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Novel reactions of oxindole compounds

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NOVEL REACTIONS OF OXINDOLE COMPOUNDS

by

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Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College
1958

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INTRODUCTION

The purpose of this research is to study the catalytic hydrogenation of 3-substituted oxindoles and examine the products for potential use in the synthesis of oxindole alkaloids.

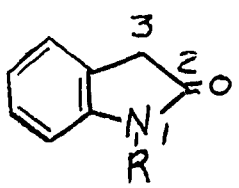
Certain 3-substituted oxindoles or their hydrogenation products can react intramolecularly to give non-oxindole products.

It is hoped to determine the influence of the reductive conditions on the degree of reaction and on the ability of the products to react intramolecularly.

HISTORICAL

Acylation of oxindoles

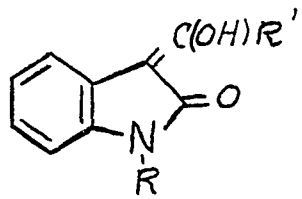
Julian conveniently synthesized a number of 3-acyl derivatives of 1-methyloxindole (Ia) by condensation of the latter with the various ethyl esters in a sodium ethoxide solution (1, 2, 3, 4). Condensations of this type have been carried out with ethyl formate (1), ethyl acetate (2), ethyl oxalate (2), ethyl malonate (2), ethyl dimethylaminoacetate (2), and ethyl tetrahydro isoquinolyacetate (4).



I

a, R=CH_3

b, R=H



II

a, R=H, R'=$CH_2C_6H_5$

b, R=H, R'=CH_3

c, R=CH_3, R'=$CH_2C_6H_5$

d, R=CH_3, R'=CH_3

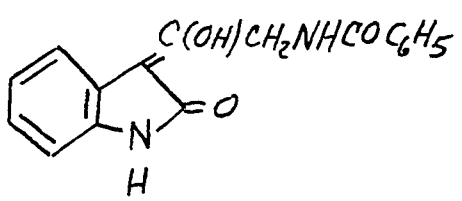
e, R=H, R'=H

f, R=CH_3, R'=H

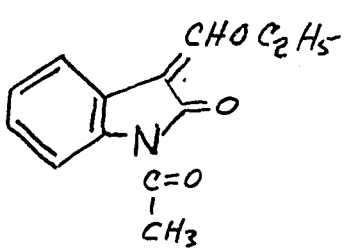
Horner (5), using oxindole (Ib), reported the same reaction with ethyl acetate, ethyl oxalate, ethyl malonate and ethyl glycolate. However, he was not able to synthesize any acyloxindole derivatives with ethyl isonitrosocyanoacetate, ethyl phthalimidomalonate, ethyl tartarate and ethyl isonitrosomalonate.

Wenkert (6) condensed oxindole (Ib) with ethyl phenylacetate and obtained 3-(α-hydroxy-β-phenylethylidene-) oxindole (IIa).

Bernstein (7) prepared the corresponding 1-methyl-3-(α-hydroxy-β-phenylethylidene-)oxindole (IIc). Hendrickson (8) synthesized 3-hippuryloxindole by condensing ethyl hippurate and oxindole (Ib). Behringer (9) reported a reaction of oxindole (Ib) and ethyl orthoformate in the presence of acetic anhydride which resulted in the formation of 1-acetyl-3-ethoxymethyleneoxindole (IV).



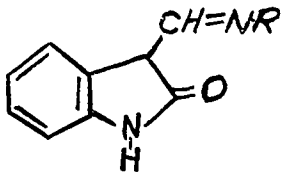
III



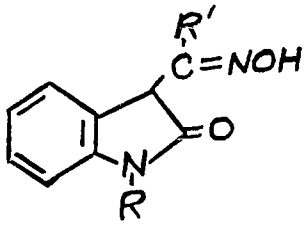
IV

Derivatives of 3-(α-hydroxyalkylidene-)oxindoles

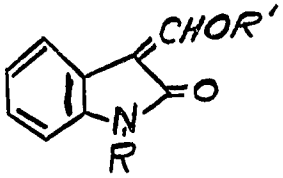
3-(α-hydroxyalkylidene-)oxindoles form characteristic derivatives of ketonic carbonyl compounds. Friedlander (10) reported a phenylhydrazone (Va) and an oxime (VIe) for 3-hydroxymethylene-oxindole (IIe), while Fischer (11) prepared the semicarbazone (Vb) and the enol acetate (VIIa) of the same compound.



V



VI



VII

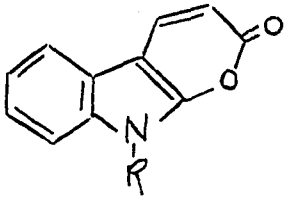
a, R=NHC_6H_5
b, R=$NHCONH_2$

a, R=H, R'=$CH_2C_6H_5$
b, R=H, R'=CH_3
c, R=CH_3, R'=$CH_2C_6H_5$
d, R=CH_3, R'=CH_3
e, R=H, R'=H

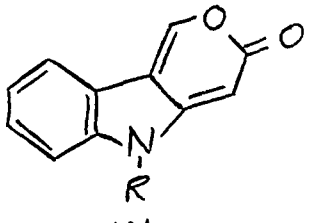
a, R=H R'=$COCH_3$
b, R=H R'=COC_6H_5
c, R=H R'=$SO_2C_6H_5$

Wenkert (6) oximinated IIa to yield VIa. Later, Bernstein (7) reported the synthesis of the oximes VIb, c and d.

Granacher (12) benzoylated and benzenesulfonated IIe to give the respective derivatives VIIb and c. Fischer (11) subjected IIe to a Perkin condensation and isolated a compound to which he assigned the structure VIII. However, Horner (5) later modified the structure to IX. Reid (14), in a reinvestigation of this reaction observed that the elemental analysis of the Perkin product did not check well for either VIII or IX. Also, catalytic reduction gave an oxindole-type compound after an uptake of one mole of hydrogen.

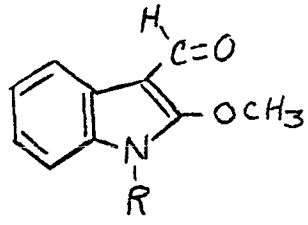


VIII



IX

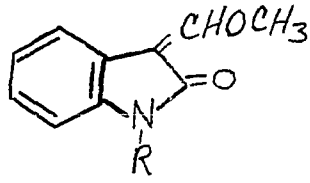
Julian (1) using the sodium salt of 1-methyl-3-hydroxymethyleneoxindole (IIf), carried out an alkylation with methyl iodide in acetone. The product of the reaction was considered to be 1-methyl-2-methoxy-3-formyloxindole (X). A reinvestigation of this product by Wenkert (13) and Reid (14), via spectral analysis, hydrogenation and hydrolysis studies, led to the conclusion that the compound was 1-methyl-3-methoxymethyleneoxindole (XI).



X

a, R=CH_3

b, R=H



XI

a, R=CH_3

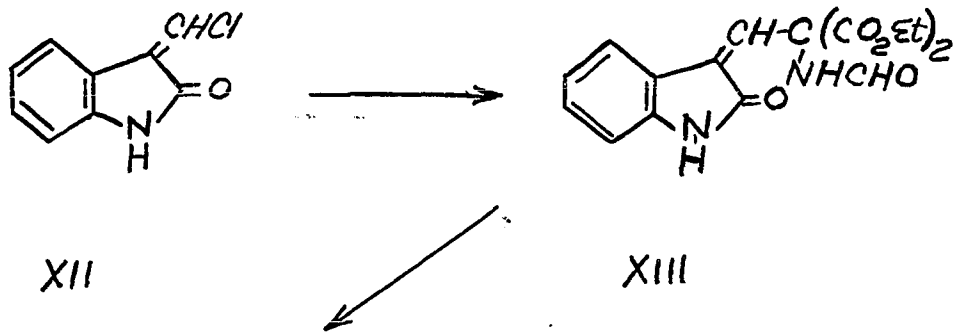
b, R=H

Wenkert (13, 15) and Reid (14) also reinvestigated the action of diazomethane on IIe and IIf. Two products had been reported from the latter (16, p. 154) and one from the former (5). Repetition of the reaction yielded two products from each compound which were identified as 2-methoxy-3-formyl-indoles Xa and b and 3-methoxymethyleneoxindoles XIa and b.

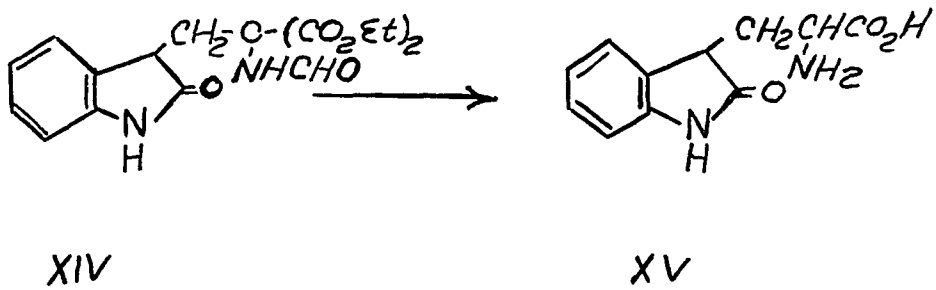
Behringer (17a) prepared 3-chloromethyleneoxindole (XII) by the action of thionyl chloride on IIe. Using diethyl-α-formaminomalonate, they obtained ethyl α-carboethoxy-α-formamino-β-isatylidene propionate (XIII) which was hydrogenated to the oxindole analogue. Hydrolysis of XIV resulted in formation of oxytryptophan (XV).

Behringer (9) used 1-acetyl-3-ethoxymethyleneoxindole (IV) to prepare 3-dimethylaminomethyleneoxindole (XVIa). Other 3-amino-methyleneoxindole derivative (XVIb, c, and d)

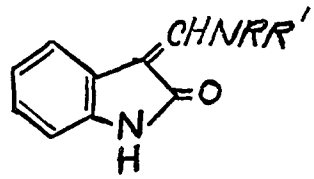
were obtained by the action of the desired amine directly on IIe.



XII XIII



XIV XV



XVI

a, R=R'=CH_3

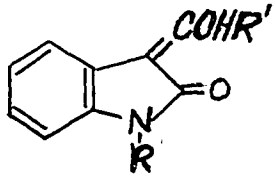
b, R=H, R'=$CH_2CH_2C_6H_5$

c, R=H, R'=$CH_2CH_2N(C_2H_5)_2$

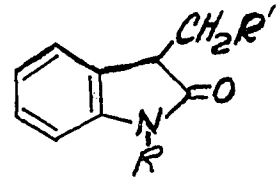
d, R=H, R'=-$CH_2CH_2CO_2Et$

Reduction of 3-(α-hydroxyalkylidene-)oxindoles and their derivatives

The catalytic hydrogenation of 3-(α-hydroxyalkylidene-) oxindoles and their derivatives has been reported by different workers with varying results. Using palladium oxide catalyst, Julian (2) hydrogenated some 1-methyl-3-(α-hydroxyalkylidene-)oxindoles (II) to the corresponding 1-methyl-3-alkyloxindoles (XVII).



