prior to C-alkylation or O-alkylation is found in the reported O-alkylation of 3-isopropyloxindole through its silver salt to produce 2-methoxy-3-isopropylindolenine[4].



In view of the well-established fact that indolenines, to be stable as such, must be 3,3-disubstituted, it seemed more probable that this compound would actually have the tautomeric indole structure, and if so, would be a good "model" compound for infrared and ultraviolet absorption spectra studies of O-alkylated oxindoles.

Consequently, this reaction was reinvestigated, the first step being the synthesis of 3-isopropyloxindole by the Brunner procedure. This involves the condensation by ring closure of a phenylhydrazide in the presence of calcium oxide, of which the following mechanism represents a possible path.



The repetition of this preparation gave a compound the melting point of which was in good agreement with that of Schwarz[4] and which possessed infrared and ultraviolet absorption spectra characteristic of an oxindole. However, using the reported conditions for the preparation of the silver salt[4] (aqueous silver nitrate plus a dilute solution of the oxindole) no reaction occurred, whereas a silver salt was readily formed when an alcoholic solution of the compound was treated with ammoniacal silver nitrate solution (a procedure previously employed by Brunner[2] with 3,3-dimethyloxindole, but stated by Schwarz[4] to be ineffective with his compound). Furthermore, on reaction of this silver salt with methyl iodide, no product identical with that reported by Schwarz could be isolated, but rather a very small amount of a compound was formed having a melting point widely different from the Schwarz product*.

This apparent anomaly was clarified somewhat when a repetition of the preparation of 3-isopropyloxindole yielded a different product, having however the same melting point as 3-isopropyloxindole but other properties more like those of the compound described by Schwarz. For example, this compound formed no silver salt on treatment with ammoniacal

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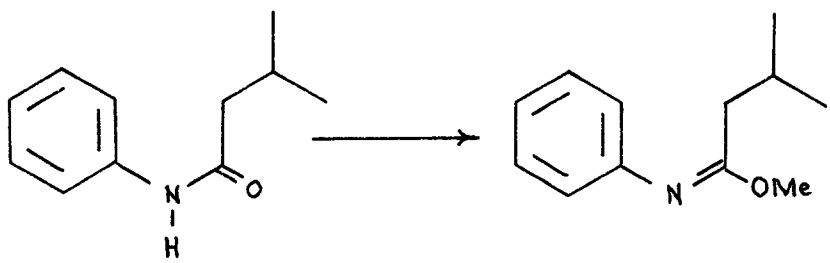
*See p. 72 for further discussion of this compound.

silver nitrate solution. A study of the analyses of this compound and its infrared and ultraviolet absorption spectra indicated it to be actually isovaleranilide, a fact confirmed on comparison by mixed melting point with an authentic sample.

This would suggest that the compound reported as 3-isopropyloxindole might have been actually isovaleranilide (their analyses differ only slightly), and that if indeed O-alkylation via the silver salt occurred, the product would be an O-alkylated anilide.



There is precedence for such a reaction in the O-alkylation of anilides via silver oxide[44], which would be completely analogous to this.

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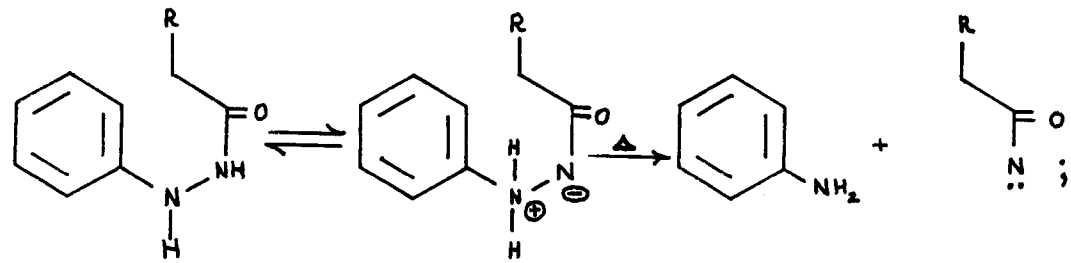
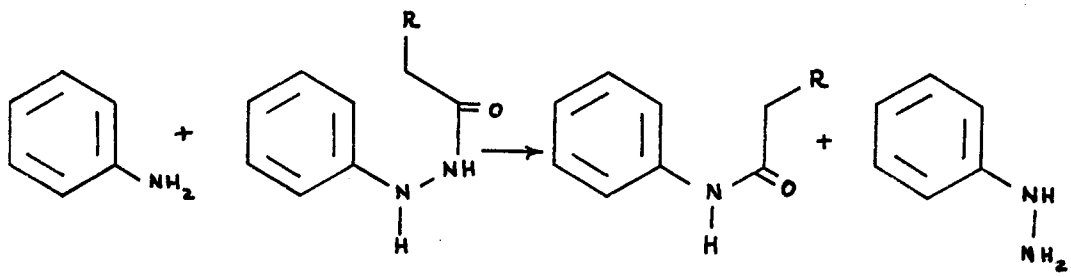
[44]G. D. Lander, J. Chem. Soc., 1900, 729-53.

A possible mechanism for the formation of isovaleranilide from isovalerylphenylhydrazide might be the following.



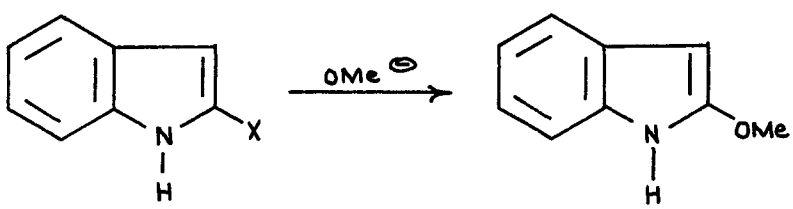


The formation of aniline as one of the products is an observed fact in reactions of this type. A summary of the infrared and ultraviolet absorption spectra of this series of compounds is shown in Figures 7 and 18.

Another possible route to the synthesis of 3-isopropyloxindole would be via 3-isopropyldioxindole (See Figures 6 and 17) which was prepared by reaction of isopropylmagnesium bromide with isatin. However, the various reductive methods attempted to convert the dioxindole to the oxindole were unsuccessful (see page 58), although it is probable that this conversion could be accomplished by further careful study.

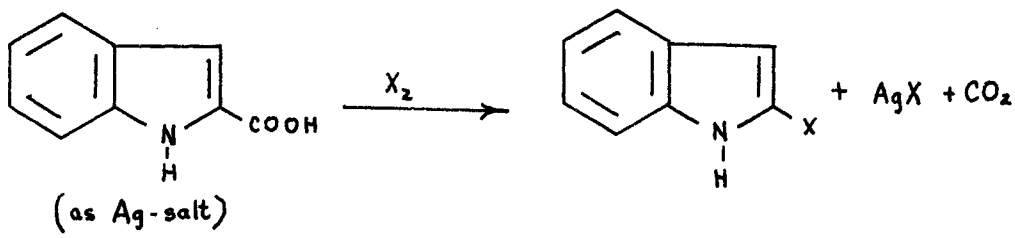
Thus it can be seen that the reported instances of simple O-alkylated oxindoles arose from structural misinterpretations, so that it became necessary to devise a synthetic route to obtain them.

One possibility which seemed to hold promise would be the reaction of a 2-haloindole with a base such as methoxide ion to produce 2-methoxyindole.

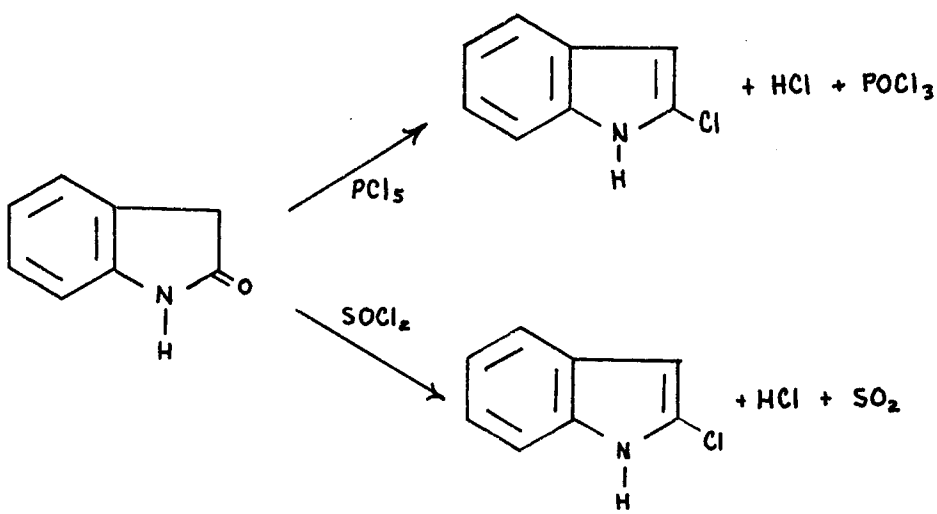


This centered attention on possible syntheses of 2-haloindoles for which, broadly speaking, there might be two main approaches. Starting with indole derivatives, as for

example, indole-2-carboxylic acid, 2-haloindole could be formed by a Hunsdiecker reaction.



On the other hand, starting with oxindole, and by the reaction with reagents such as phosphorus pentachloride or thionyl chloride, it might be possible to form 2-haloindoles.



However, the reaction of 3-isopropyloxindole with phosphorus pentachloride produced chlorination in the 3-position to yield 3-chloro-3-isopropyloxindole as evidenced by analyses and comparison with the product formed on reaction of isopropyldioxindole with thionyl chloride, with which it was identical. It is well known that phosphorus pentachloride is a chlorinating agent and in fact the reactions of acetanilide and chloroacetanilides with phosphorus pentachloride produce chlorination in the methyl group together with the chlorimine, the amount of chlorination depending on the quantity of phosphorus pentachloride used[45]. Infrared and ultraviolet absorption spectra are shown in Figures 8 and 19.

It was thought therefore that thionyl chloride which is not a chlorinating agent and which has recently been employed to convert o-nitrophenylacetamide to o-nitrophenylacetonitrile[36], a process which must involve intermediate formation of a chlorimine would be a suitable reagent to convert oxindoles to 2-chloroindoles.

The reaction of thionyl chloride with oxindole itself or 1-methyloxindole produced a dark-red crystalline material, which in the case of the product from 1-methyloxindole seems

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[45] J. von Braun, F. Jostes and W. Münch, Ann., 453, 113-47 (1927).

to be dimeric by analyses and probably involves double-bond formation at the 3-position since in "test-tube" runs using 3-monoalkyloxindoles, no such red color developed. Infrared and ultraviolet absorption spectra are shown in Figures 9 and 20.

The use of diazomethane as an alkylating agent for the β-dicarbonyl system contained in 1-methyl-3-hydroxymethyleneoxindole[6], and 3-hydroxymethyleneoxindole[19] has been mentioned previously. Whereas Horner[19] reported the formation of 3-methoxymethyleneoxindole from the reaction carried out in methanol, Julian[6] reports the formation of both 1-methyl-3-methoxymethyleneoxindole and 1-methyl-2-methoxy-3-formylindole but does not specify the solvent.

The reaction of diazomethane with 1-methyl-3-hydroxymethyleneoxindole in various solvents was therefore investigated. When ether was used as the solvent, the isolable product melted at 137-138°, and showed depression in melting point on admixture with 1-methyl-3-methoxymethyleneoxindole. Infrared and ultraviolet absorption spectra also indicated a structure radically different from that of 1-methyl-3-methoxymethyleneoxindole. Analyses however indicated the same empirical formula as 1-methyl-3-methoxymethyleneoxindole so that tentatively, 1-methyl-2-methoxy-3-formylindole

could be assigned as the structure pending rigorous proof by other chemical means.

The reaction of diazomethane with 1-methyl-3-hydroxymethyleneoxindole in methanol gave products which were very hard to purify so that even using chromatography, samples pure enough for mixed melting point determination were difficult to obtain. However, infrared spectra on several fractions from the chromatography showed all the characteristics of 1-methyl-3-methoxymethyleneoxindole, so that with the reservation that rearrangement could have occurred on the alumina chromatography column, the product was identified as 1-methyl-3-methoxymethyleneoxindole.

Infrared and ultraviolet absorption spectra are shown in Figures 10 and 21.

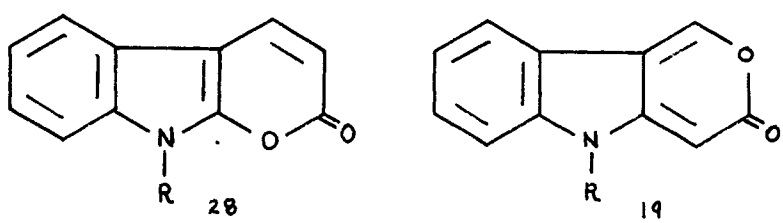
The procedure used for the alkylation of 1-methyloxindole using sodium hydride in benzene has been mentioned previously. It was employed successfully in the preparation of 1,3-dimethyloxindole, 1-methyl-3-(β-dimethylaminoethyl)-oxindole and 1-methyl-3-(β-bromoethyl)-oxindole. In all instances the reaction was carried out via the prior formation of the anion from 1-methyloxindole and an equivalent amount of sodium hydride in benzene followed by reaction with the appropriate alkyl halide. The reaction was of course heterogeneous, and it was felt that this heterogeneity was

advantageous in obtaining monoalkylation since the possibility for anion exchange would be greatly diminished under these conditions. The reported difficulty in obtaining monoalkylation of 1-methyloxindole[7], although the various methods attempted were not described, would be understandable for homogeneous conditions. In such cases, anion exchange would occur so that even with molar ratios at unity, mixtures of mono- and dialkylated products could result. This would be particularly true if the criterion is followed that the introduction of the second alkyl group is much easier than the first[7]. In fact, dialkylation has been shown to proceed well under homogeneous conditions[16,17].

It was hoped that this heterogeneous alkylation procedure could be applied to oxindole itself if the oxindole nitrogen was "protected" by a grouping which could later be removed. The compound decided on was 1-acetyloxindole, but unfortunately when the alkylation of 1-acetyloxindole was attempted, it was unsuccessful. The attempted formation of the anion with sodium hydride did not proceed well, giving color changes attributable perhaps to anion rearrangements and interactions. The further reaction with an alkyl halide such as β-phthalimidoethyl bromide resulted in recovery of the major portion of the alkyl halide. Some experiments were initiated using sodium dispersions and potassium tertiary

butoxide but again with little success. However further study of other possible "protecting" groups and of other possible bases should lead to the 3-alkylation of oxindole.

It has been mentioned previously that attempted Perkin condensations of 3-hydroxymethyleneoxindole and 1-methyl-3-hydroxymethyleneoxindole gave products to which various structures have been assigned[19,28].



(R=H or Me)

It was hoped that a study of the catalytic hydrogenation of the Perkin product from 1-methyl-3-hydroxymethyleneoxindole would aid in a better understanding of the correct structure. Under catalytic hydrogenation using platinum oxide in glacial acetic acid, there was a rapid uptake of one mole of hydrogen with complete loss of the dark red color of the solution to yield a product melting at 182-183° and having infrared and ultraviolet spectra consistent with those

of a simple oxindole. The analyses checked quite well for bis-(1-methyloxindolyl-3)-methane.

These results cast doubt on the structural assignments made for these compounds[19,28], as any mechanism for obtaining an oxindole from these structures by the catalytic absorption of one mole of hydrogen seemed highly impossible.