II



XVII

a, R=H, R'=$CH_2C_6H_5$

b, R=H, R'=CH_3

c, R=CH_3, R'=$CH_2C_6H_5$

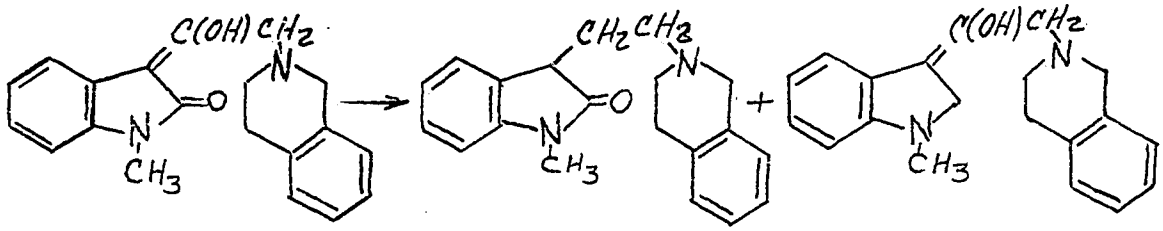
d, R=CH_3, R'=CH_3

e, R=H, R'=H

f, R=CH_3, R'=H

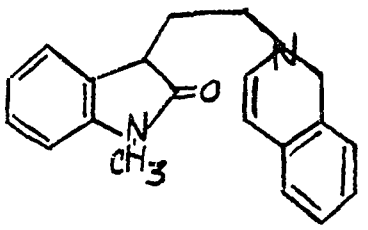
g, R=H, R'=OH

However, during some investigations on a projected yohimbine synthesis, the formation of two products was observed in the catalytic hydrogenation of 1-methyl-3-(α-hydroxy-β-tetradehydroisoquinolylethylidene-)oxindole (XVIII) to which he assigned the structures XIX and XX.

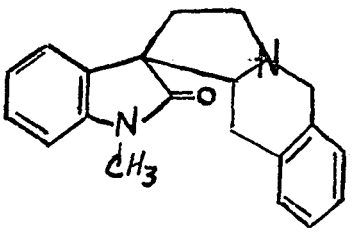


XVIII XIX XX

A palladium dehydrogenation was carried out on the compound XIX giving a product which was thought at first to be β-dehydroisoquinolyethyloxindole (XXI). However Belleau (17b), in a re-examination of the dehydrogenation product, questioned the stability of Julian's partially dehydrogenated structure XXI. He assigned the product structure XXII, its formation being the result of a Mannich reaction of an active intermediate having the structure XXI.



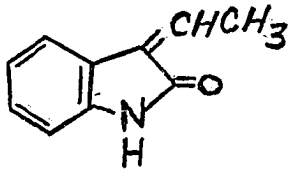
XXI



XXII

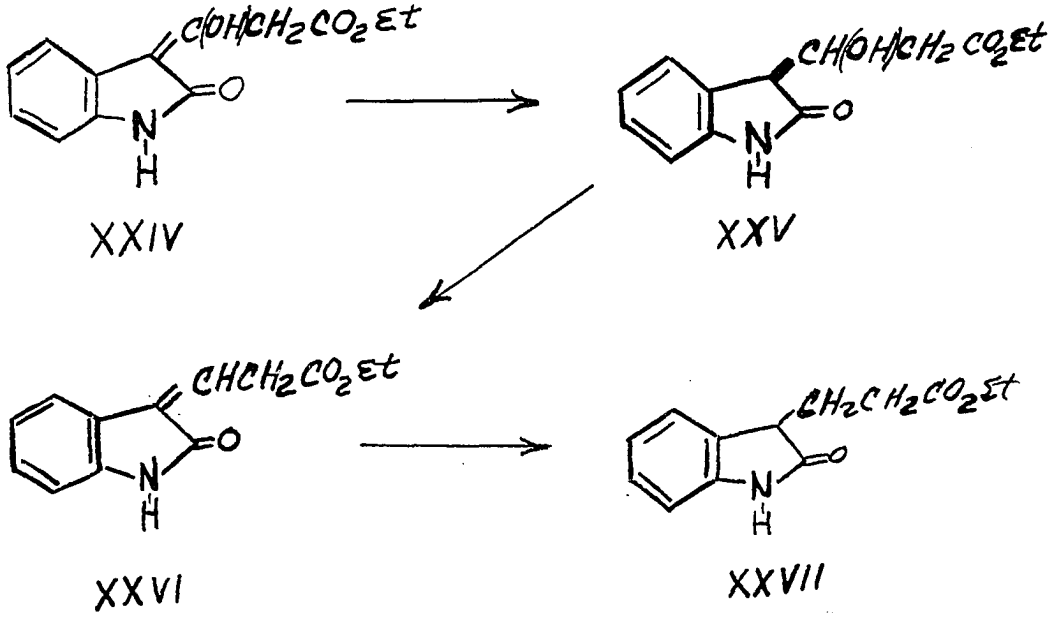
Horner (5) was unable to reduce the 3-(α-hydroxyalkylidene-)oxindoles, which were unsubstituted on the ring nitrogen, to the corresponding alkyl derivatives. An attempt to synthesis 3-hydroxy-methyloxindole (XVIIg) by Meerwein-Ponndorf reduction of IIe resulted in dimeric material. However, Horner (5) did effect hydrogenation of the enol benzoate of IIe to benzoic acid and 3-methyloxindole (XVIIe) over platinum oxide.

Kondo (18), in an effort to prepare 3-ethyloxindole (XVIIb) by catalytic hydrogenation of 3-(α-hydroxyethylidene-)oxindole (IIb), observed no reaction using palladium oxide in alcohol and isolated but a trace of unidentifiable material using platinum oxide in acetic acid. Further attempts to reduce IIb by Wolff-Kishner or Clemmensen reduction led only to oxindole (Ib). The 3-ethyl derivative (XVIIb) was obtained by Kondo (18) by hydrogenation of 3-ethylideneoxindole (XXIII).



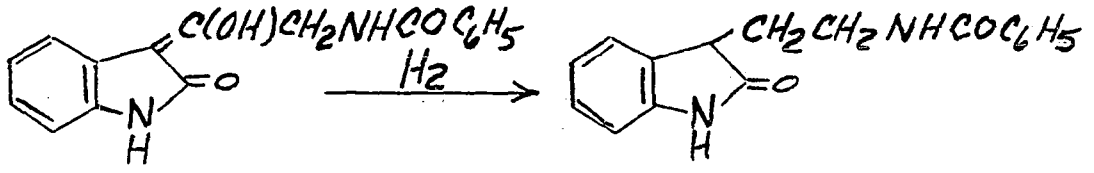
XXIII

Julian (3), in a more recent report, disclosed the hydrogenation of ethyl β-isatylidene-β-hydroxypropionate (XXIV) to ethyl β-hydroxy-β-oxindolepropionate (XXV) over palladium-charcoal in ethanol. Following dehydration of XXV to ethyl β-isatylidenepropionate (XXVI), further catalytic hydrogenation was observed to yield ethyl β-oxindolepropionate (XXVII).



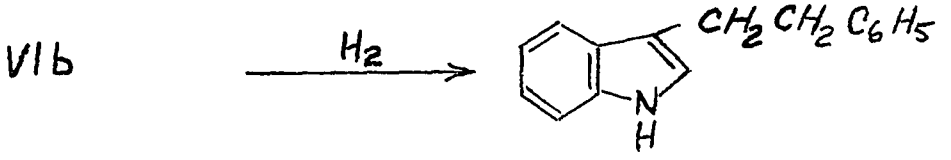
XXIV XXV XXVI XXVII

Hendrickson (8) obtained 3-(β-benzamidoethyl-)oxindole (XXVIII) from the palladium charcoal in acetic acid reduction of 3-hippuryloxindole (III).



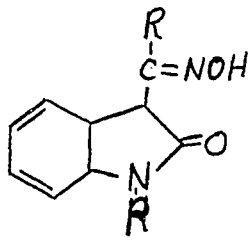
III XXVIII

Wenkert (6, 19) reported the conversion of 3-(α-hydroxy-β-phenylethylidene-)oxindole oxime VIb to 3-(β-phenylethyl-) indole (XXIX) using platinum and acetic acid.

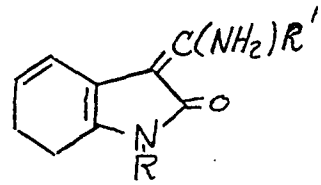


XXIX

However, Bernstein (7) studied the hydrogenation of several oxindole oximes (VIa, b, c and d) with platinum and acetic acid and obtained the corresponding 3-(α-amino-alkylidene-)oxindoles (XXXa, b, c and d).



VI a, b, c and d



XXX

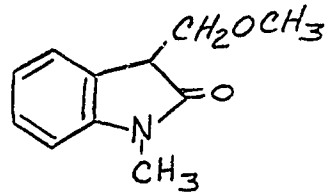
a, R=H, $R'=CH_2C_6H_5$

b, R=H, $R'=CH_3$

c, $R=CH_3$, $R'=CH_2C_6H_5$

d, $R=CH_3$, $R'=CH_3$

Wenkert (13) obtained 1,3-dimethyloxindole (XVIIf) by the hydrogenation of 1-methyl-3-methoxymethyleneoxindole (XIb), over palladium oxide or palladium on barium carbonate, but 1-methyl-3-methoxymethyloxindole (XXXI) over pallidized barium sulfate.

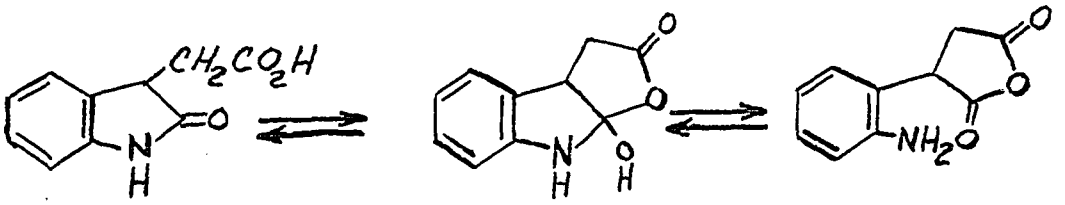


XXXI

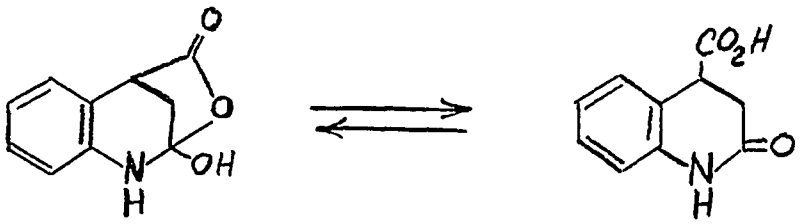
Intramolecular reactions of the oxindole derivatives

The lactam ring of simple oxindole compounds is stable to mild acid or base treatment, but cleaves in barium hydroxide solution at high temperature (20). Acidification of the salt of 2-aminophenylacetic acid reforms oxindole (Ib).

Much controversy existed in the literature over the existence of oxindole-3-acetic acid (XXXII) and its derivatives (16, p. 161). Most structures containing the oxindole nucleus had to be revised to derivatives of 2-quinolone-4-carboxylic (XXXIV). All previous methods of obtaining XXXII included a hydrolytic treatment in which the oxindole nucleus was supposedly cleaved to o-aminophenylsuccinic acid which subsequently lactamized to the quinolone. Wenkert (19) pointed out that this explanation ignored the relative stability of the oxindole nucleus toward hydrolysis and that the presence of the side chain carboxyl, which could interact with the lactam carbonyl group as illustrated, must contribute to the ease of rearrangement. Wenkert further indicated that any of the reaction intermediates might be hydrolyzed to o-aminophenylacetic acid although the latter is not a necessary precursor to quinolone.

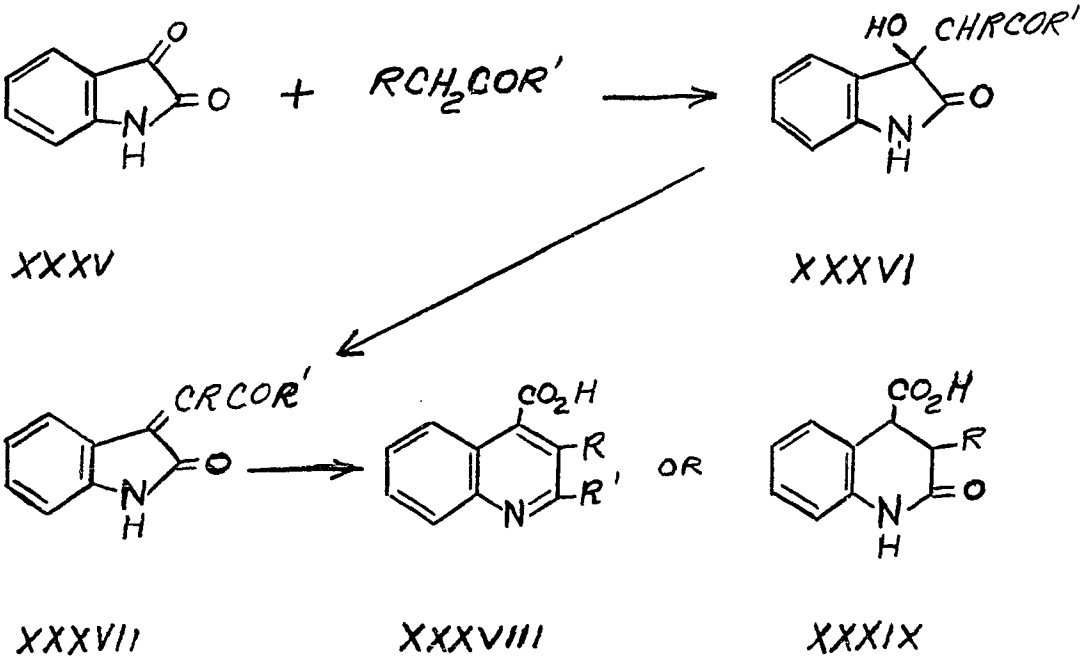


XXXII XXXIII

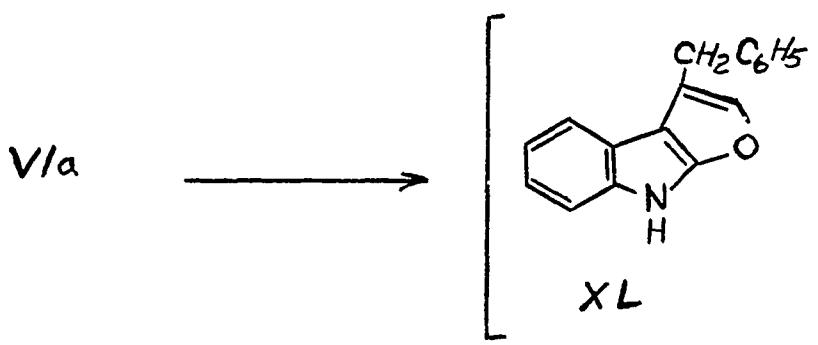


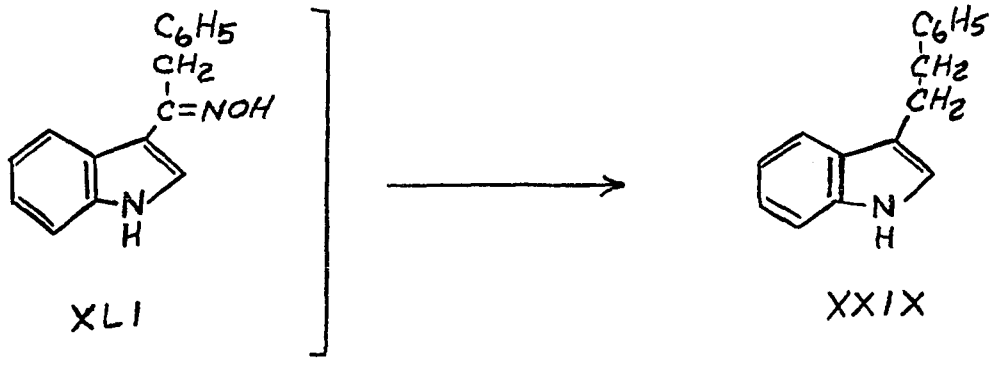
XXXIV

Lindwall (21) Braude (22) and DuPuis (23) synthesized a number of dioxindole derivatives (XXXVI) by the condensation of isatin (XXXV) with reactive methylene compounds. These dioxindole compounds as well as their dehydration products (XXXVII) were transformed into quinoline-4-carboxylic acids by treatment with mineral acids. In those cases, where the dioxindole was prepared from a ketone, the rearrangement product was a 2-substituted quinoline-4-carboxylic acid while 2-quinolone-4-carboxylic acids were obtained from dioxindoles and malonic esters.



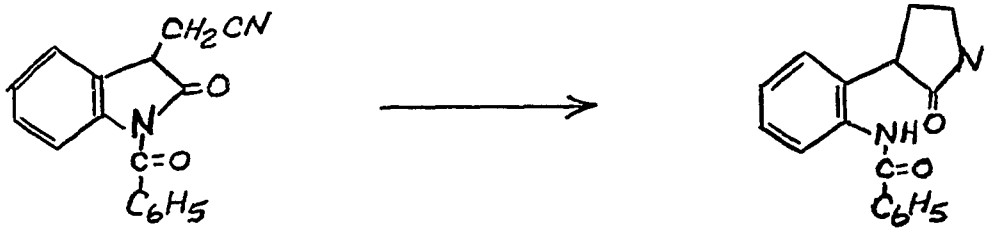
In a previously mentioned reaction, the oxime (VIb) was hydrogenolyzed to 3-(β-phenylethyl-)indole (XXIX) (6, 19). This conversion was portrayed as proceeding by interaction of the oxime with the lactam carbonyl to give an isoxazole intermediate (XL), followed by hydrogenolysis of XL to the oxime of 3-phenylacetylindole (XLI), further hydrogenation and hydrogenolysis.





XLI XXIX

Wenkert (6) catalytically hydrogenated 1-phenylacetyl-3-cyanomethyloxindole (XLII) and obtained a product whose ultra-violet spectra indicated it to be the pyrrolidone (XLIII).