On checking the analyses reported for the Perkin condensation product of 3-hydroxymethyleneoxindole[28] it was found that they did not agree too well with the calculated values.

Anal.[28] Calcd. for $C_{11}H_7O_2N$: C, 71.33; H, 3.81; N, 7.57. Found: C, 70.95; H, 4.37; N, 7.75.

The analyses for the corresponding 1-methyl compound were not given, it being assumed that it had the analogous structure to the desmethyl compound[28].

The idea suggested itself that the Perkin product might have a bis-methyne structure* which on hydrogenation would give a bis-(oxindolyl)-methane.

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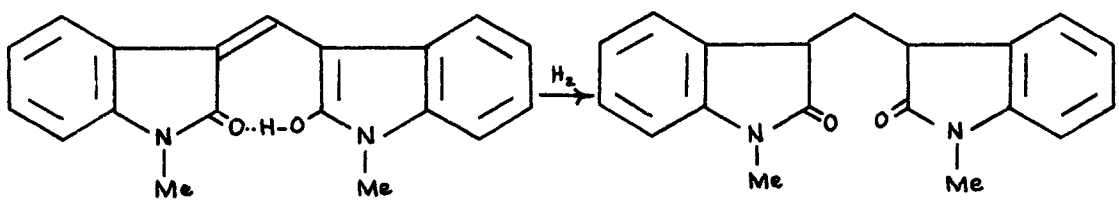
*The hydrogen-bonded structure shown for this compound although it involves a seven-membered ring would explain the red color of the compound and also its ultraviolet spectrum which is widely different from "model" oxindole compounds.

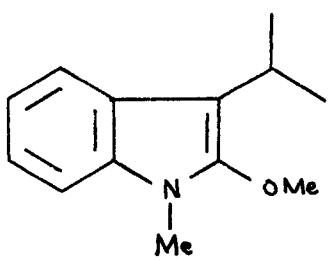


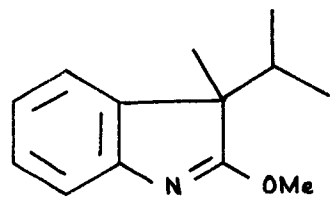
The synthesis of the bis-methyne compound was carried out by the reaction of the anion of 1-methyloxindole (prepared from 1-methyloxindole and sodium hydride in benzene) with 1-methyl-3-chloromethyleneoxindole (prepared from 1-methyl-3-hydroxymethyleneoxindole and thionyl chloride) to produce a yellow crystalline compound melting at 248-250°, not the same as the Perkin product and having analyses which do not check well for the bis-methyne compound, although infrared and ultraviolet spectra are consistent with this formulation.

Analyses of the Perkin product itself however showed that it must have a structure other than those reported[19,28].

Infrared and ultraviolet absorption spectra are shown in Figures 11 and 22.

The compound mentioned previously (see page 60), isolated from an attempted methylation of the silver salt of 3-isopropyloxindole, was obtained in too small a yield for analyses to be run. However, from the infrared and ultraviolet spectra (see Figures 7 and 18) tentative structures could be assigned. The infrared spectrum showed no oxindole carbonyl absorption and was void in the >NH region. The ultraviolet spectrum was different from that of a simple oxindole*. From a consideration of these facts the possible structures would be 1-methyl-2-methoxy-3-isopropylindole or 2-methoxy-3-methyl-3-isopropylindolenine, resulting from O-alkylation and N-alkylation in the one case, and from O-alkylation and C-alkylation in the other. It has been reported[46] that the ultraviolet spectrum of 2-methoxy-3,3-dimethylindolenine is quite similar to that of a simple oxindole which fact would cast some doubt on the substituted indolenine structure and thus favor the substituted indole structure.





*The log ϵ values may be incorrect due to errors in weighing the very small sample.

[46] M. Tomita, S. Uyeo and R. Yamamoto, J. Pharm. Soc. Japan, 64, 164-8 (1944).

SPECTRA

Infrared absorption spectra were run on all compounds using a Baird Double Beam infrared spectrophotometer except in one instance where high gain was required and a Perkin-Elmer Model 13 Direct Ratio infrared spectrophotometer was employed. Ultraviolet absorption spectra were run on all compounds using a Cary recording spectrophotometer. Special thanks are due to Dr. H. Shull, Dr. M. Margoshes, and Mr. R. M. Hedges for instruction in the operation of the Baird spectrophotometer and to Drs. H. Svec and S. Jaffe for instruction in the operation of the Cary spectrophotometer.