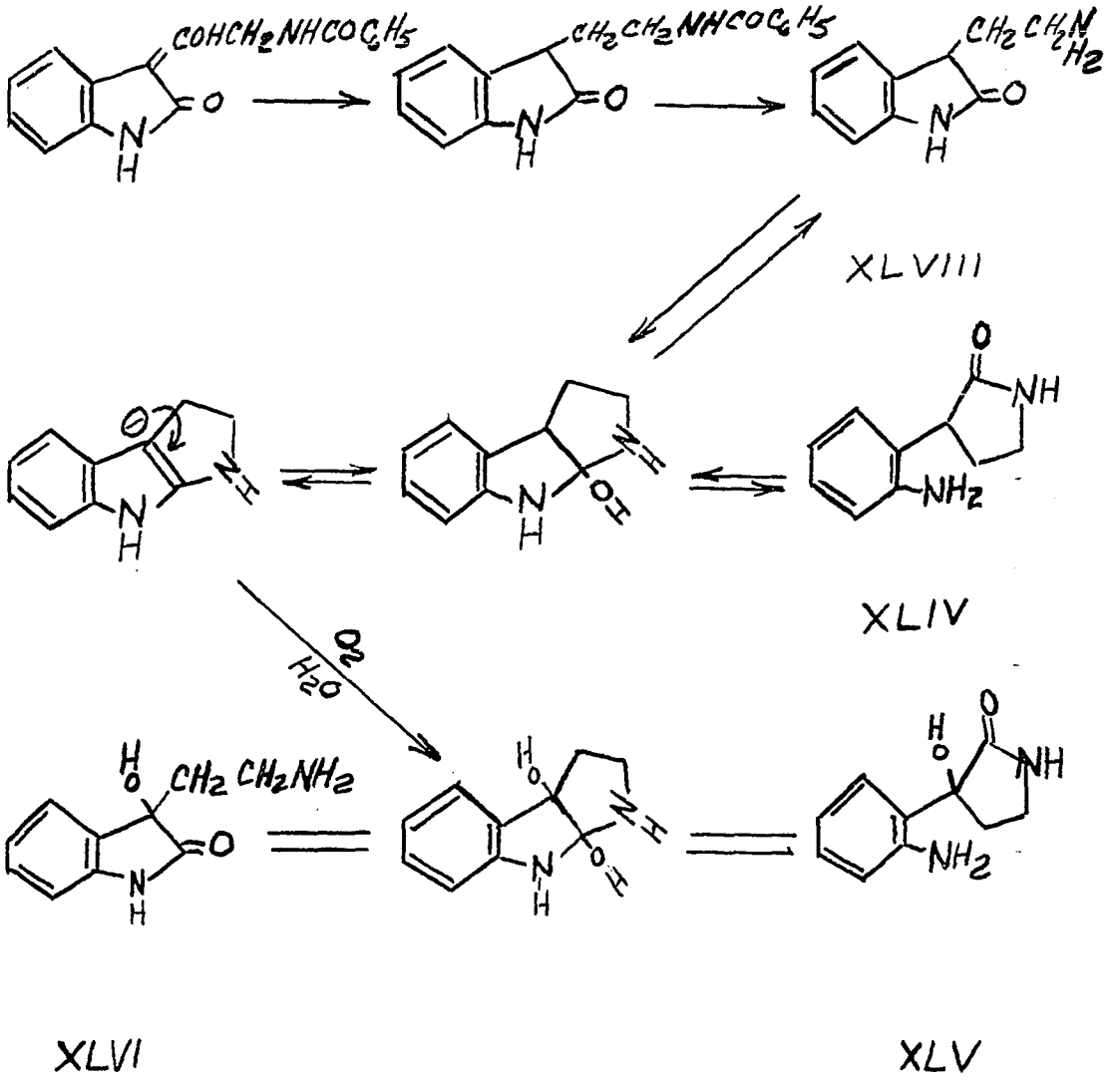


XLII XLIII

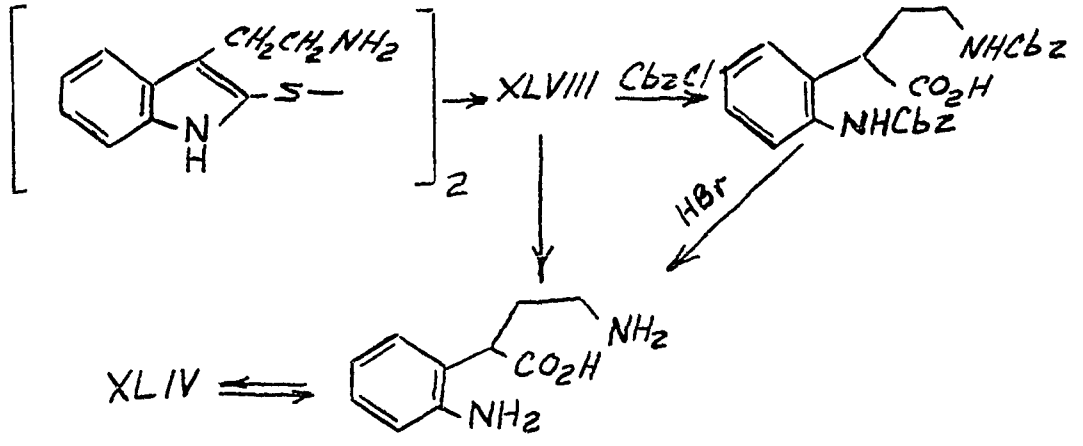
The transformation was a result of the aminoethyl group, produced by reduction of the cyano function, interacting with the oxindole carbonyl linkage, rupturing the oxindole ring and forming the pyrrolidone.

Hendrickson (8) isolated three basic products from the acid hydrolysis of 3-(β-benzamidoethyl-)oxindole, to which he assigned the structures XLIV, XLV, and XLVI. The formation

of the two hydroxy derivatives XLV and XLVI was ascribed to air oxidation of the intermediate as shown below.



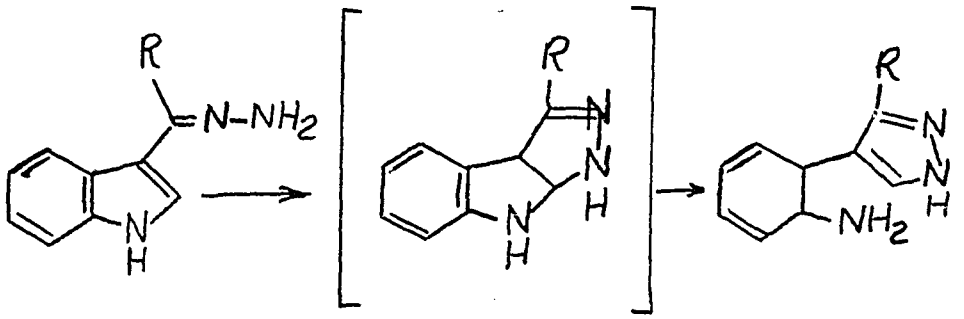
In more recent work (24), oxytryptamine (XLVIII) was prepared by the mild reductive hydrolysis of the symmetric disulfide (XLVII).



Although the hydrochloride of XLVII was not susceptible to acid hydrolysis, the oxindole ring was cleaved by base to yield α-(o-aminophenyl-)-γ-aminobutyric acid (XLIX), which cyclized to the pyrrolidone (XLIV). Treatment of XLVIII with carbobenzyloxychloride yielded N,N'-dicarbobenzyloxy-α-(o-aminophenyl-)-γ-butyric acid (L) which was converted to XLIX with hydrogen bromide in acetic acid.

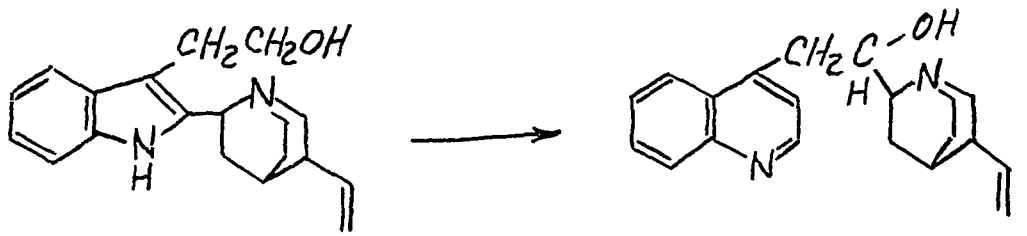
Beside the interactions of C-3 substituents of oxindoles with the lactam carbonyl, there are reports of similar reactions involving 3-substituted indoles.

Alberti (25) observed the thermal rearrangement of 3-acyl-indolehydrazones (LI) to give o-aminophenylpyrazoles (LII).



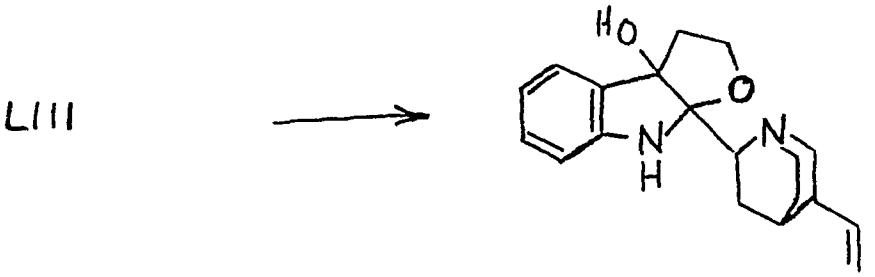
LI LII

Goutarel (26) in his biogenetic interpretations of cinchona alkaloids, portrayed the transformation of an indole LIII into a quinoline nucleus (LIV).



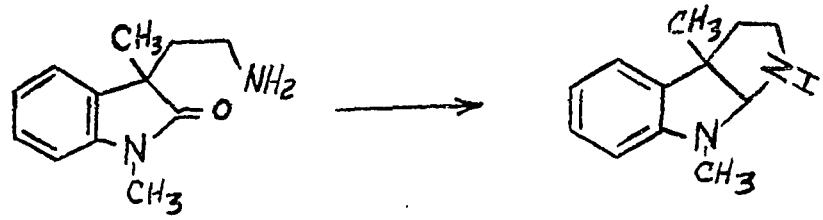
LIII LIV

Witkop (27) converted cinchonamine (LIII) to quinamine (LV) via peracid oxidation of the indole.



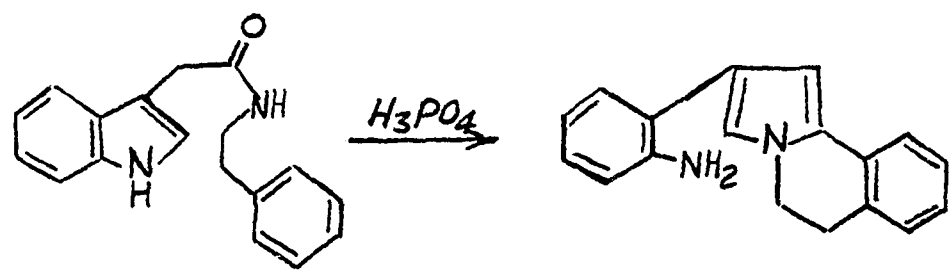
LIII LV

Julian (28) prepared the physostigmine type compound (LVI) via the sodium in alcohol reduction of the 1,3-disubstituted oxytryptamine (LVII).



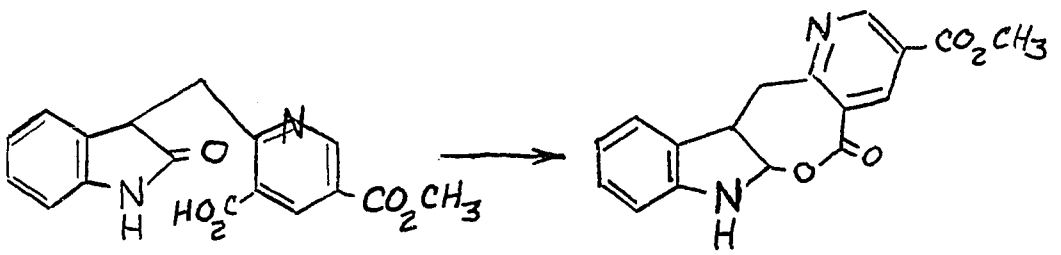
LVI LVII

The conversion of the indolic compound (LVIII) to the pyrrole (LIX) was effected by Thesing using polyphosphoric acid (29). The reaction supposedly proceeded by interaction of the amide nitrogen with the indole ring, followed by rupture of the ring.



LVIII LVIX

Plieninger (30) recently reported the interaction of the lactam carbonyl of an oxindole (LX) and a carboxyl group on the side chain under the influence of acetic anhydride.



LX LXI

Oxindole alkaloids

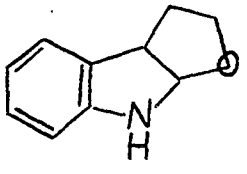
The number of known oxindole alkaloids is few relative to the indole alkaloids. One of the earliest of these was gelsemine which was considered to be a 3,3-disubstituted oxindole as its ultraviolet spectra was superimposable on 3,3-dimethyloxindole (31). Two other minor alkaloids, gelsevirine and gelsedine were isolated from the gelsemium species. These were considered to be 1,3,3-tri-substituted and 1,3-disubstituted oxindole derivatives.

Raymond-Hamet (33) showed that rhynocophylline, mitraphylline and formosanine, were oxindole systems by the application of ultraviolet spectra.

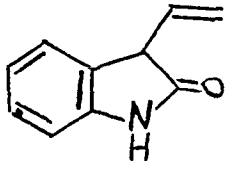
Two other oxindole alkaloids, uncarine-A and -B were isolated by Kondo and Nozoye from Uncaria kawakimii (34).

Rhyncophylline is a monoacidic tertiary base which has been shown to contain one active hydrogen (35) and two methoxyl groups, of which one is a part of a carbomethoxy group (36). Kondo suggested the presence of a $CH_3O_2CC=CHOCH_3$ grouping due to the enhanced intensity of the ultraviolet spectra around the 250 mμ region. However he presented no chemical evidence to support this suggestion.