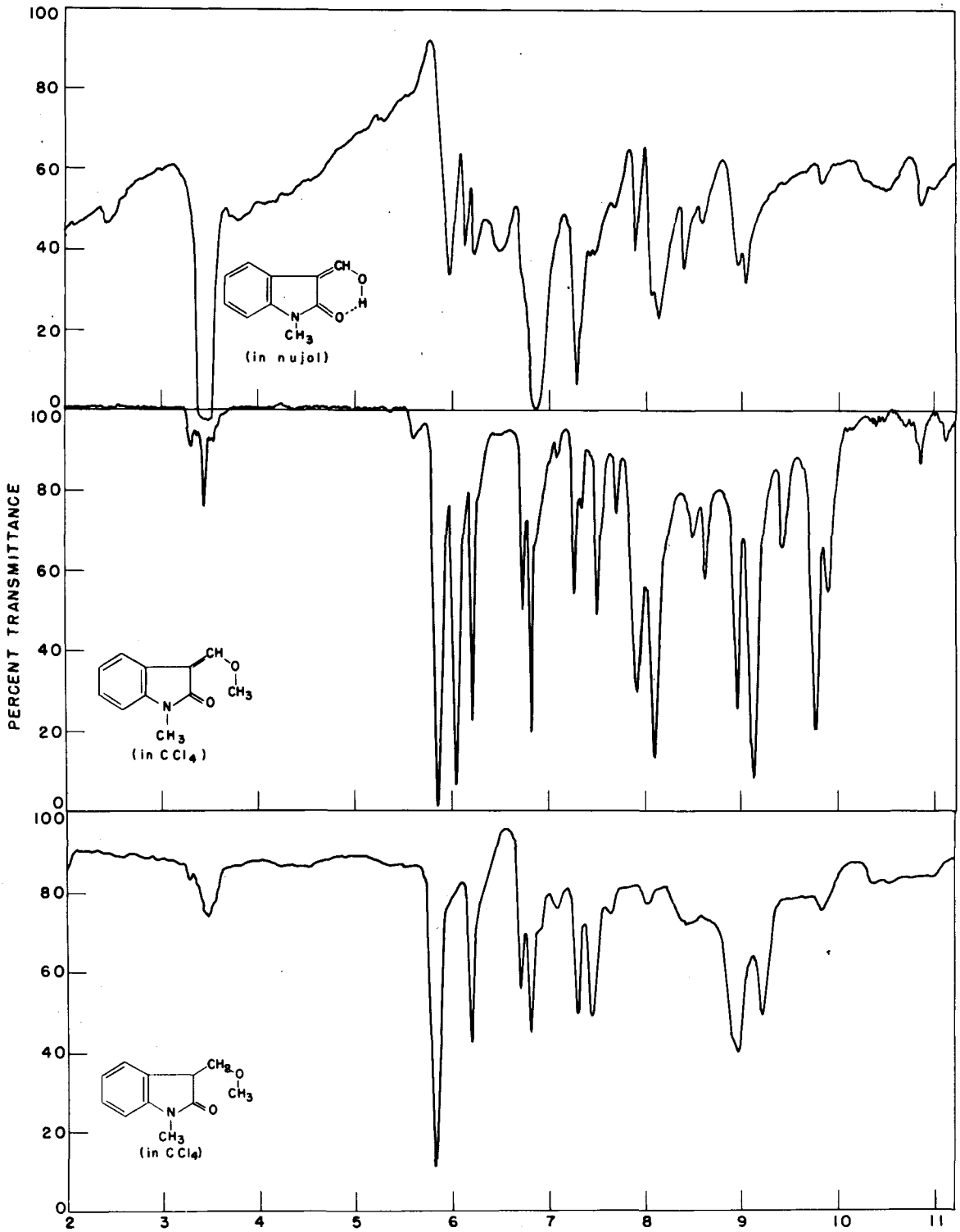


FIG. 1 INFRARED SPECTRA

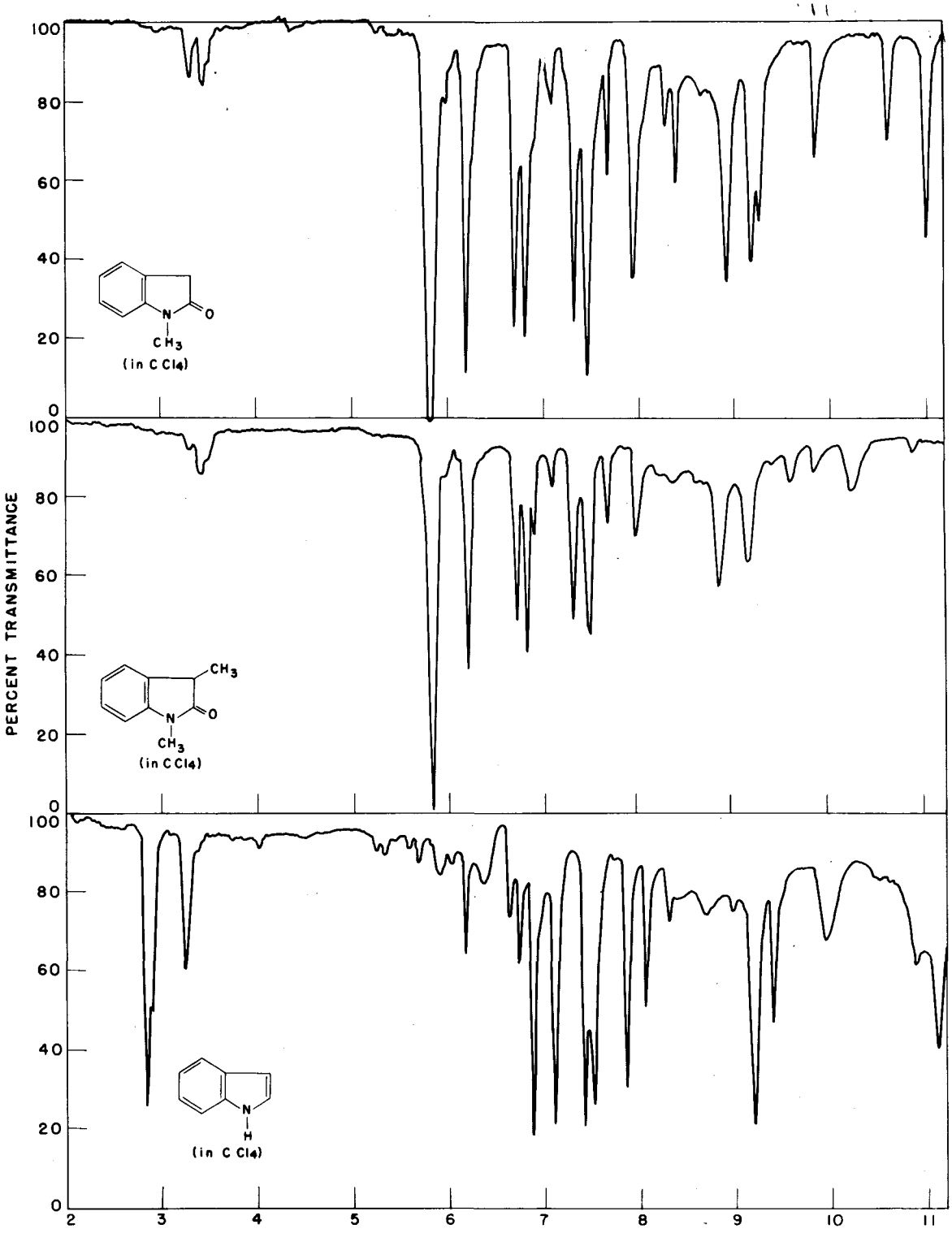


FIG. 2 INFRARED SPECTRA

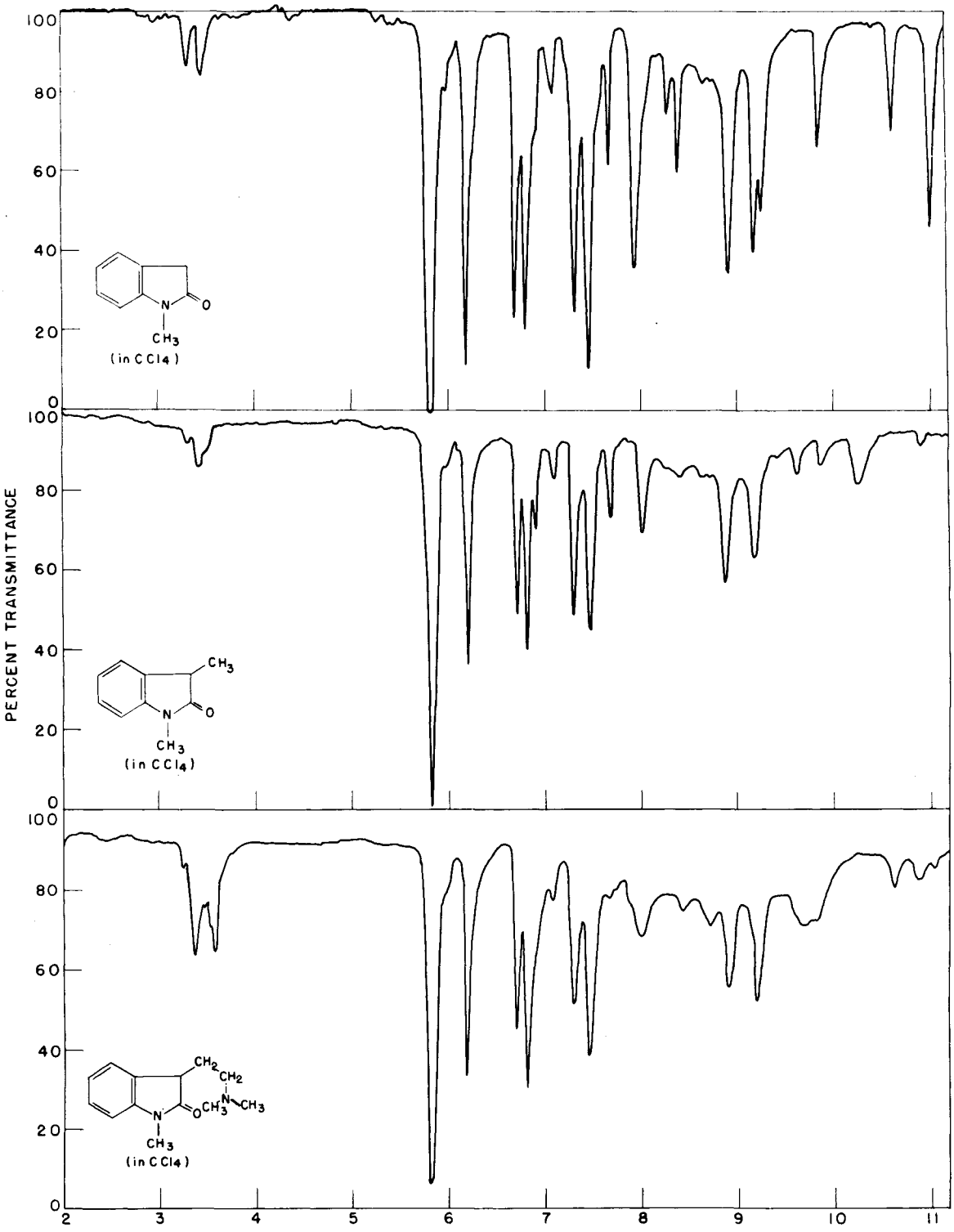


FIG. 3 INFRARED SPECTRA

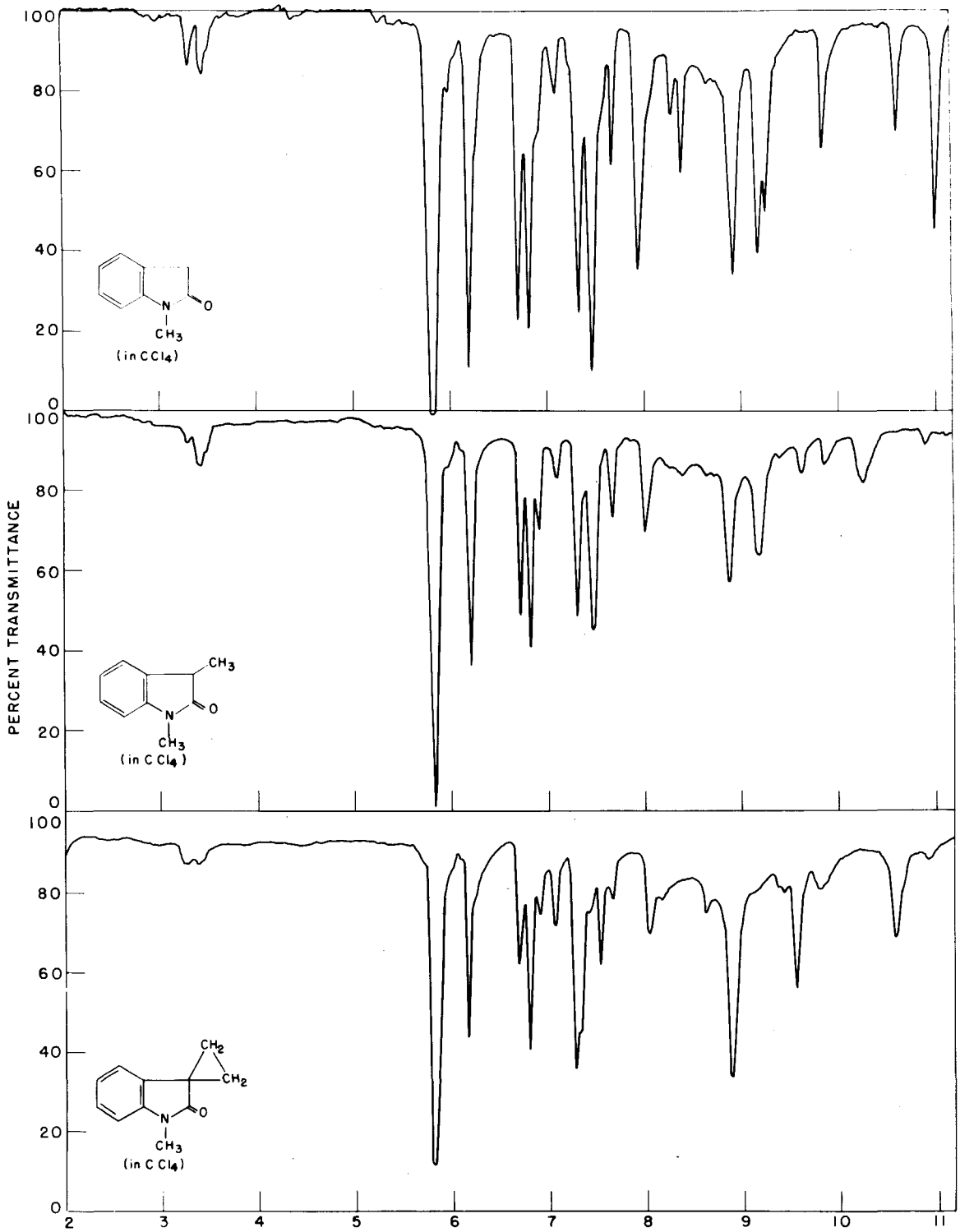


FIG. 4 INFRARED SPECTRA

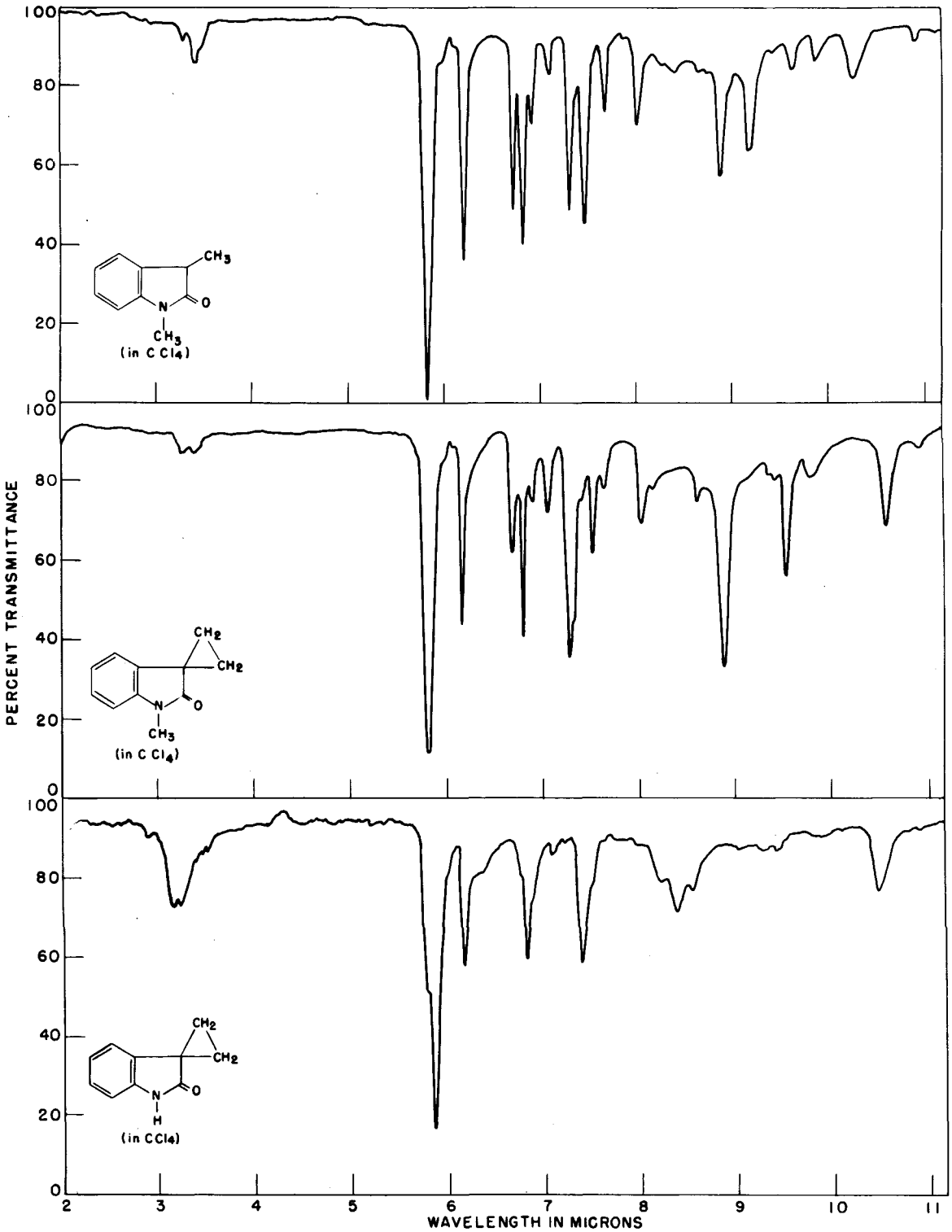


FIG. 5 INFRARED SPECTRA

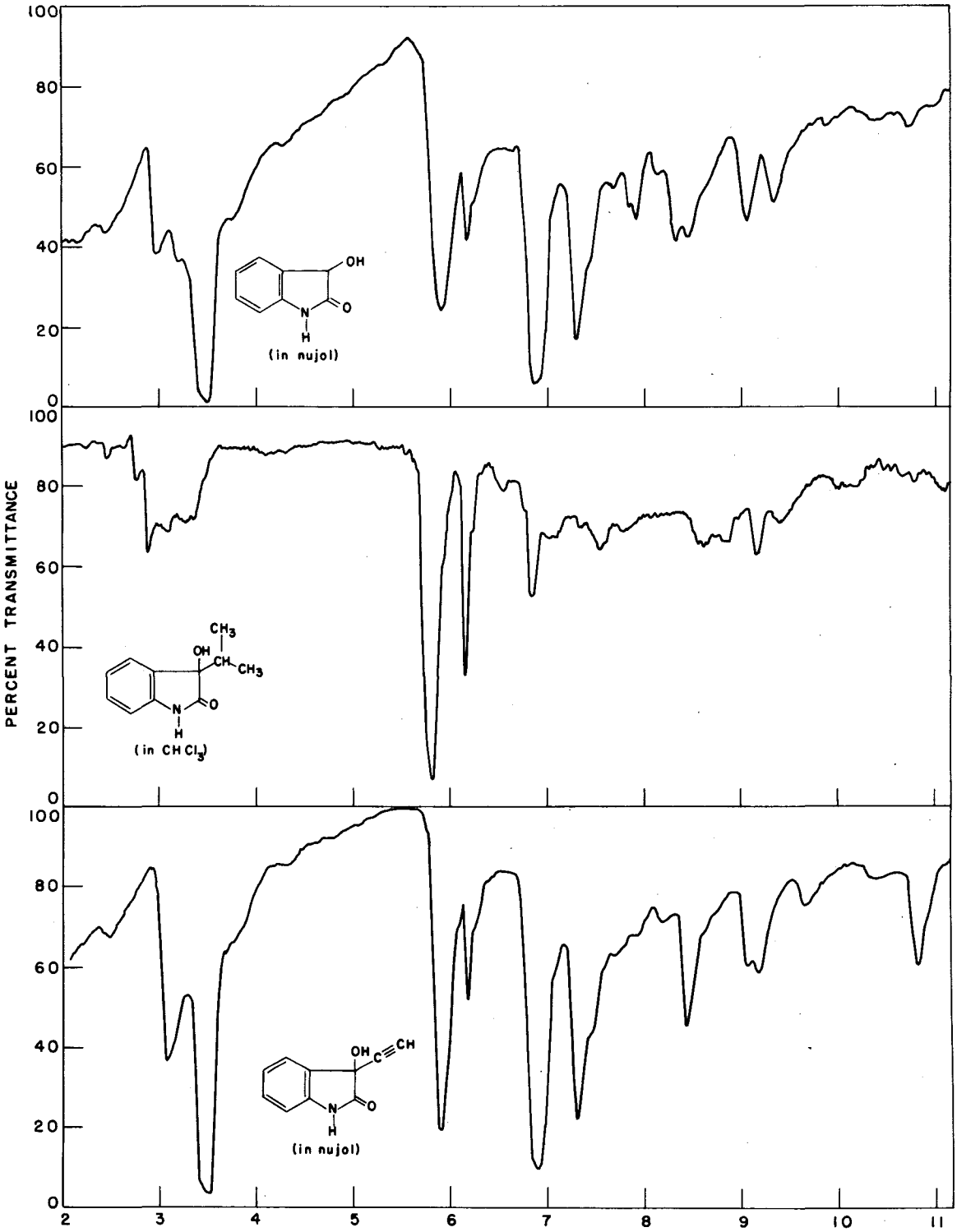


FIG. 6 INFRARED SPECTRA

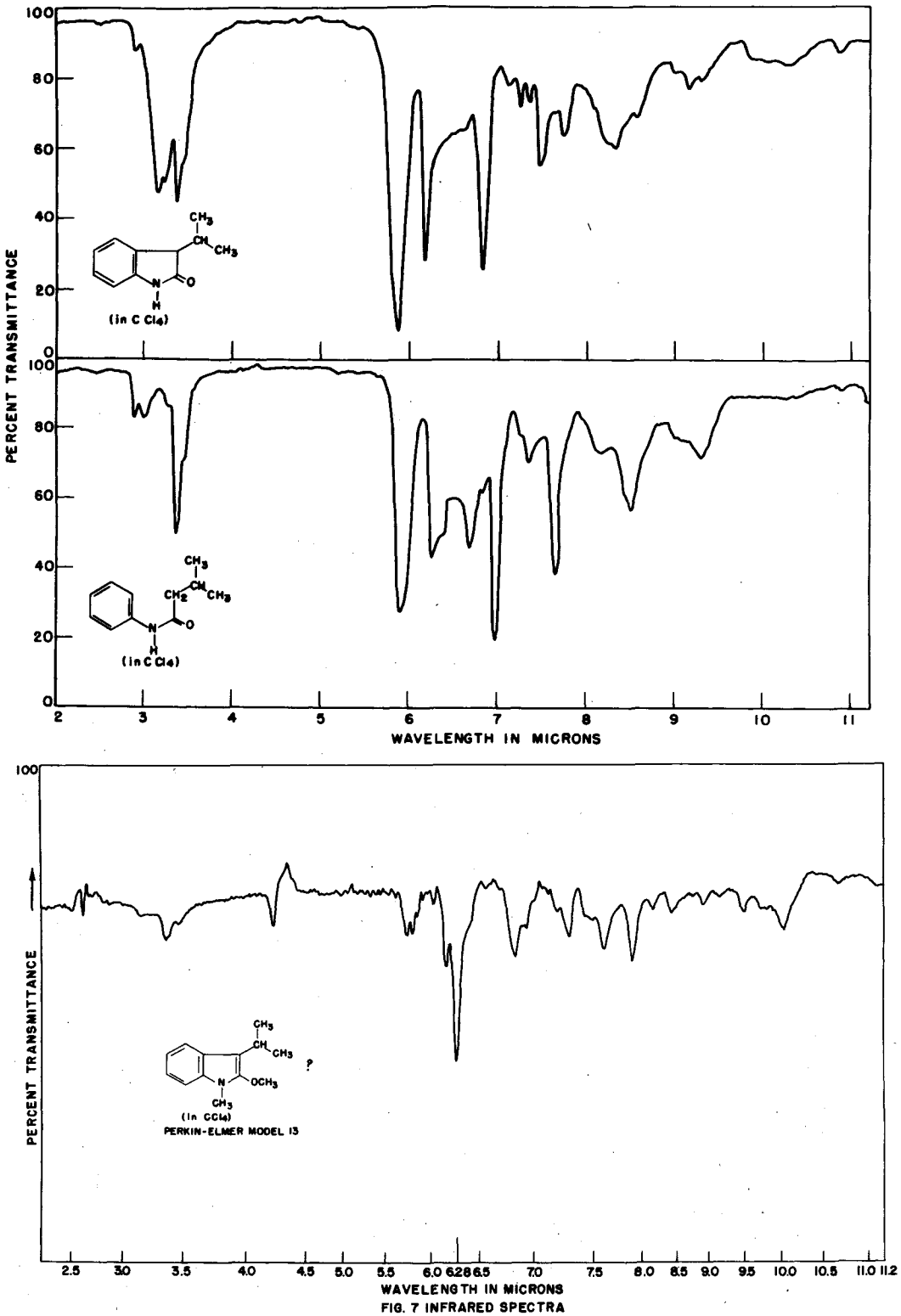


FIG. 7 INFRARED SPECTRA

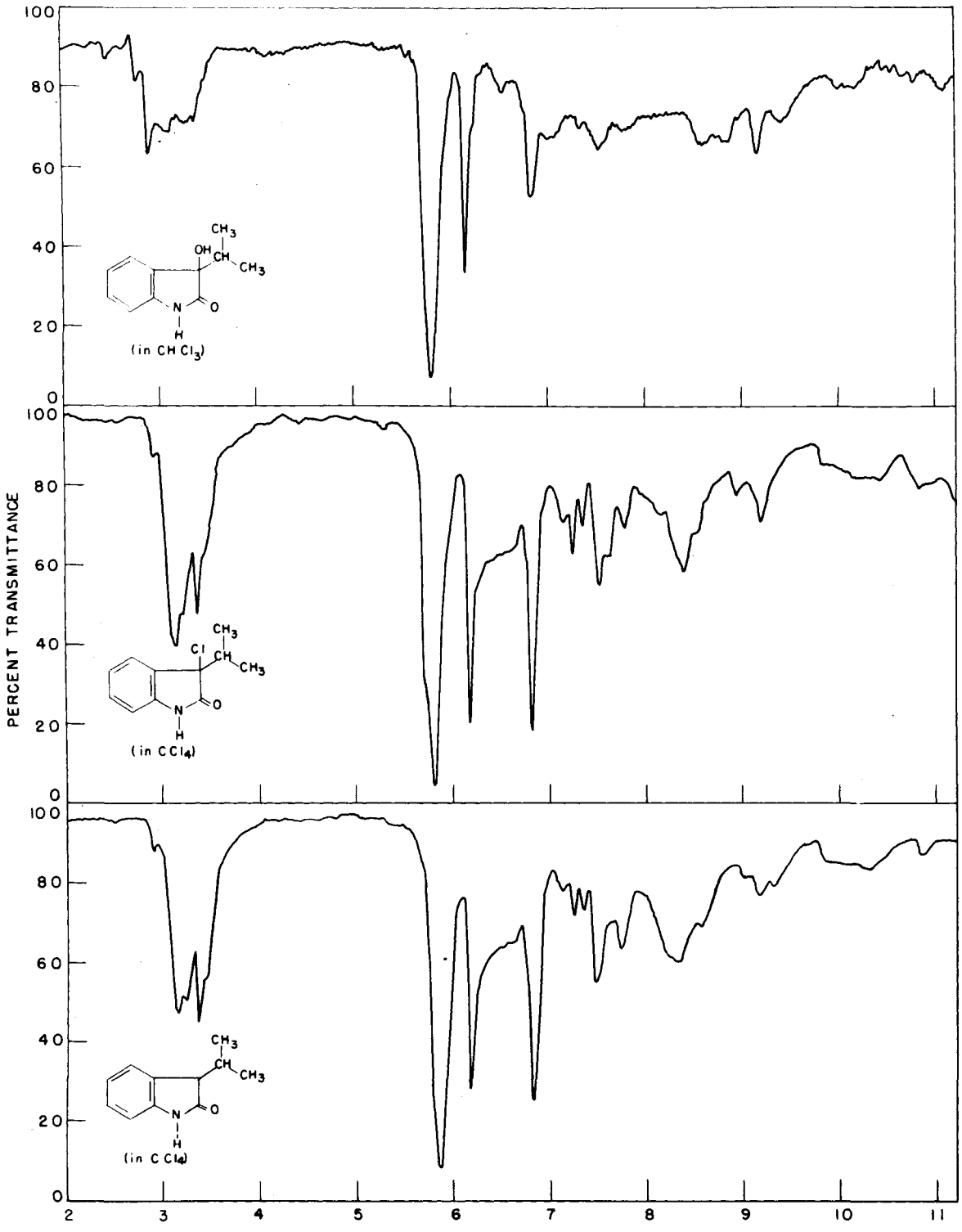


FIG. 8 INFRARED SPECTRA

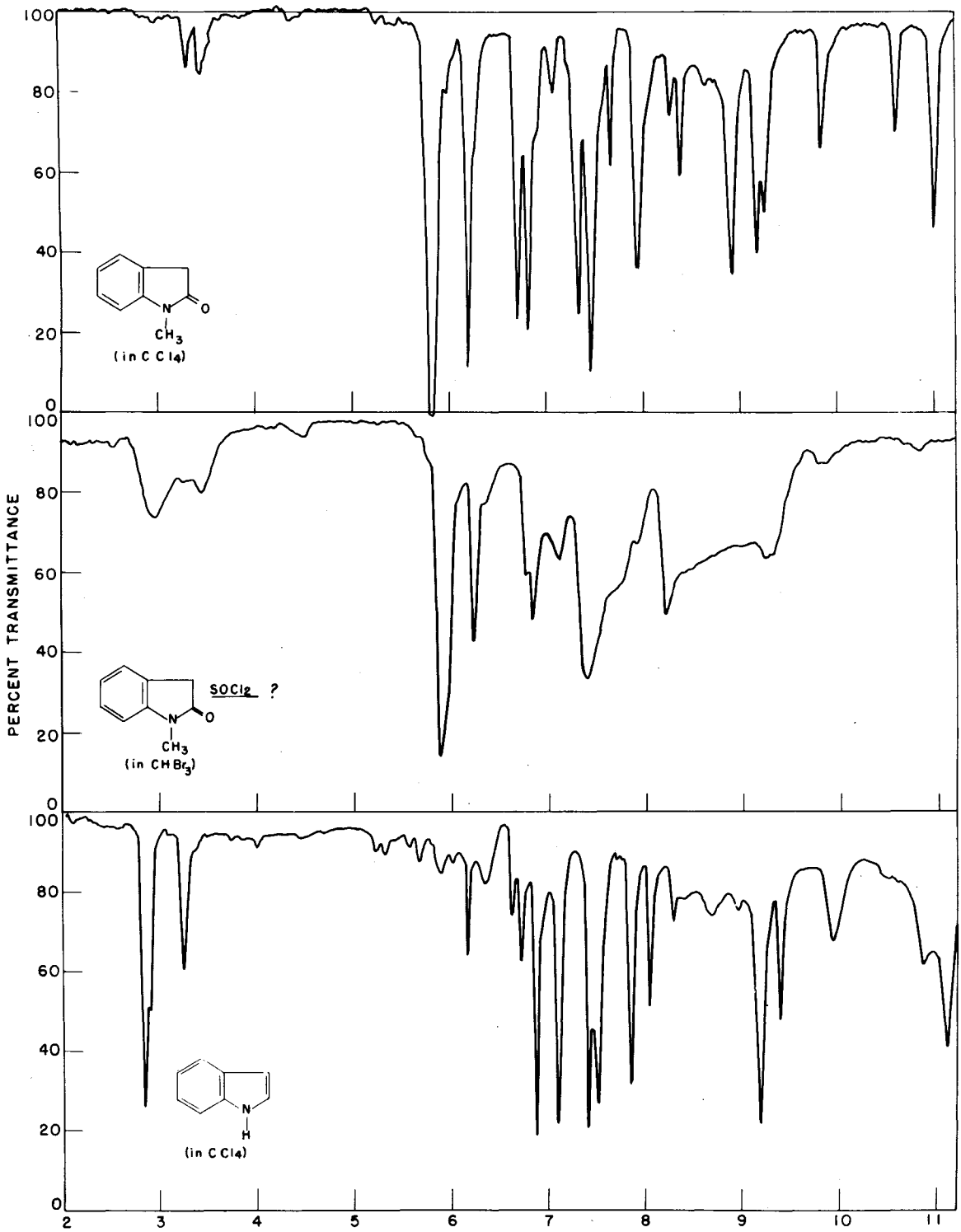


FIG. 9 INFRARED SPECTRA

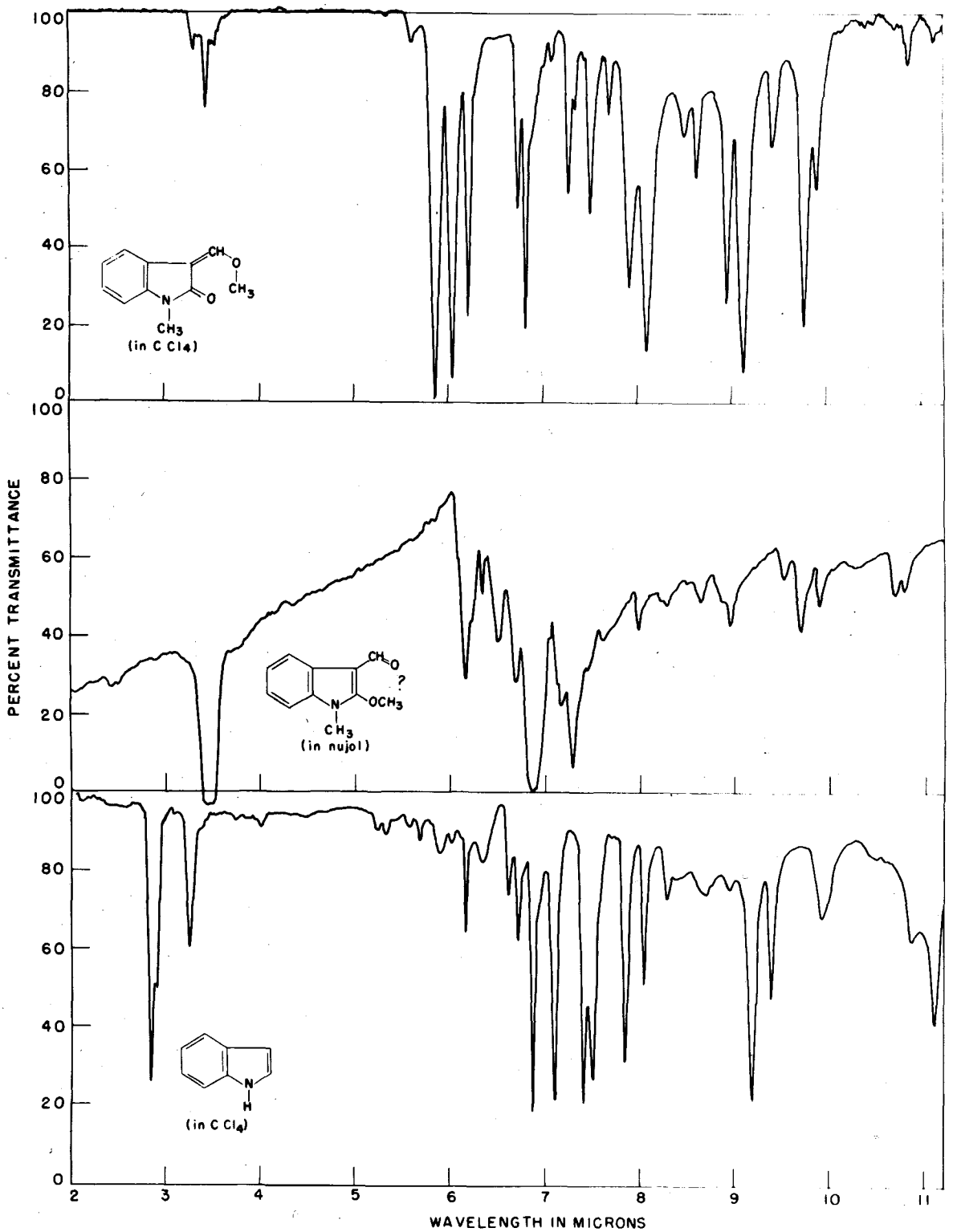


FIG. 10 INFRARED SPECTRA

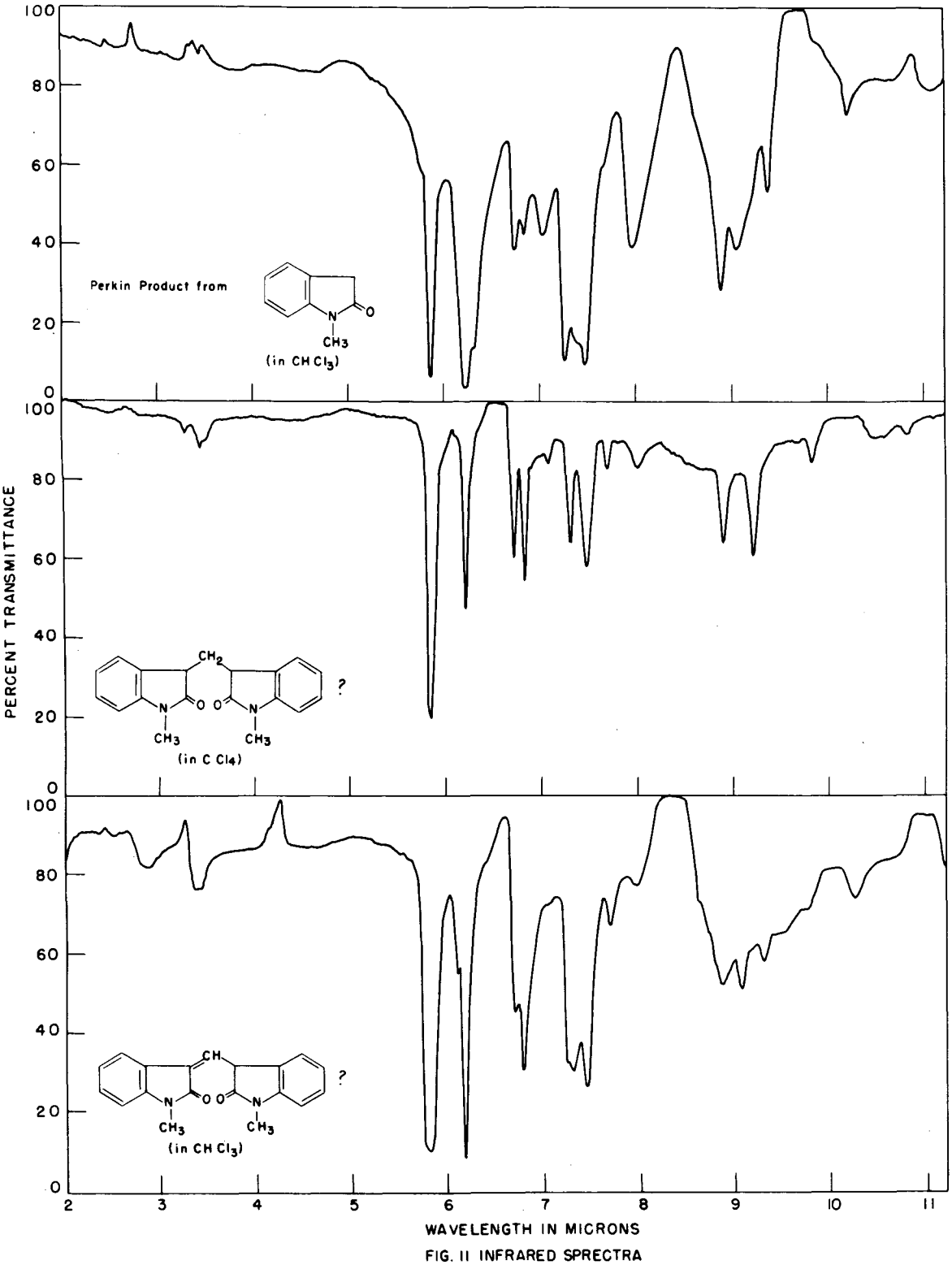


FIG. II INFRARED SPRECTRA

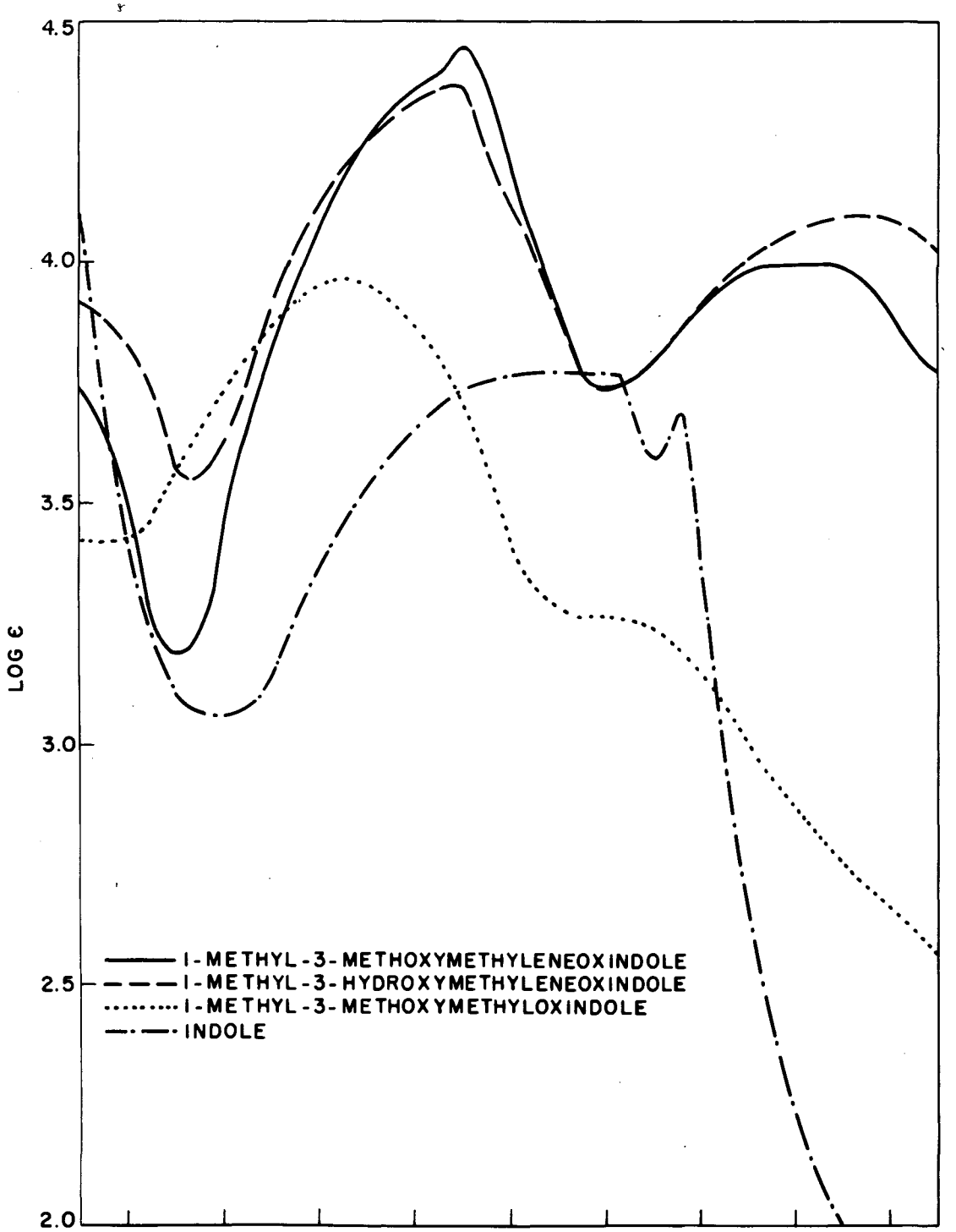


FIG. 12 ULTRAVIOLET SPECTRA

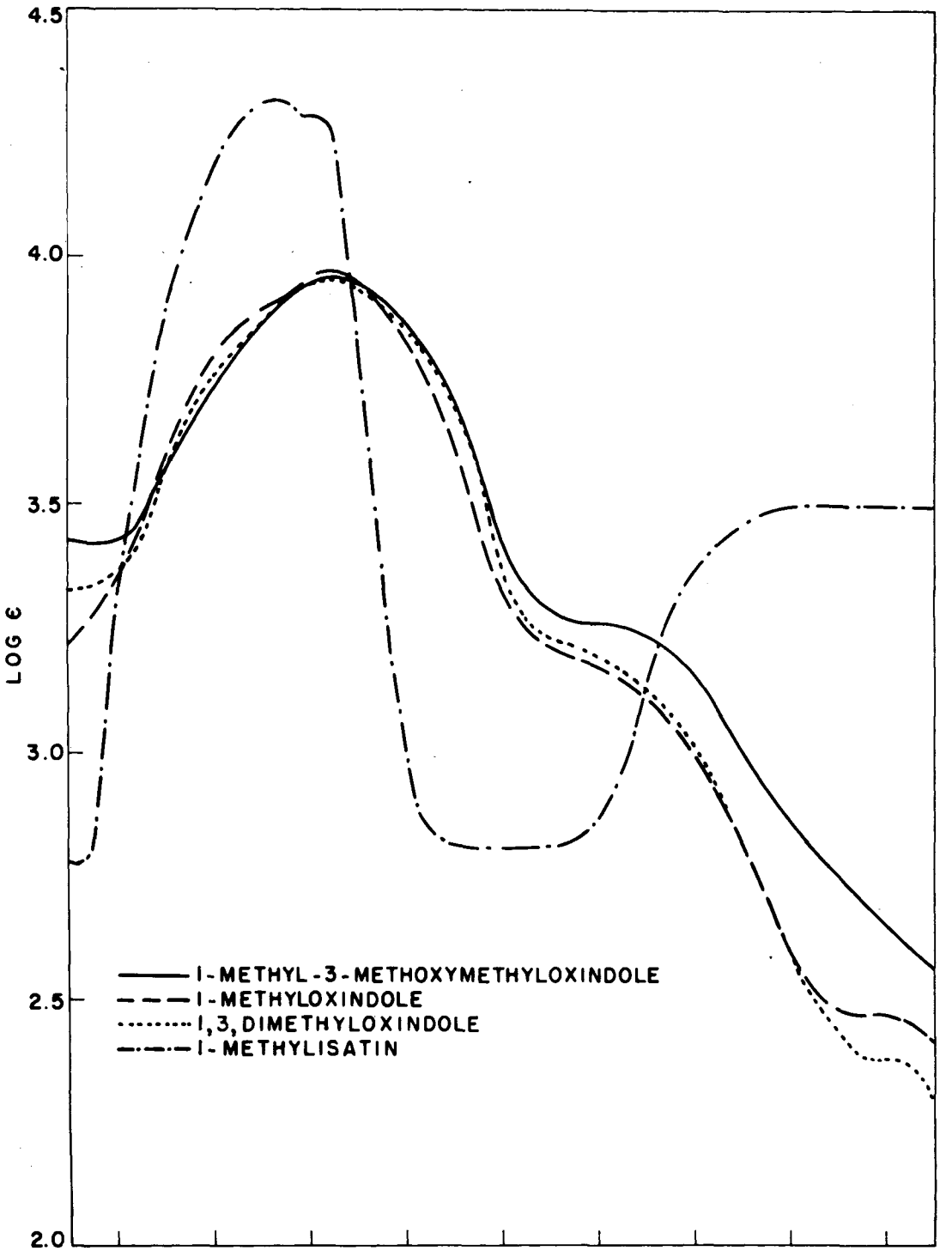


FIG. 13 ULTRAVIOLET SPECTRA

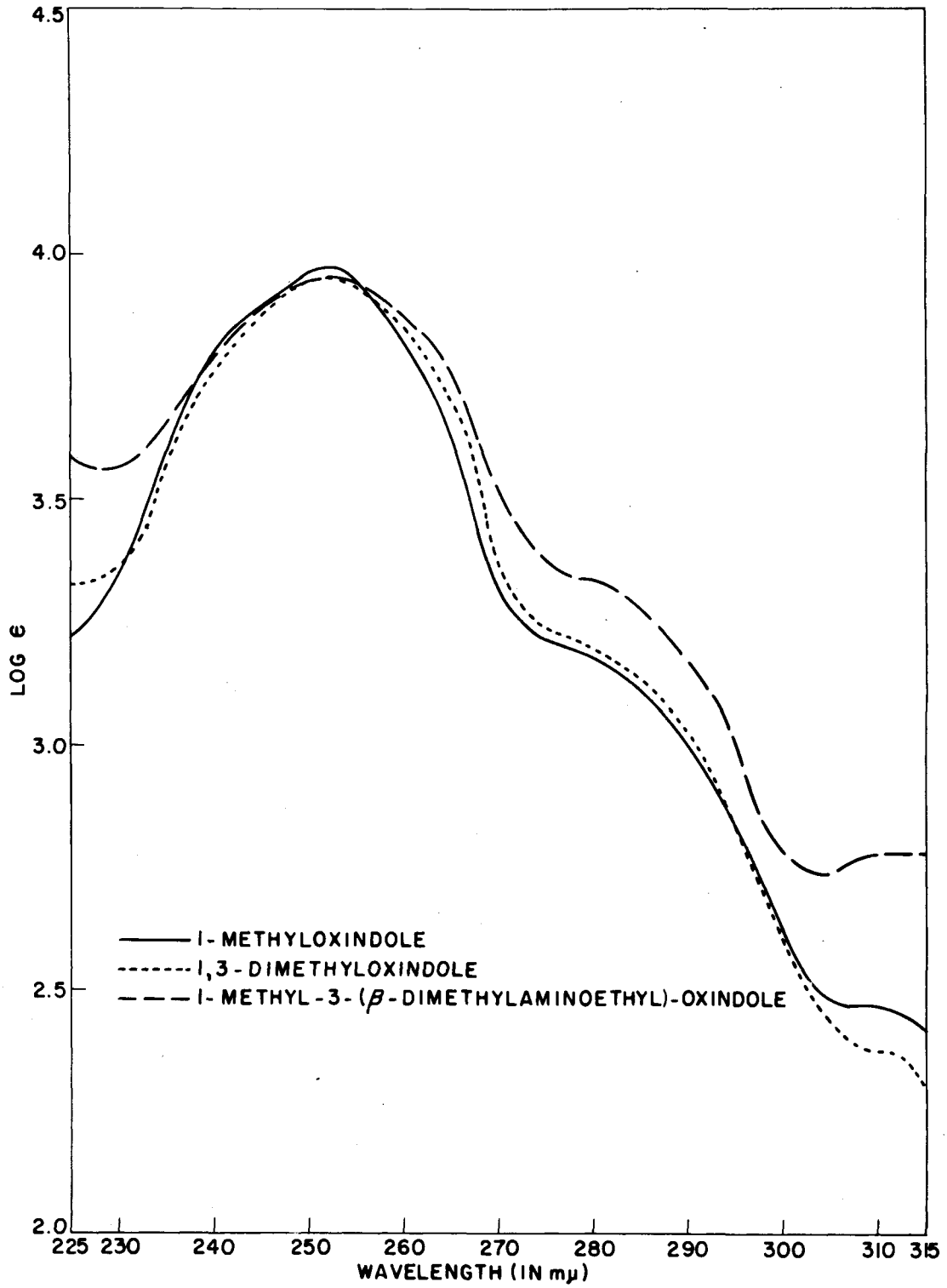


FIG. 14 ULTRAVIOLET SPECTRA

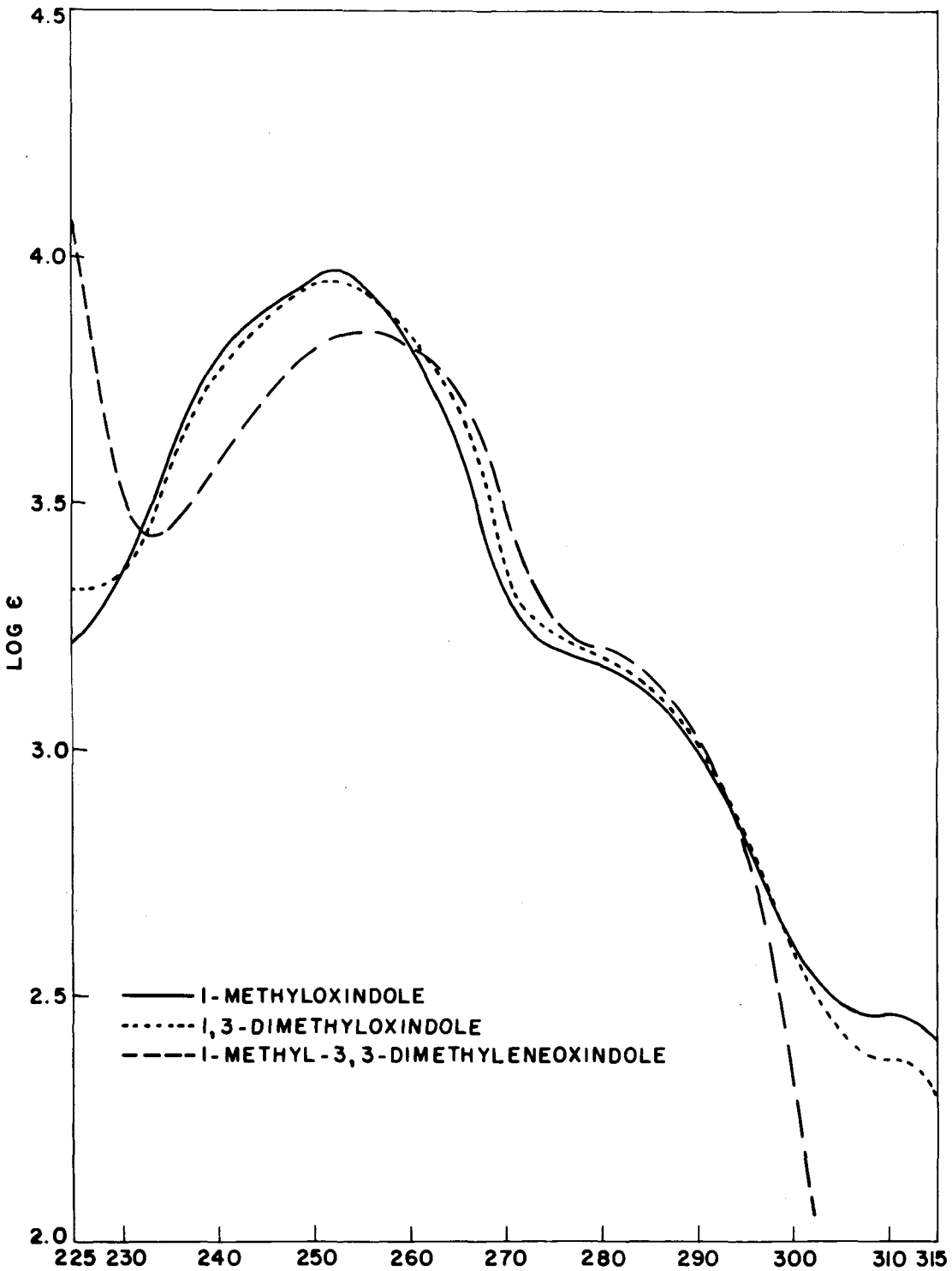


FIG. 15 ULTRAVIOLET SPECTRA

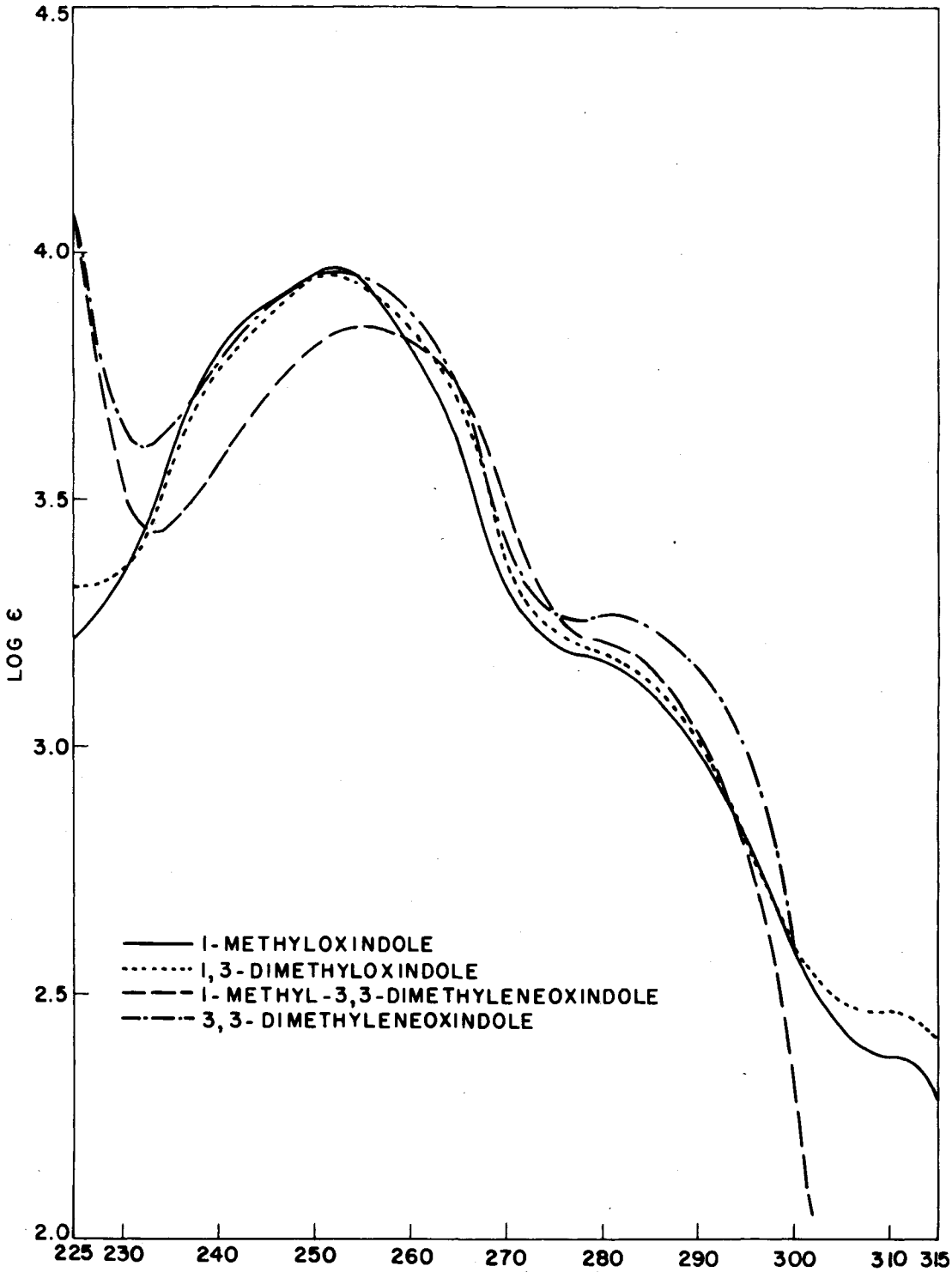


FIG. 16 ULTRAVIOLET SPECTRA