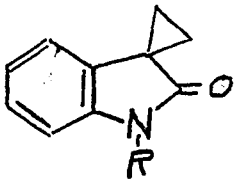
A common degradation product was obtained from uncarine-A by Kondo (34), rhyncophylline by Barger (35) and mitraphylline by Cook (37) on calcium oxide, zinc dust, palladium or vacuum distillation of the alkaloid. Although Kondo thought it to be a dihydrofuroindole (LXII) and Barger, a methylcarbostyril, Cook assigned it a 3-vinyloxindole structure (LXIII).



LXII



LXIII



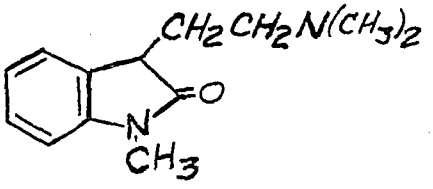
LXIV

a, R=H

b, $R=CH_3$

However, Wenkert (38) and Reid (14) later showed this degradation product to be 3,3-dimethyleneoxindole (LXIVa) by comparison with the spectra of the 1-methyl analogue (LXIVb). Kondo (39) later concurred with the spiro structure. He also

prepared LXIVb by pyrolysis of 1-methyl-3-(β-dimethylamino-ethyl-)oxindole (LXVI) (40).

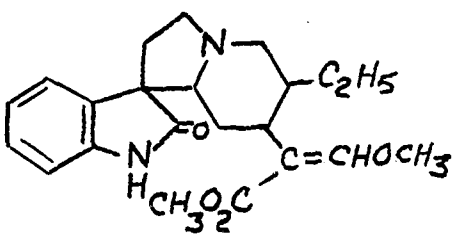


LXV

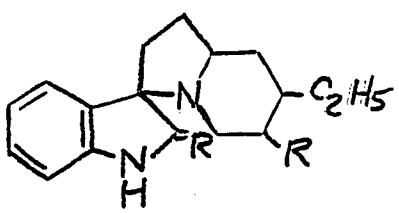
Seaton (41) obtained chemical evidence which permitted them to put forth a total structure of rhyncophylline. Hydrolysis of the alkaloid led to rhyncophyal which contained an aldehyde but not the methoxyl, the double bond and the carbomethoxy group originally present. This compound, called rhyncophyllal, was reduced by sodium borohydride to give rhyncophyllol, the alcoholic counterpart of the aldehyde. Both the alcohol and the aldehyde were reduced by lithium aluminum hydride to dihydrodesoxy-rhyncophyllol, which exhibited properties of an aromatic amine. Since 3,3-disubstituted oxindoles give aromatic amines on lithium aluminum hydride treatment whereas 3-monosubstituted oxindoles give indoles, Seaton concluded that the alkaloid was 3,3-disubstituted.

Palladium-charcoal dehydrogenation of rhyncophyllal led to 3-ethyl-4-methyl pyridine, while the same treatment of

rhyncophyllane, obtained by Wolff-Kishner reduction of the aldehyde, gave 3,4-diethyl pyridine. This established the position of the aldehyde side chain on the piperidine ring. Using biogenetic derivations similar to those described for corynantheine, Seaton then advanced the structure LXVI for rhyncophylline with rhyncophyllal represented by LXVIIa, rhyncophyllol by LXVIIb, the dihydrodesoxy-derivative by LXVIIc and rhycophyllane by LXVIId. Ring C lacks chemical confirmation and was constructed as in LXXVI on biogenetic grounds.



LXXVI



LXXVII

a, R=CH_2CHO, R'=O

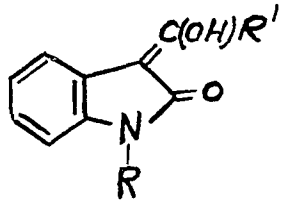
b, R=CH_2CH_2OH, R'=O

c, R=CH_2CH_2OH, R'=H_2

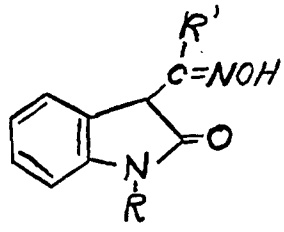
d, R=CH_2CH_3, R'=O

DISCUSSION

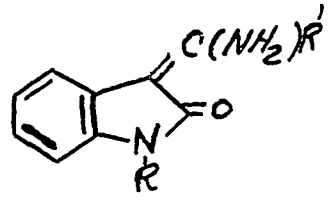
A reinvestigation of the catalytic hydrogenation of the oximes of various acyloxindoles was prompted by the irreproducibility encountered among different workers (6, 7). The derivatives studied were the oximes VIa, b, c, d, e and f. Both the acyloxindoles and their oximes were prepared by the standard methods discussed earlier (6, 7). The repetition of the hydrogenation of VIa, b, c and d over platinum in acetic acid yielded results in partial agreement with each of the previous workers. The oximes of those oxindoles with no substituent on the lactam nitrogen, VIa and b, gave indole derivatives. However, the N-methylated oxindoles (VIc and d) yielded 1-methyl-3-(α-aminoalkylidene-)oxindoles (XXXc and d).



II



VI



XXX

a, R=H, R'=$CH_2C_6H_5$

b, R=H, R'=CH_3

c, R=CH_3, R'=$CH_2C_6H_5$

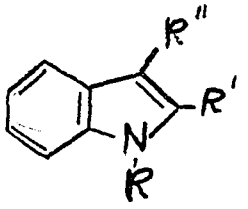
d, R=CH_3, R'=CH_3

e, R=H, R'=H

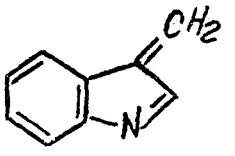
f, R=CH_3, R'=H

A change of the reaction conditions to palladium-charcoal in ethanol gave slightly different overall results. The N-methylated oxindoles (VIc and d) yielded the same eneamines (XXXc and d) but VIa and b gave mixtures of eneamines (XXXa and b) and indoles. In all four cases, the yields of eneamines were higher than in the platinum and acetic acid hydrogenations.

Although the melting point of the indole from the oxime (VIa) was in agreement with that reported earlier by Wenkert (6), it differed from that reported for 3-(β-phenylethyl-) indole (LXIXa) by Snyder (43). However an unambiguous synthesis of LXIXa was necessary because the reported preparation (43) involved the interaction of gramine methiodide LXIX and benzylmagnesium chloride, which could have led to either 2-benzyl-3-methylindole LXX. Julian (2) had reported the hydrogenation of 3-acyloxindoles to the corresponding 3-alkyloxindoles over platinum in acetic acid. Thus, hydrogenation of IIa under the same conditions gave 3-(β-phenylethyl-)oxindole XVIIa, which was reduced by sodium in butanol to 3-(β-phenylethyl-)indole whose physical properties were different from those of the oxime reduction product but identical with those of the product obtained by Snyder.



LXIX



LXX

a, R=R'=H, R"=$CH_2CH_2C_6H_5$

b, R=R'=H, R"=CH_2CH_3

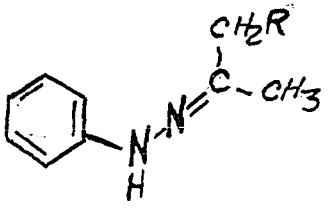
c, R=R"=H, R'=$CH_2C_6H_5$

d, R=R"=H, R'=CH_3

e, R=CH_3, R'=$CH_2C_6H_5$, R"=H

f, R=R'=H, R"=$CH_2N^{\oplus}(CH_3)_3I^{\ominus}$

g, R=H R'=CH_3 R"=C_6H_5



LXXI

a, R=H

b, R=C_6H_5

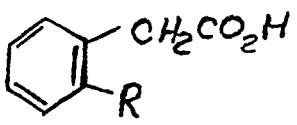
On exposure to light and air, the indolic products of the oxime hydrogenations developed color which is characteristic of 2-substituted indoles (44). A review of the literature disclosed that 2-benzylindole (LXIXc) and its picrate had melting points which were the same as the hydrogenation product (44). The hydrogenation product of VIb, which was presumed to be 3-ethylindole, (LXIXb) had a melting point which was the same as 2-methylindole (LXIXd).

An authentic sample of LXIXd was prepared via the Fischer indole synthesis. Comparison of it with the hydrogenation product showed that they were the same compound.

A sample of 2-benzylindole could not be prepared in a similar manner because the ring closure of the phenylhydrazone (LXXIb) takes place in such a manner to give 2-methyl-3-phenylindole (LXIXg) (45).

Although the synthesis of LXIXc was reported by two independent workers (44, 46), it became of interest to attempt the preparation in a novel, yet unambiguous manner. Baeyer and Jackson (47) had reduced o-nitrophenylacetone (LXXVb) with zinc and obtained LXIXd in trace amounts. Since the synthesis of LXXII involved a nitration which yielded di-substituted products, it did not appear practical.

King (48) reported a one-step synthesis of phenylacetone (LXXVa) from phenylacetic acid (LXXIIa) and acetic anhydride (LXXIIIa) in pyridine. A similar reaction involving o-nitrophenylacetic acid (LXXIIb) and LXXIIIa could presumably give LXXVb, while LXXIIb and LXXIIIb would yield 1-o-nitrophenyl-3-phenylacetone (LXXVc). However each of these reactions yielded mixtures, which on chromatographic separation, could not be characterized as ketones.

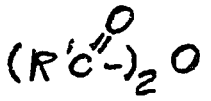


LXXII

a, R=H

b, R=NO_2

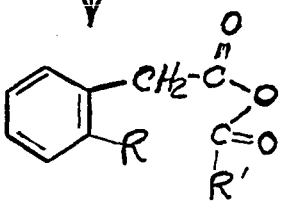
+



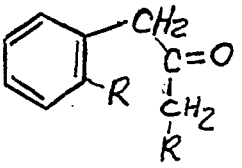
LXXIII

a, R'=CH_3

b, R'=$CH_2C_6H_5$



LXXIV



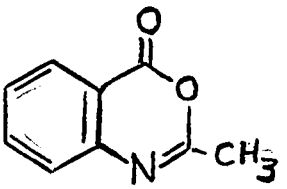
LXXV

a, R=H R'=CH_3

b, R=NO_2 R'=CH_3

c, R=NO_2 R'=$CH_2C_6H_5$

A clue to the difficulty was brought out by Walker (49) who reported the reaction of LXXIIb and LXXIIIa to give acetyl anthranil (LXXVI), which was readily hydrolyzed to the acid.

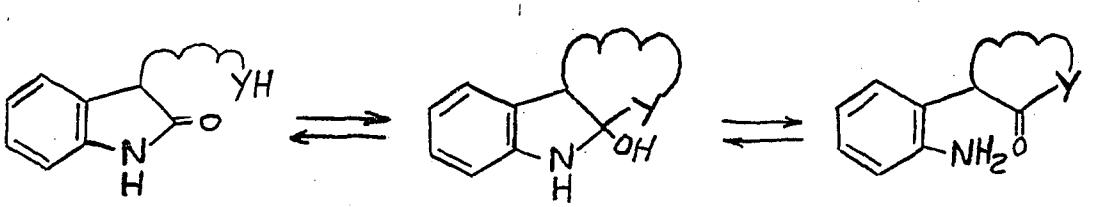


LXXVI

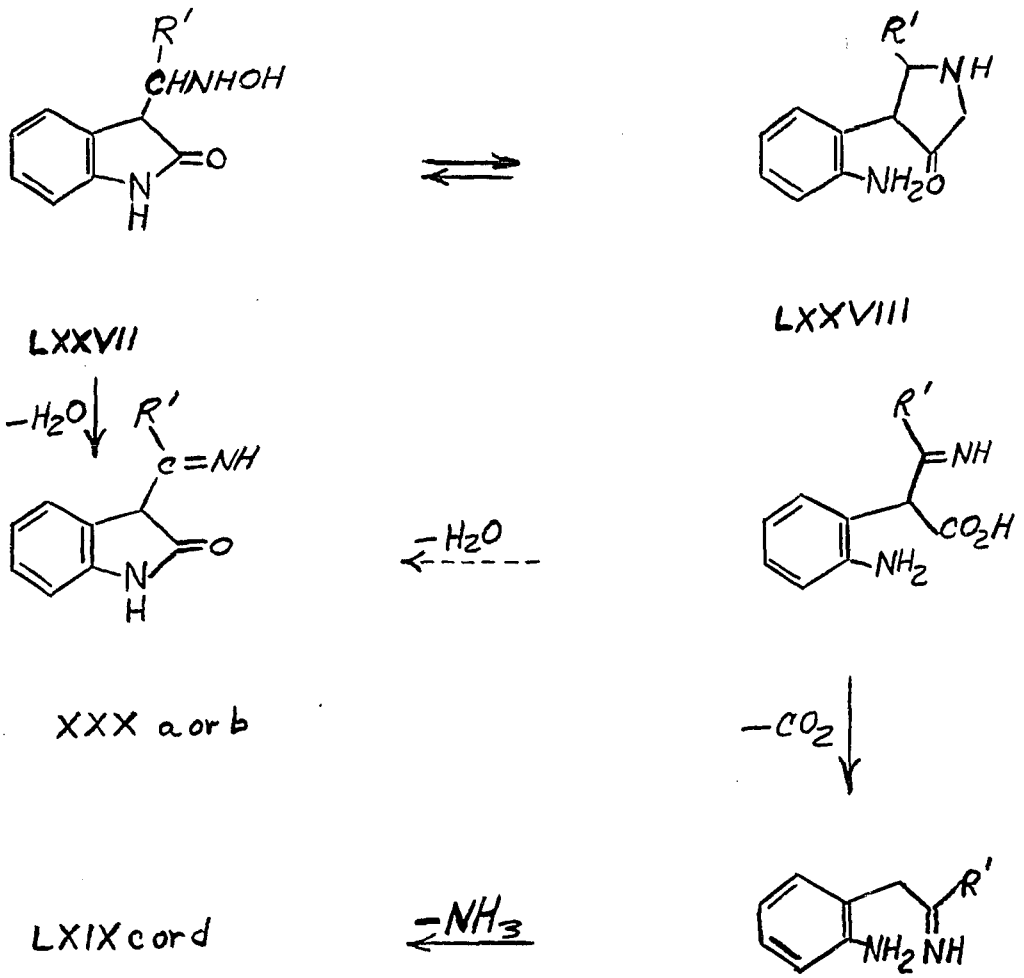
An attempt to prepare LXXVc via the attack of benzylcadmium on o-nitrophenylacetyl chloride also failed. It is feared that the difficulty encountered with o-nitrophenylacetic acid is due to the adjacent positions of the nitro group and the active methylene which might undergo internal redox reactions.

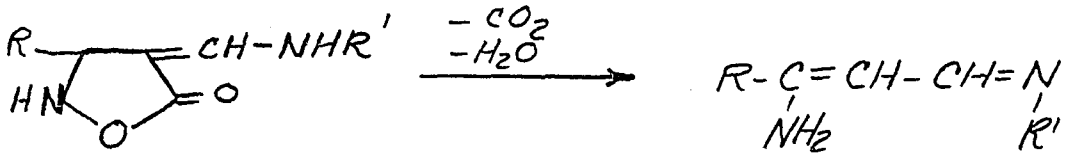
An authentic sample of 2-benzylindole was prepared by the method of Clemo (46). Comparison with the indolic hydrogenation product of VIa showed that they were identical in all physical properties.

The formation of 2-substituted indoles in the hydrogenation of VIa and b appeared to be an example of intramolecular oxindole ring opening (6, 8, 19, and 24). In all cases, a hetero atom was contained on the 3-side chain a convenient number of carbon atoms away from the oxindole carbonyl so as to make interaction and subsequent ring cleavage quite feasible.



The primary reduction product (LXXVII) of VIa or VIb could interact with oxindole to yield the dihydroisooxazolone (LXXVIII) which could subsequently breakdown to the indole or eneamine products. This is analogous to the acid-catalyzed cleavage of dihydroisooxazolones (LXXIX) which Shaw (50a) observed to give eneamine-type compounds (LXXX).





LXXIX LXXX

The absence of indolic products from the N-methylated oxindoles can be attributed to a slower rate of conversion of LXXVII into LXXVIII because of the greater steric requirements for the carbonyl addition intermediate and thus, a more favorable competitive removal in the direction of XXX.

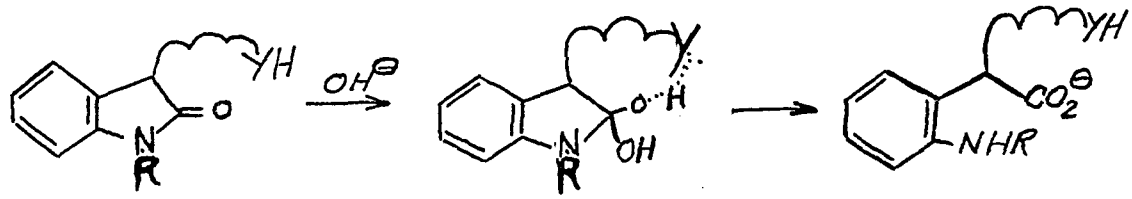
An attempt was made to prepare LXXVII from 3-ethylideneoxindole (XXIII) and hydroxylamine at different pHs, but 3-ethyloxindole (XVIIc) was the sole product isolated. This was the first instance of hydroxylamine reducing an α,β-unsaturated carbonyl system instead of adding to it.

The fact that the rearrangement of oxindole oximes (VIa and b) into indoles took place under reducing conditions suggested that the conversion could take place under hydrolytic conditions. Refluxing the oximes (VIa, b and c) in a potassium acetate solution transformed them into the indoles (LXIXc, d and e). Since the reaction conditions for the hydrolytic rearrangements were similar to those used in the synthesis of the oximes from the 3-acyloxindoles, it became of interest to see whether the indoles were side products in the oxination. Chromatographic separation of the oily

material obtained from the mother liquors from the preparation of VIb, led to 2-methylindole (LXIXd).

To insure that the indole was not a hydrolysis product of 3-acyloxindole, but of the oxime, IIb was exposed to a 5% sodium hydroxide hydrolysis and a 5% hydrochloric acid hydrolysis. The former led to the retro-Claisen product oxindole (Ib) while the latter gave starting material.

Although the opening of the oxindole nucleus during the hydrolytic process requires the participation of the side chain hetero atom, the mechanistic pathway need not be the same as the reductive conversions. Instead of adding to the lactam carbonyl group, it could internally solvate the hydration intermediates and thus lower the activation energy of the reaction.

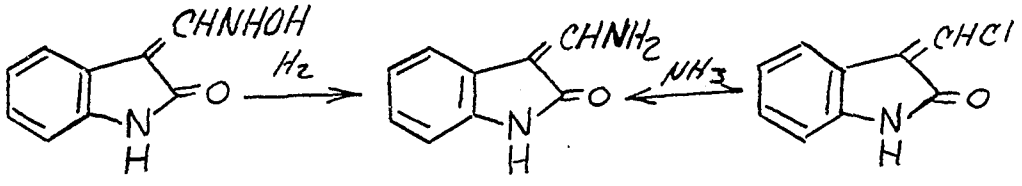


At this point, it became of interest to study the behavior of the oximes (VIe and f) of 3-hydroxymethyleneoxindole and its N-methyl analogue. Bernstein (7) reported the possible formation of 1,3-dimethyloxindole (XVIIg) and 1-methyl-3-aminomethyleneoxindole (XXXf) by the hydrogenation

of VIf over platinum in acetic acid. The ultraviolet absorption spectra of VIe and f were not consistent with those of VIa, b, c and d and their melting points were not in agreement with those reported in the literature (10). A second oximination product (LXXXI) was obtained from IIe by decreasing the reaction time. The second compound had a lower melting point and could be converted to VIe by warming in 95% ethanol or pyrolysis.

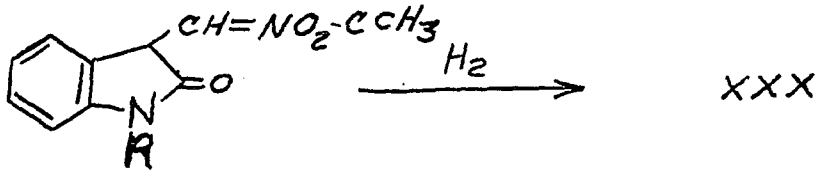
The infrared spectrum of LXXXI showed a shift of the carbonyl group above 6.0 μ, indicating a conjugated double bond. Also, the ultraviolet spectrum was more indicative of an oxindole with a substituent doubly bonded to C-3.

Palladium-charcoal hydrogenation of VIe and f gave 3-methyloxindole (XVIIe) and 1,3-dimethyloxindole (XVII). At the conclusion of each hydrogenation, the reaction mixture reacted basic to litmus and smelled of ammonia. However LXXXI yielded 3-aminomethyleneoxindole (XXXe), identical with a sample prepared by the action of ammonia on 3-chloromethyleneoxindole (LXXXII).



LXXXI XXXe LXXXII

Acetylation of VIe gave a product (LXXXIIIa) whose absorption spectra were similar to those of the acetylation product (LXXXIIIb) of VIf obtained by Bernstein (7). Hydrogenation of each of LXXXIIIa and b led to the corresponding 3-aminomethyleneoxindoles (XXXe and f).