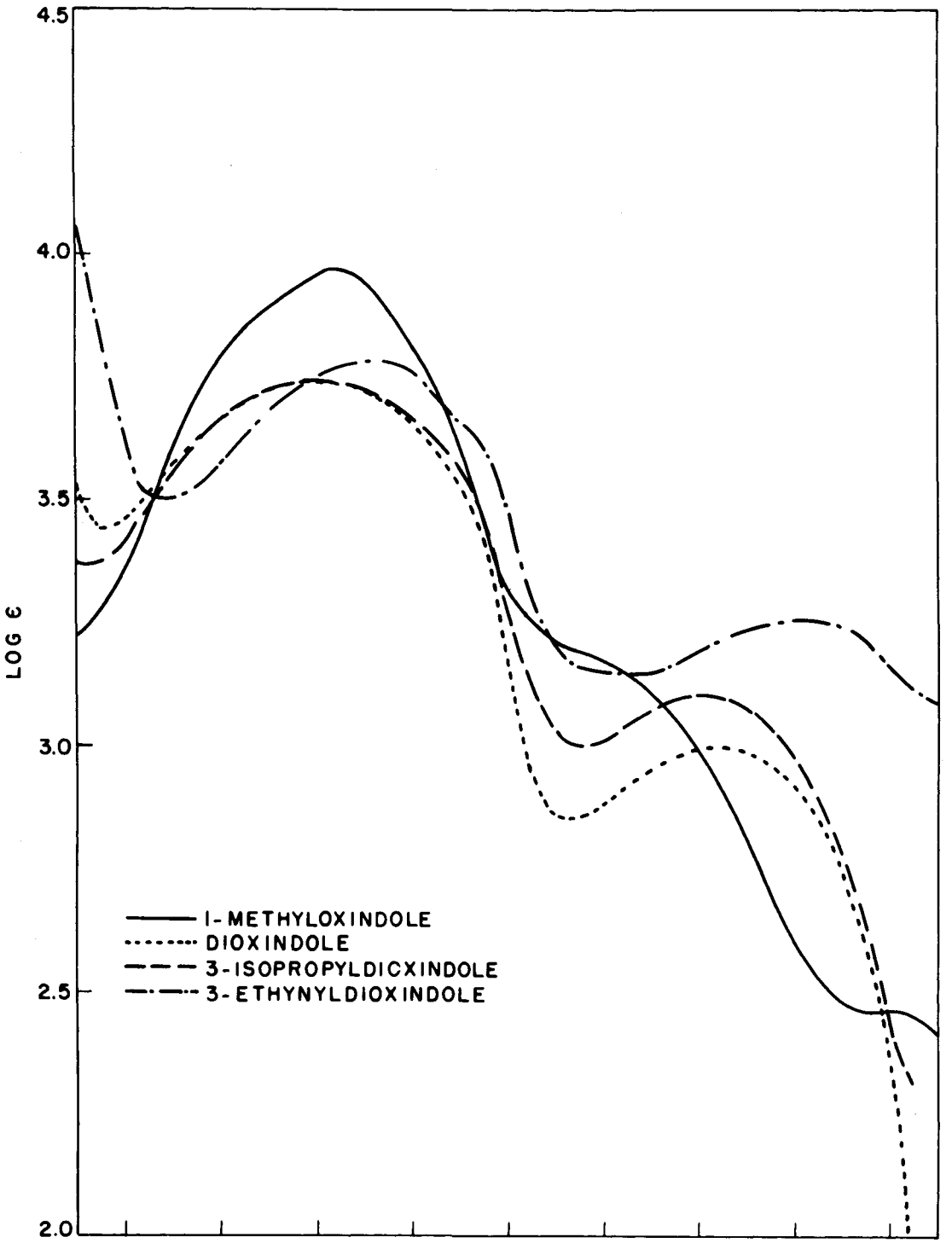


FIG. 17 ULTRAVIOLET SPECTRA

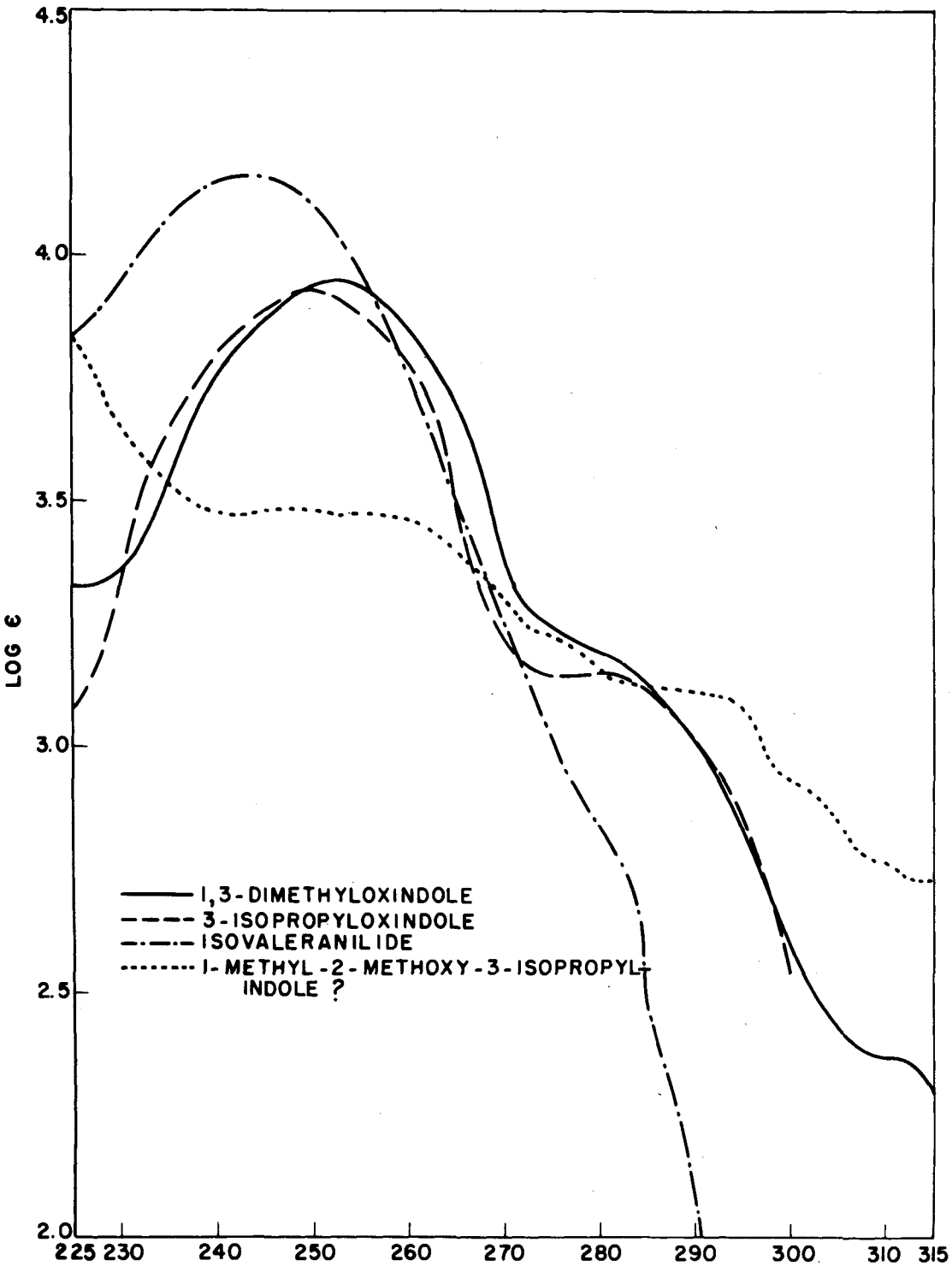


FIG. 18 ULTRAVIOLET SPECTRA

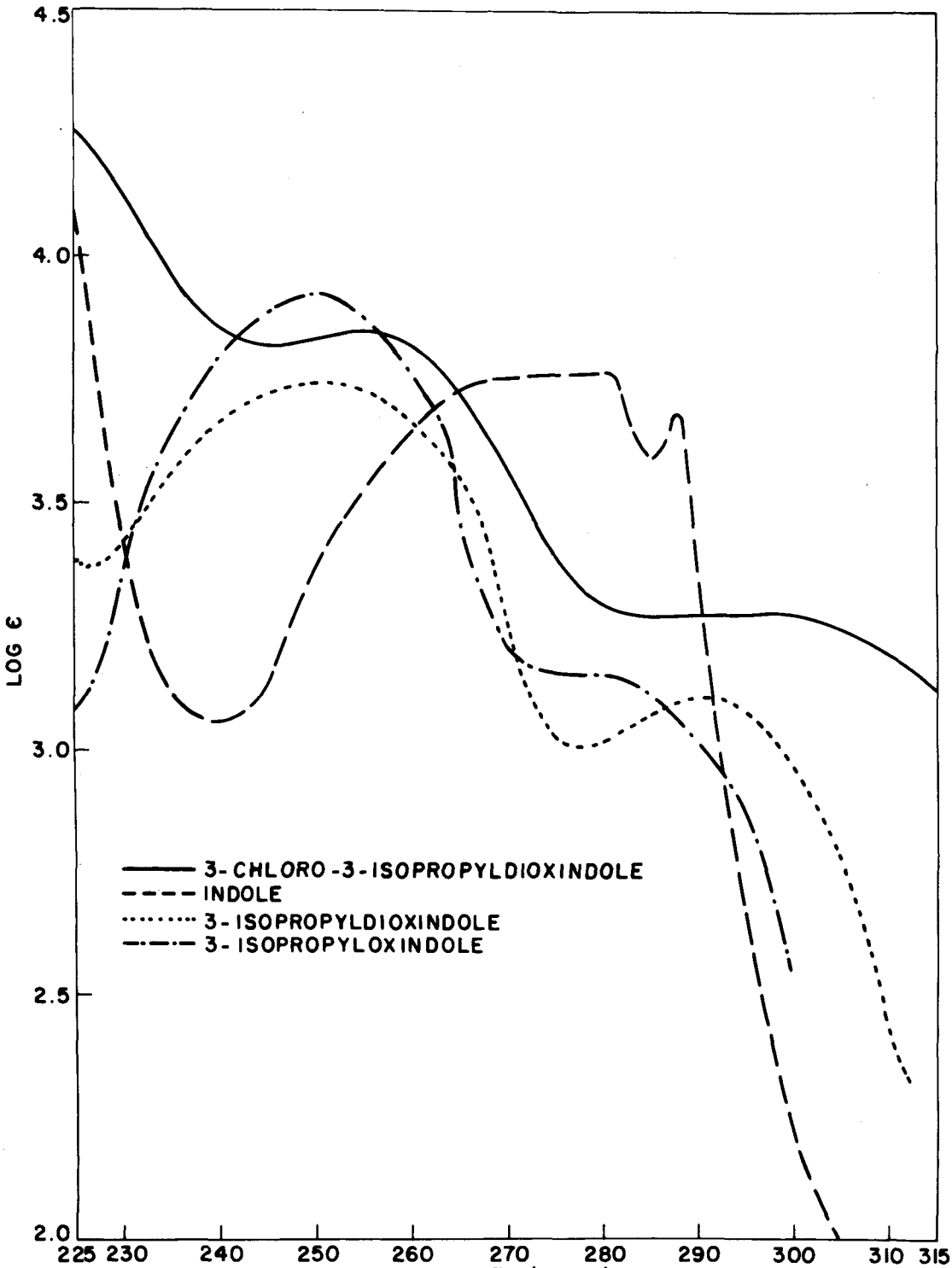


FIG. 19 ULTRAVIOLET SPECTRA

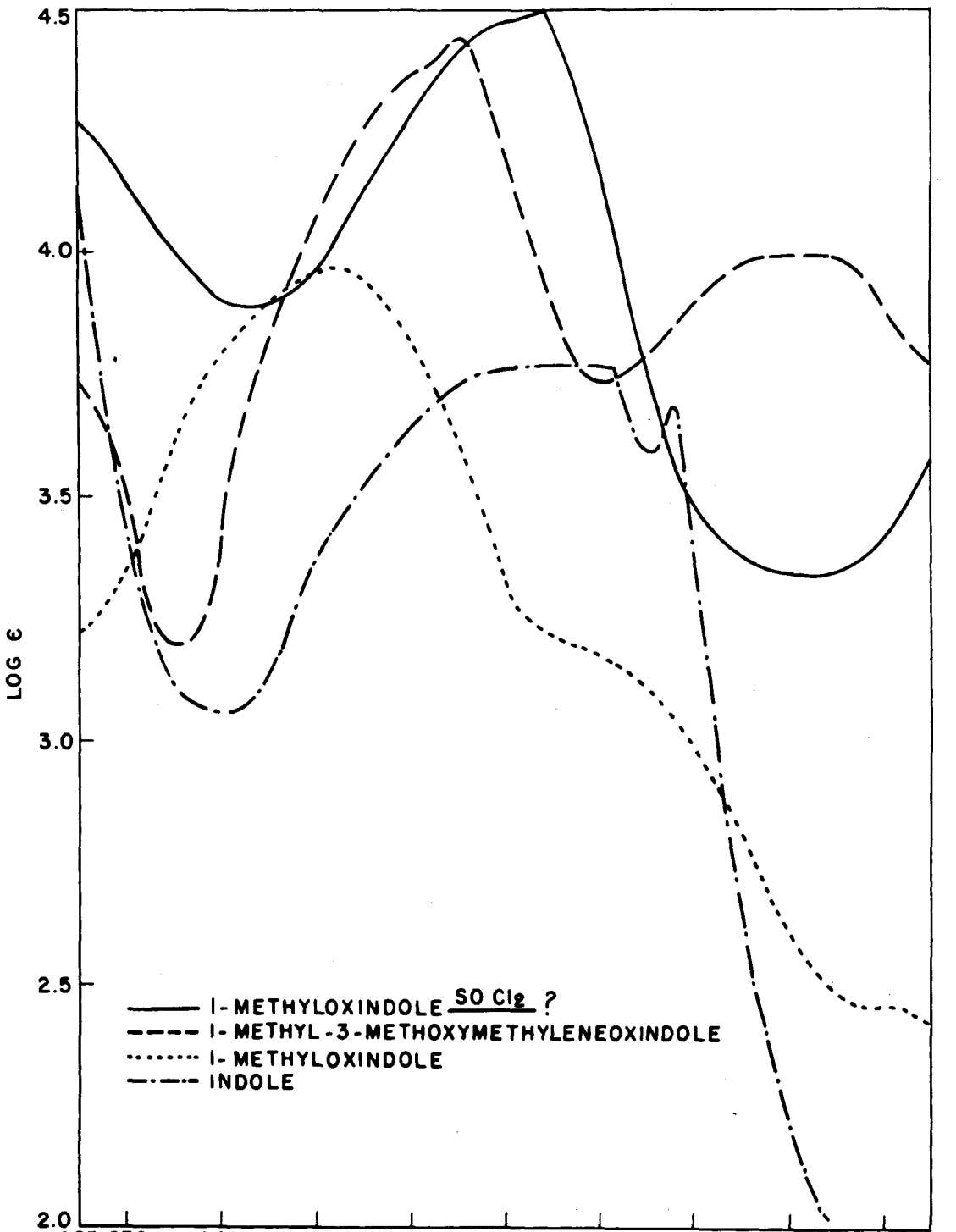


FIG. 20 ULTRAVIOLET SPECTRA

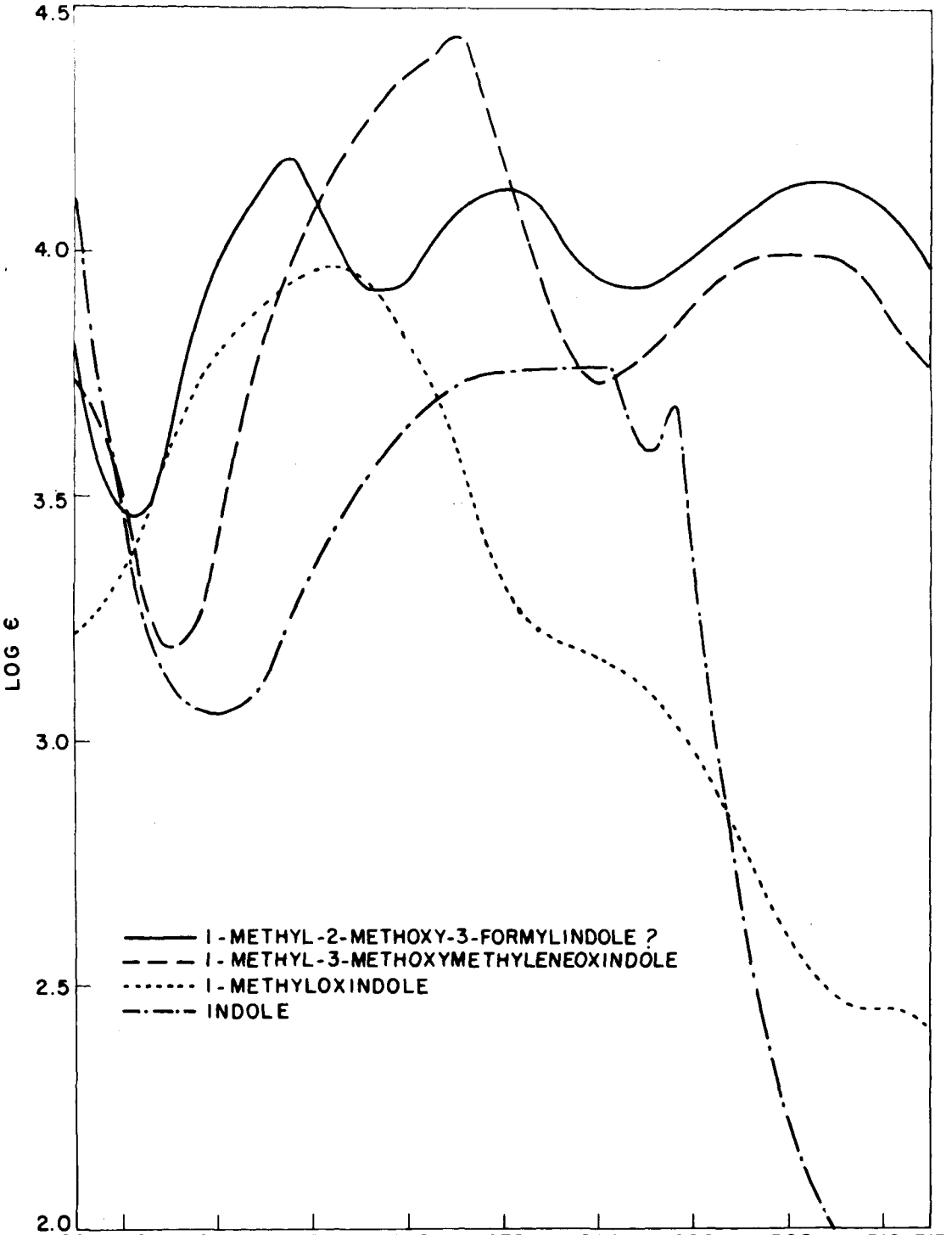


FIG. 21 ULTRAVIOLET SPECTRA

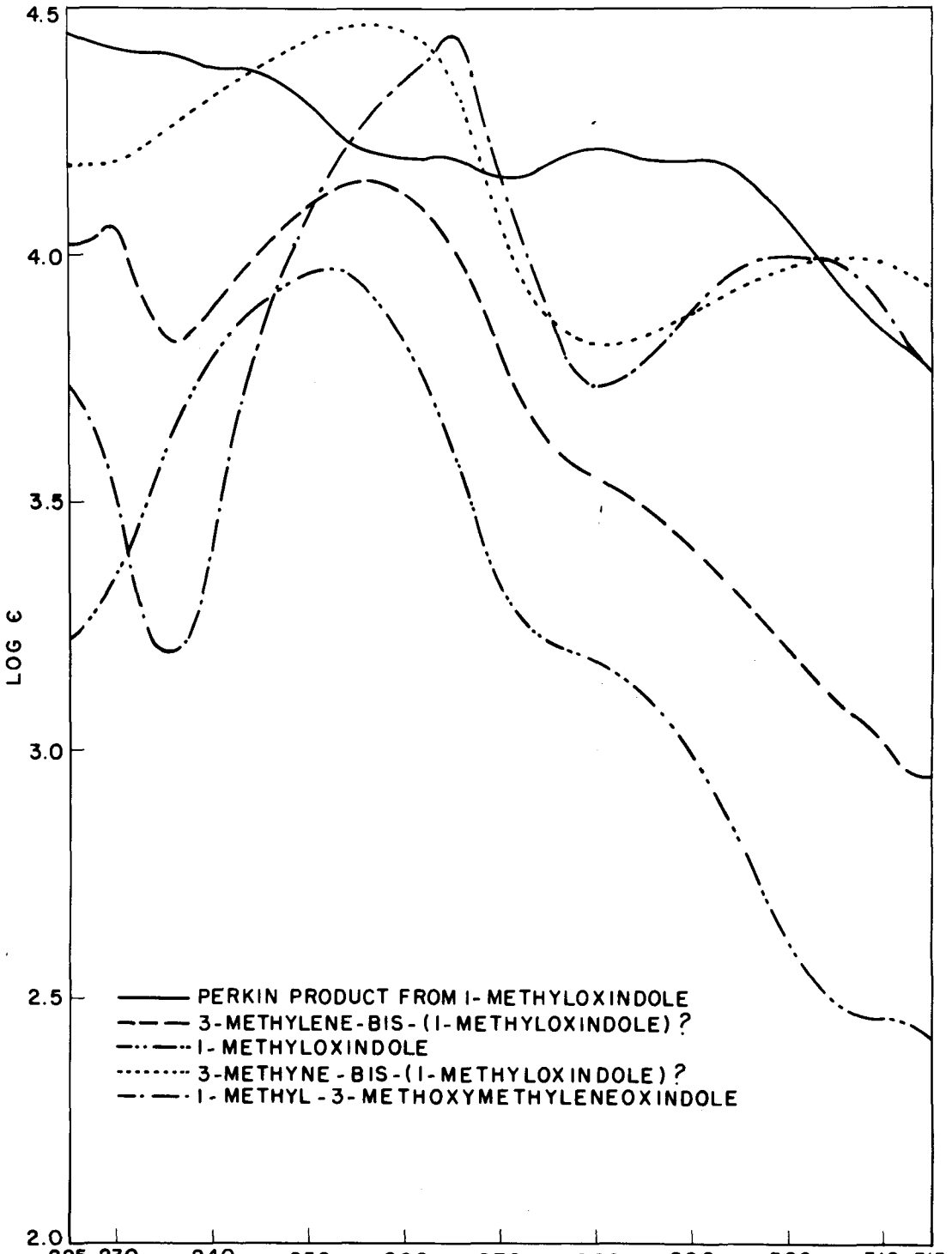


FIG. 22 ULTRAVIOLET SPECTRA

EXPERIMENTAL*

1-Methyl-3-methoxymethyleneoxindole

To 3.0 g. (0.015 mole) of the sodium salt of 1-methyl-3-hydroxymethyleneoxindole (prepared in 80% yield from 1-methyl-3-hydroxymethyleneoxindole and sodium ethoxide) suspended in 40 ml. of acetone, was added 20 ml. of methyl iodide. The mixture was stirred and refluxed under nitrogen for nine hours, at which time complete solution had taken place to give a light yellow solution. A ferric chloride test was still positive. The volume of the solution was decreased to about 15 ml. by evaporation under decreased pressure in an atmosphere of nitrogen. Upon cooling, 0.9 g. of a white solid melting at 210-213° separated, and