LXXXIII

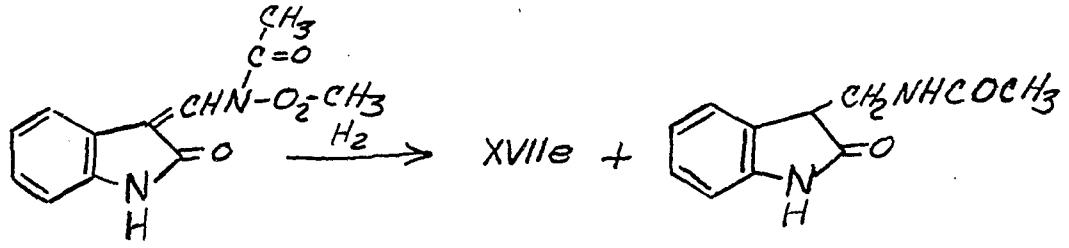
a, R = H

b, R = CH_3

e, R=H

f, R=CH_3

Acetylation of LXXXI yielded the diacetylated material LXXXIV. Catalytic hydrogenation of LXXXIV gave 3-methyloxindole (XVIIe) and 3-acetamidomethyloxindole (LXXXVa), the synthesis of which is reported in a later section.



LXXXIV

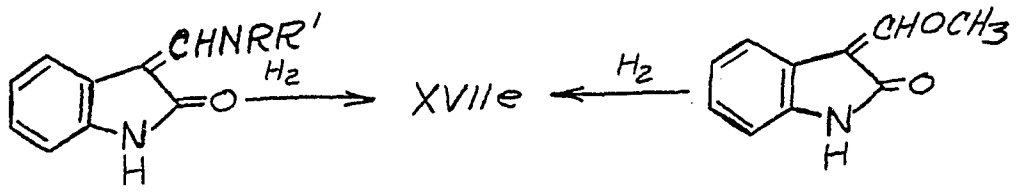
LXXXVa

Since XXXe was stable toward hydrogenation, it could not have been an intermediate in these reductions which yielded XVIIe. However, its imine tautomer resulting from the hydrogenolysis of the N-O bond in a -CH=N-O- system might undergo hydrogenation prior to equilibration to the eneamine.

The fact that XXXe was not susceptible to hydrogenation is quite reasonable. The unshared pair of electrons on the amine nitrogen are in conjugation with the carbonyl group of the oxindole ring, thus lessening the olefinic character of the carbon-carbon double bond at position 3.

In order to investigate the generality of the stability of aminomethylene derivatives toward hydrogenation, 3-methylaminomethyleneoxindole (XVIa) and 3-dimethylaminomethyleneoxindole (XVIe) were prepared by the action of methylamine and dimethylamine respectively on LXXXII. The hydrogenation of each of these derivatives proceeded rapidly yielding XVIIe.

The formation of XVIIe was due to β-elimination of ammonia from the intermediate aminomethyloxindole and further reduction of the resultant 3-methyleneoxindole (LXXXIII). The elimination must have been due to the basicity of the catalyst surface since Wenkert observed the formation of 1-methyl-3-methoxymethyloxindole (XXXI) from XIb by using the least basic catalyst obtainable (38). Use of more basic catalysts in the same hydrogenation had led to XVIIe.

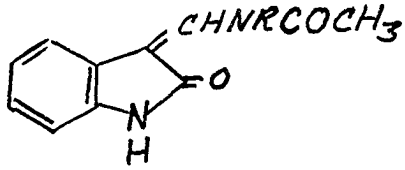


XVI XIb

a, R=R'=CH_3

e, R=H, R'=CH_3

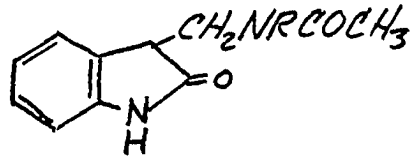
Acetylation of XXXe and XVIe led to the corresponding 3-acetamidomethyleneoxindole (LXXXVIa) and 3-(N-methylacetamidomethylene-)oxindole (LXXXVIb). Catalytic hydrogenation of these acetyl derivatives over palladium-charcoal in ethanol led to 3-acetamidomethyloxindole (LXXXVa) and 3-(N-methylacetamidomethyl-)oxindole (LXXVb). This represented only the second and third instances of the catalytic hydrogenation of a 3-methyleneoxindole containing a hetero atom on the methylene carbon, to the corresponding methyloxindole with the hetero atom still intact.



LXXXVI

a, R=H

b, R=CH_3

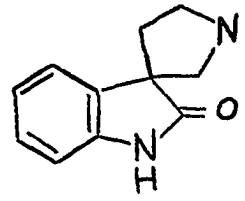


LXXXV

a, R=H

b, R=CH_3

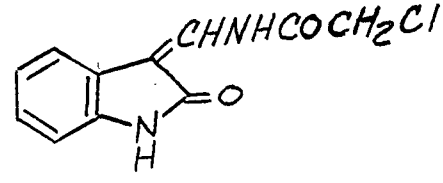
With various 3-aminomethyleneoxindoles and 3-aminomethyloxindoles at hand, it became of interest to attempt the synthesis of the spiro system (LXXVII).



LXXXVII

Attempted alkylation of 3-aminomethyleneoxindole (XXXe) with ethylene bromide under various reaction conditions yielded starting materials. A similar attempt to alkylate 3-acetamidomethyleneoxindole (LXXXVIa) also yielded starting material. It became apparent from these observations that XXXe and LXXXVIa could not be alkylated under standard conditions.

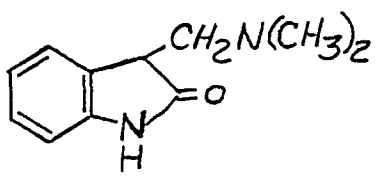
As alternative, an oxindole system with a halogen located on a 3-substituent, a suitable number of atoms away from C-3 was prepared, which might eventually undergo internal displacement of the halogen to give the five membered spiro system. Chloroacetylation of XXXe resulted in the formation of 3-chloroacetamidomethylene oxindole (LXXXVIII). However, attempted internal alkylation of this compound using potassium carbonate and acetone gave starting materials. A sodium ethoxide treatment of LXXXVIII removed the chloroacetyl group to give XXXe. Also reduction of LXXXVIII in acid media in an effort to obtain the corresponding methyl derivative yielded instead LXXXVa.



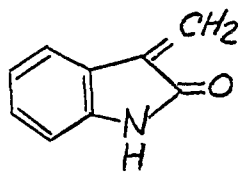
LXXXVIII

It was hoped that 3-acetamidomethyloxindole (LXXXVa) might be of potential use in this endeavor. However, treatment of it with ethylene bromide in a potassium tert-butoxide solution resulted in the formation of a glassy polymeric material. This same polymer was observed in a 5% sodium hydroxide hydrolysis of LXXXVa. The formation of this polymer

is actually quite reasonable, since β-elimination of acetamide gives easily polymerizable 3-methyleneoxindole (LXXXIII) (13). This is analogous to an attempted synthesis of oxygramine (LXXXIX) by the treatment of oxindole (Ia) with formaldehyde and dimethylamine in acetic solution (50b). Instead of oxygramine, there was obtained polymeric material.

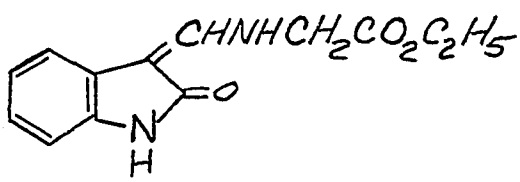


LXXXIX



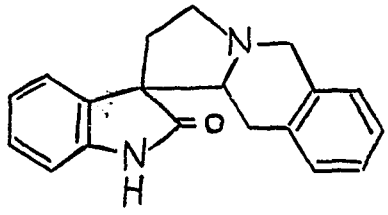
LXXXIII

Another possible route to the spiro system was through 3-carboethoxymethylaminomethyleneoxindole (LC) which was prepared by treatment of 3-hydroxymethyleneoxindole (IIe) with ethyl glycinate. However, hydrolysis of LC, in an effort to form the acid and eventually the acid chloride, resulted in cleavage to IIb.

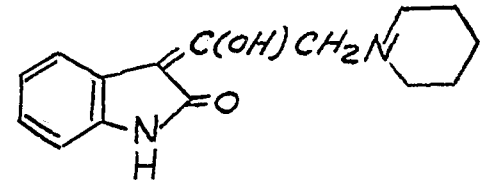


LC

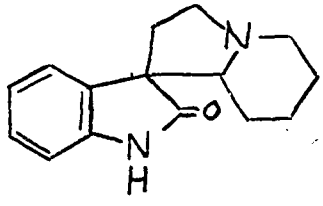
In his projected yohimbine synthesis Julian (4) had occasion to dehydrogenate 1-methyl-3-(β-isoquinolylethyl-) oxindole (XIX) and obtained a product which was assigned the spiro structure XXII by Belleau (17a). It was hoped that a similar dehydrogenation could be carried out on 3-(β-piperidinoethyl-)oxindole (LCII) to give LCIII.



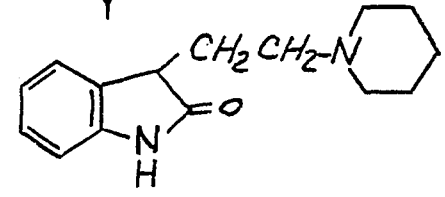
XXII



LCI



LCIII

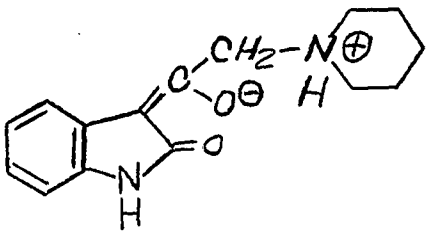


LCII

Oxindole was condensed with ethyl piperidinoacetate to give 3-(α-hydroxy-β-piperidinoethylidene-)oxindole (LCI). Hydrogenation of LCI with platinum and acetic acid did not stop after a two mole uptake and yielded mixtures whose components could not be identified as 3-alkyl oxindoles. Julian

experienced a similar difficulty with the N-unsubstituted analogue of LCI, and as a result, worked exclusively with the N-methyl series. Milder hydrogenation conditions as palladium charcoal in ethanol resulted in recovery of starting material. However, the perchlorate of LCII was readily hydrogenated to a 3-alkyloxindole perchlorate, which then liberated as the free base could not be purified by chromatography or sublimation.

LCI showed no carbonyl absorption in the 5.8 to 6.1μ region, although a medium band was in evidence at 6.23μ. The perchlorate of LCI had a peak at 6.02μ and the sodium salt of LCI, a sharp peak at 6.17μ. It is felt that LCI exists as the zwitterion LCIV.