on the addition of ether to the filtrate an additional 1.9 g. of white solid separated. Treatment of this white solid with water and recrystallization from dilute methanol afforded 0.69 g. (24%) of white crystals melting at 134-135°.

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*All melting points are corrected.

Catalytic reduction of 1-methyl-3-methoxymethyleneoxindole

Depending on the catalyst used different products or mixtures of products were obtained.

Palladium oxide. To 10 mg. of palladium oxide (prereduced in 20 ml. of 95% ethanol with hydrogen at one atmosphere) was added 100 mg. of 1-methyl-3-methoxymethyleneoxindole, and hydrogenation at one atmosphere was carried out while hydrogen absorption was measured volumetrically. An amount of hydrogen corresponding to 1.95 moles was absorbed. The alcohol solution was filtered to remove the catalyst and concentrated to dryness under reduced pressure. The residue on recrystallization from petroleum ether (b.p. 60-70°) deposited 70 mg. (74%) of white crystals melting at 54-55°, and showing no depression of melting point on admixture with authentic 1,3-dimethyloxindole.

Palladium hydroxide on barium carbonate. To 0.5 g. of $Pd(OH)_2/BaCO_3$ catalyst (prereduced in 50 ml. of 95% ethanol) was added 1.0 g. of 1-methyl-3-methoxymethyleneoxindole. Hydrogenation at one atmosphere was carried out and hydrogen absorption was measured volumetrically. An amount of hydrogen corresponding to 1.21 moles was absorbed. The reaction mixture was filtered to remove catalyst and concentrated to dryness under reduced pressure. Fractional recrystallization

of the residue from petroleum ether (b.p. 60-70°) gave two products, one melting at 54-55°, and showing no depression in melting point on admixture with authentic 1,3-dimethyloxindole, the other melting at 57-58°, and showing depression in melting point on admixture with 1,3-dimethyloxindole.

Palladium hydroxide on barium sulfate. To 0.5 g. of $Pd(OH)_2/BaSO_4$ catalyst (prereduced in 15 ml. of 95% ethanol) was added 95.5 mg. of 1-methyl-3-methoxymethyleneoxindole. Hydrogenation at one atmosphere was carried out and an amount of hydrogen corresponding to 0.96 mole was absorbed. The reaction mixture was filtered to remove catalyst and concentrated to dryness under reduced pressure. The residue, on recrystallization from petroleum ether (b.p. 60-70°) gave 50 mg. (52%) of white crystals melting at 57-58° showing depression in melting point on admixture with 1,3-dimethyloxindole but no depression in melting point on admixture with the compound of the same melting point mentioned in the previous experiment. Infrared and ultraviolet absorption spectra together with analyses indicated this compound to be 1-methyl-3-methoxymethyloxindole.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.08; H, 6.86; N, 7.32. Found: C, 69.87, 69.87; H, 6.77, 6.82; N, 7.43, 7.43.

1-Methylisatin

A solution of 15.0 g. of isatin dissolved in 80 ml. of 10% sodium hydroxide was shaken for two hours with 24.0 g. of dimethylsulfate. After filtration, washing and repeated recrystallizations from 25% ethanol, red crystals melting at 125-126° were obtained. The final purification was carried out by chromatography on alumina using benzene as solvent and eluent to give red crystals melting at 131-132°.

Ozonization of 1-methyl-3-methoxymethyleneoxindole

Ozonized oxygen was passed through a solution of 100 mg. of 1-methyl-3-methoxymethyleneoxindole in 20 ml. of ethyl acetate, while cooling the solution in an ice-bath. The solution turned yellow. After hydrolysis by shaking with ice-water, the layers were separated, and the water layer washed repeatedly with ether. The ether and ethyl acetate layers were combined and solvent was removed. Various recrystallizations from water and benzene-petroleum ether mixtures were unsuccessful. Chromatography on alumina using benzene as solvent and eluent gave red crystals melting at 130-131° and showing no depression in melting point on admixture with authentic 1-methylisatin.

1,3,3-Trimethyloxindole

To a mixture of 0.24 g. (0.01 mole) of sodium hydride in 10 ml. of dry benzene was added, with stirring under nitrogen, 1.61 g. (0.01 mole) of 1,3-dimethyloxindole. A white precipitate formed, and after all hydrogen evolution had ceased, 1.24 ml. (0.02 mole) of methyl iodide in 5 ml. of dry benzene was added. After stirring overnight at room temperatures, the reaction mixture was filtered, and the filtrate evaporated to dryness. The residue on being subjected to high vacuum distillation gave 1.3 g. (75%) of a water-clear oil which solidified to a white crystalline solid on standing. Recrystallization from petroleum ether (b.p. 60-70°) gave white crystals melting at 50-51°.

1,3-Dimethyloxindole

To 0.72 g. (0.03 mole) of sodium hydride in 20 ml. of dry benzene was added, with stirring under nitrogen, 4.41 g. (0.03 mole) of 1-methyloxindole in 15 ml. of dry benzene. A white precipitate formed and after the evolution of hydrogen had ceased, 0.06 mole of methyl iodide was added. After stirring at room temperature overnight, the reaction was filtered and the filtrate concentrated to dryness.

Distillation at 0.35 mm. of mercury yielded 4 g. of oil (b.p. 80-90°). On standing, a small amount of 1-methyloxindole crystallized out. Seeding of the residual oil with 1,3-dimethyloxindole induced crystallization of 3 g. (62%) of 1,3-dimethyloxindole melting at 54-55°.

1-Methyl-3-(β-bromoethyl)-oxindole

To 0.24 g. (0.01 mole) of sodium hydride in 15 ml. of dry benzene was added, with stirring under nitrogen, 1.47 g. (0.01 mole) of 1-methyloxindole in 10 ml. of dry benzene. A white precipitate formed, and after all hydrogen evolution had ceased, 1.88 g. (0.01 mole) of ethylene dibromide was added. The reaction mixture was stirred overnight at room temperature.

After filtration of the reaction mixture, and concentration of the filtrate to dryness under reduced pressure, the residual reddish oil was induced to crystallize by scratching, and on recrystallization from petroleum ether (b.p. 60-70°) yielded 1.5 g. (60%) of 1-methyl-3-(β-bromoethyl)-oxindole melting at 61-62°.

1-Methyl-3,3-dimethyleneoxindole

To 1 g. of 1-methyl-3-(β-bromoethyl)-oxindole was added an excess of sodium ethoxide solution. After standing for thirty minutes, water was added and the reaction mixture was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and after filtration the ether solution was concentrated to dryness. Crystallization of the residual oil from petroleum ether (b.p. 60-70°) yielded 0.55 g. (80%) of 1-methyl-3,3-dimethyleneoxindole melting at 81-82°.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.67, 76.63; H, 6.38, 6.44; N, 8.05.

1-Methyl-3-(β-dimethylaminoethyl)-oxindole

This compound was synthesized in several ways; by two different alkylation procedures, and by an acylation and reduction procedure.

Sodium hydride in benzene. To 0.24 g. (0.01 mole) of sodium hydride in 5 ml. of dry benzene was added, with stirring under nitrogen, 1.47 g. (0.01 mole) of 1-methyloxindole in 10 ml. of dry benzene. A white precipitate formed, and after the evolution of hydrogen had ceased, 1.1 g. (0.01 mole)

of β-dimethylaminoethyl chloride in 5 ml. of dry benzene was added. The reaction was stirred at room temperature overnight, filtered, and the filtrate concentrated to dryness. The residual oil was subjected to vacuum distillation yielding 1.1 g. (50%) of light yellow oil which formed a yellow picrate melting at 155-156°.

Anal. Calcd. for the picrate $C_{19}H_{21}N_5O_8$: C, 51.00; H, 4.73; N, 15.7. Found: C, 51.30, 51.27; H, 4.88, 4.99; N, 15.53, 15.38.

Sodamide in toluene. To a solution of 0.01 mole of sodamide, prepared in liquid ammonia by the procedure of Vaughn and co-workers[47], was added 15 ml. of dry toluene, and the mixture was stirred until all the ammonia was evolved. To this suspension of sodamide in toluene, 1.1 g. (0.01 mole) of β-dimethylaminoethyl chloride was added, with stirring under nitrogen. After stirring at room temperatures overnight, the reaction mixture was filtered and the filtrate subjected to distillation yielding 1 g. (45%) of a light yellow oil, which formed a yellow picrate melting at 155-156°, showing no depression in melting point on admixture with the picrate prepared in the previous experiment.

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[47] T. H. Vaughn, R. R. Vogt and J. A. Niewland, J. Am. Chem. Soc., 56, 2120-2 (1934).

Acylation and reduction. To 5 g. (.022 mole) of 1-methyl-3-dimethylaminoacetyloxindole, prepared according to the method of Julian[7], was added 50 ml. of ethanol, 5 ml. of glacial acetic acid and 0.2 g. of palladium oxide. Reduction was carried out at 50 p.s.i. and a temperature of 70°. After a long induction period, reduction took place and on filtration and distillation of the filtrate, 3 g. (64%) of a light yellow oil was obtained which formed a yellow picrate melting at 154-155°, and showed no depression in melting point on admixture with either of the two previously described picrates, or with an authentic sample obtained from Dr. J. L. Julian.

3-Isopropyloxindole

An intimate mixture of 27 g. (0.14 mole) of the phenylhydrazide of isovaleric acid and 108 g. of calcium oxide powder was heated at 250-260° for 8 hours at which time the evolution of ammonia had about ceased. The reaction mixture cake was broken up and dissolved in water and concentrated hydrochloric acid. Liquid-liquid extraction of the acidified mixture gave a dark brown ether solution, which was extracted three times with dilute hydrochloric acid, washed with water once, and dried over anhydrous sodium

sulfate. Removal of the ether gave a dark brown oil, crystallizing to a semi-solid on standing. The product was dissolved in benzene and chromatographed on alumina using benzene as the eluent. From several of the first fractions collected there was obtained after recrystallization from petroleum ether (b.p. 60-70°), 4 g. (16%) of 3-isopropyloxindole melting at 107-108°.

Isovaleranilide

This compound was obtained on repetition of the previous experiment. An intimate mixture of 70 g. of the phenylhydrazide of isovaleric acid and 280 g. of calcium oxide powder was heated at 225-230° for 4 hours, at which time, the evolution of nitrogen had ceased. The reaction mixture cake was broken up and dissolved in water and concentrated hydrochloric acid. The acid solution was extracted with ether, the ether extracts were combined and extracted first with dilute hydrochloric acid, then dilute sodium carbonate, and finally with water. After drying over anhydrous sodium sulfate and removal of the ether, the residue was subjected to distillation at reduced pressure, yielding 20 g. of a heavy, yellow oil. This oil was dissolved in petroleum ether (b.p. 60-70°) and on long standing, 4 g. of light yellow crystals were formed

melting at 104-105° and showing a depression in melting point on admixture with 3-isopropyloxindole, but no depression on admixture with authentic isovaleranilide.

Anal. Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 73.89, 73.88; H, 8.19, 8.27; N, 7.90, 7.72.

Attempted O-alkylation of 3-isopropyloxindole[4]

To 0.5 g. (0.0029 mole) of 3-isopropyloxindole dissolved in a minimum amount of absolute ethanol, was added an equivalent amount of alcoholic ammonia. To this solution was added an excess of alcoholic silver nitrate solution. The voluminous white precipitate so formed was filtered, washed with absolute alcohol, and then with dry ether. The ether-wet precipitate was transferred immediately to a Parr Bomb, to which was added dry ether and an excess of methyl iodide, after which the bomb was closed and immersed in refluxing ethyl acetate for 12 hours. At the end of this time, the bomb was cooled, opened, and the reaction mixture filtered. The filtrate was evaporated to dryness and the residue fractionally recrystallized from petroleum ether (b.p. 60-70°). The major substance obtained was starting material together with a very small amount of white crystals melting at 127-127.5°.

3-Isopropyldioxindole

To a suspension of 44 g. (0.3 mole) of isatin in dry benzene was added an ether solution of 0.65 mole of isopropylmagnesium bromide. The reaction mixture turned a dark brown with the formation of a dark brown precipitate. After stirring and refluxing under nitrogen for two hours, the reaction mixture was hydrolyzed by pouring onto a mixture of crushed ice and concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and on evaporation of part of the solvent and cooling, light yellow crystals were deposited. On further purification by recrystallization from a benzene-methanol mixture, 15 g. (26%) of white crystals melting at 170-171° were obtained.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.65, 68.55; H, 6.96, 6.67; N, 7.38, 7.32.

Attempted preparation of 3-ethynyldioxindole

To a suspension of 0.25 mole of lithium acetylide in liquid ammonia (prepared by passing acetylene through lithium in liquid ammonia) was added 18 g. (0.122 mole) of isatin. An immediate greyish precipitate formed, and the reaction mixture turned dark brown. After stirring for eight hours

at -33°, the ammonia was allowed to evaporate, and the reaction was worked up by addition of water and concentrated hydrochloric acid, followed by extraction with benzene. The benzene extract was dried over anhydrous sodium sulfate and concentrated to dryness yielding a solid residue, which on recrystallization from 95% ethanol yielded 5 g. of light tan crystals melting at 246-247°.

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09; mol. wt., 173. Found: C, 70.46, 70.35; H, 5.47, 5.38; N, 14.7, 14.8; mol. wt., 299, 299.

This indicates that the compound is not 3-ethynyldioxindole, but a consideration of the analytical results, particularly the nitrogen values does not lead to any obvious structural assignment.

3-Ethynyldioxindole

To a stirred ether suspension of 0.25 mole of lithium acetylide (prepared from n-butyllithium and acetylene), was added a suspension of 18 g. (0.122 mole) of isatin in dry benzene. The reaction mixture was stirred and refluxed under nitrogen for 48 hours, after which time, the reaction was worked up by pouring onto a mixture of crushed ice and concentrated hydrochloric acid. The organic layer was separated,

and the water layer further subjected to liquid-liquid extraction with ether. From the combined organic extracts, after chromatography on alumina using benzene both as solvent and eluent, there was obtained 4 g. (19%) of light tan crystals melting at 205-206°.

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09; mol. wt., 173. Found: C, 69.51, 69.49; H, 4.17, 3.99; N, 8.30, 8.23; mol. wt., 194, 198.

Reaction of 1-methyloxindole with thionyl chloride

To 1.47 g. (0.01 mole) of 1-methyloxindole dissolved in dry benzene was added an excess of thionyl chloride. An immediate dark red color formed, and after four hours of reflux under nitrogen, a dark red crystalline mass had formed in the solution. After cooling, filtration, and recrystallization from benzene, there was obtained 1 g. of dark red needles melting at 265-6° (with decomposition).

Anal. Found: C, 73.84, 73.83; N, 4.92, 4.83; N, 10.0, 9.93; mol. wt., 350, 318.

3-Chloro-3-isopropyloxindole

To a suspension of 0.63 g. (0.003 mole) of phosphorus pentachloride in dry benzene, was added 0.525 g. (0.003 mole) of 3-isopropyloxindole with stirring under nitrogen. Complete solution took place and a slow evolution of hydrogen chloride gas was observed. After stirring at room temperature overnight, solvent was removed by distillation under reduced pressure. The residue was subjected to vacuum sublimation yielding a light yellow solid which on recrystallization from petroleum ether (b.p. 60-70°) yielded 0.13 g. (20%) of white crystals melting at 146-147° and showing no depression in melting point on admixture with the product from the reaction of 3-isopropyldioxindole with thionyl chloride.

Anal. Calcd. for $C_{11}H_{12}ONCl$: C, 63.01; H, 5.77; N, 6.68; Cl, 16.91. Found: C, 62.95, 63.18; H, 5.78, 5.83; N, 6.67, 6.79; Cl, 16.65, 16.85.

Reaction of 1-methyl-3-hydroxymethyleneoxindole with diazomethane

Depending on the solvent used, different products or mixtures of products were obtained.

Ether. To 2 g. (0.011 mole) of 1-methyl-3-hydroxymethyleneoxindole was added an excess of an ethereal solution of diazomethane. A vigorous reaction took place with gas evolution, complete solution being obtained after 15 minutes. Ether and excess diazomethane were removed under diminished pressure and the resulting dark red oil was dissolved in methanol. From the methanol solution 0.7 g. of light tan crystals melting at 137-138° were obtained which showed depression in melting point on admixture with 1-methyl-3-methoxymethyleneoxindole.

Methanol. To a methanolic solution of 3.52 g. (0.03 mole) of 1-methyl-3-hydroxymethyleneoxindole was added an excess of an ethereal solution of diazomethane, and the reaction allowed to stand overnight. Partial evaporation of the solvent and cooling yielded 1 g. (28%) of recovered 1-methyl-3-hydroxymethyleneoxindole. The residue after removal of the rest of the solvent was recrystallized from petroleum ether (b.p. 60-70°) and gave 1 g. of yellowish crystals m.p. 115-30°. Chromatography on alumina using benzene as both solvent

and eluent yielded several crystalline fractions melting at 128-131°, which showed identical infrared spectra to that of 1-methyl-3-methoxymethyleneoxindole.

Perkin product from 1-methyloxindole

This compound was prepared by the method of Fischer and Smeykal[28] to give a red crystalline compound melting at 245°.

Anal. Found: C, 75.56, 75.37; H, 5.17, 5.13; N, 9.31.

3-Methylene-bis-(1-methyloxindole)

To 0.5 g. of platinum oxide (prereduced in 50 ml. of glacial acetic acid with hydrogen at one atmosphere) was added 4 g. of the Perkin product from 1-methyloxindole, and hydrogenation at one atmosphere was carried out while hydrogen absorption was measured volumetrically. When an amount of hydrogen corresponding to one mole had been absorbed, the red color of the solution had disappeared, at which time the hydrogenation was discontinued. Filtration to remove the catalyst, and concentration to dryness under reduced pressure, gave a white crystalline residue melting at 165-175°. After repeated recrystallizations from methanol white crystals melting at 182-183° were obtained.

Anal. Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.43, 74.41; H, 5.86, 5.92; N, 9.09, 9.04.

SUMMARY

A new method for the C-alkylation of N-alkyloxindoles has been developed.

The structures of several reported oxindole O-alkylation products were found to be actually 3-alkyloxindoles.

The structure of a common degradation product of several oxindole alkaloids was elucidated.

The structures of products from several oxindole reactions were shown to be incorrect although new structural assignments are as yet incomplete.

Infrared and ultraviolet spectrographic analysis was extensively used in the above work.