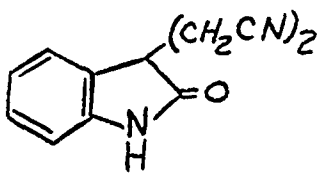


LCIV

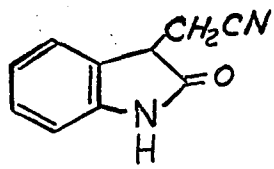
The synthesis of 3-monoalkylated oxindoles by direct alkylation of oxindole has always been a difficult process because of the ready formation N-alkylated as well as 3,3-dialkylated oxindoles (14). Reid (14) conveniently prepared 1-methyl-3-alkyloxindoles by a prior formation of the anion from 1-methyloxindole (Ia) and an equivalent amount of sodium

hydride in benzene followed by reaction with the appropriate alkyl halide. The heterogeneity of the reaction was advantageous in obtaining monoalkylation as the possibility for anion exchange was greatly diminished.

Wenkert (6) reported the preparation of 3,3-dicyanomethyloxindole (LCV) by treatment of an acetone solution of 3-(α-hydroxy-β-phenylethylidene-)oxindole (IIa) with anhydrous potassium carbonate and excess chloroacetonitrile. A similar run with an equimolar quantity of the halide to the oxindole led to 3-cyanomethyloxindole (LCVI).



LCV



LCVI

In order to investigate the generality of this method, 3-(α-hydroxyethylidene-)oxindole (IIb) was treated with various halides. Bhattacharyya* initially carried out alkylation of IIb with chloroacetonitrile and obtained LCVI. Methyl iodide treatment of IIb gave a 50% yield of 3-methyloxindole

*N. K. Bhattacharyya, Iowa State College, Ames, Iowa. Private communication. 1955.

(XVIIe) trace amount of 3,3-dimethyloxindole (LCVII). A 30 hour run with isopropyl bromide led to recovery of two-thirds of IIb and a 50% yield (based on recovered IIb) of 3-isopropyloxindole (LCVIII). An attempted preparation of 3-(β-phthalimidoethyl-)oxindole led to a recovery of both starting materials.

Catalytic hydrogenation of LCVI in an attempt to isolate oxytryptamine (LCIX) led to an oxindole type product whose hydrochloride was hygroscopic and consequently rather difficult to handle. However, this study was interrupted because of similar investigations in other laboratories (8, 24, *).

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*J. Harley-Mason, Cambridge University, Cambridge, England. Private communication. 1955.

SPECTRA

Ultraviolet spectra were run in 95% ethanol using a Beckman model DU quartz spectrophotometer. All infrared absorption spectra were recorded with a Baird Double Beam infrared spectrophotometer.

Figure 1. Ultraviolet spectra

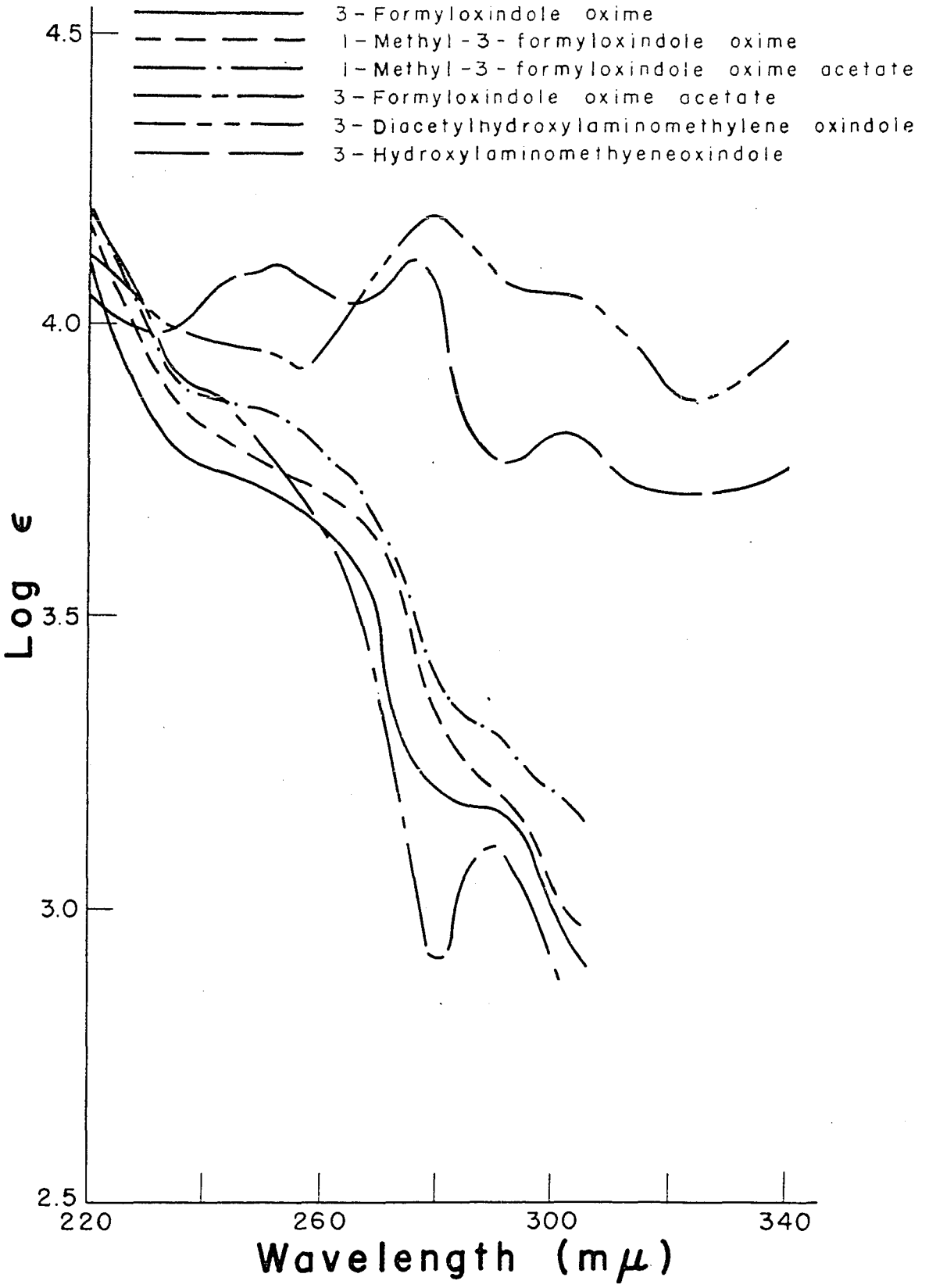

3 - Formyloxindole oxime
1 - Methyl - 3 - formyloxindole oxime
1 - Methyl - 3 - formyloxindole oxime acetate
3 - Formyloxindole oxime acetate
3 - Diacetylhydroxylaminomethylene oxindole
3 - Hydroxylaminomethyeneoxindole
4.5
4.0
3.5
3.0
2.5
Log ε
220
260
300
340
Wavelength (mμ)

Figure 2. Ultraviolet spectra

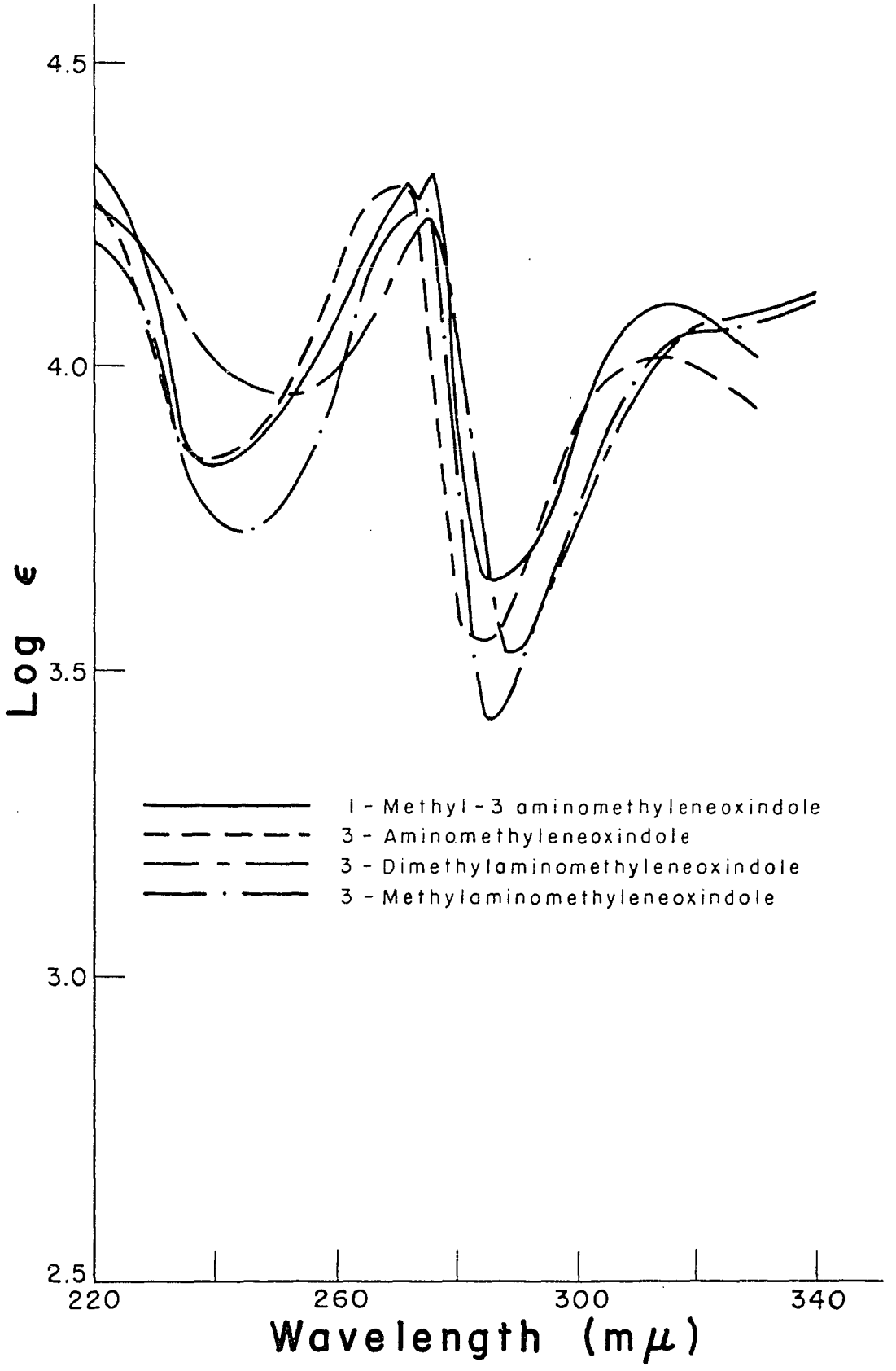

4.5
4.0
3.5
3.0
2.5
Log ε
220
260
300
340
Wavelength (mμ)
1 - Methyl - 3 aminomethyleneoxindole
3 - Aminomethyleneoxindole
3 - Dimethylaminomethyleneoxindole
3 - Methylaminomethyleneoxindole

Figure 3. Ultraviolet spectra

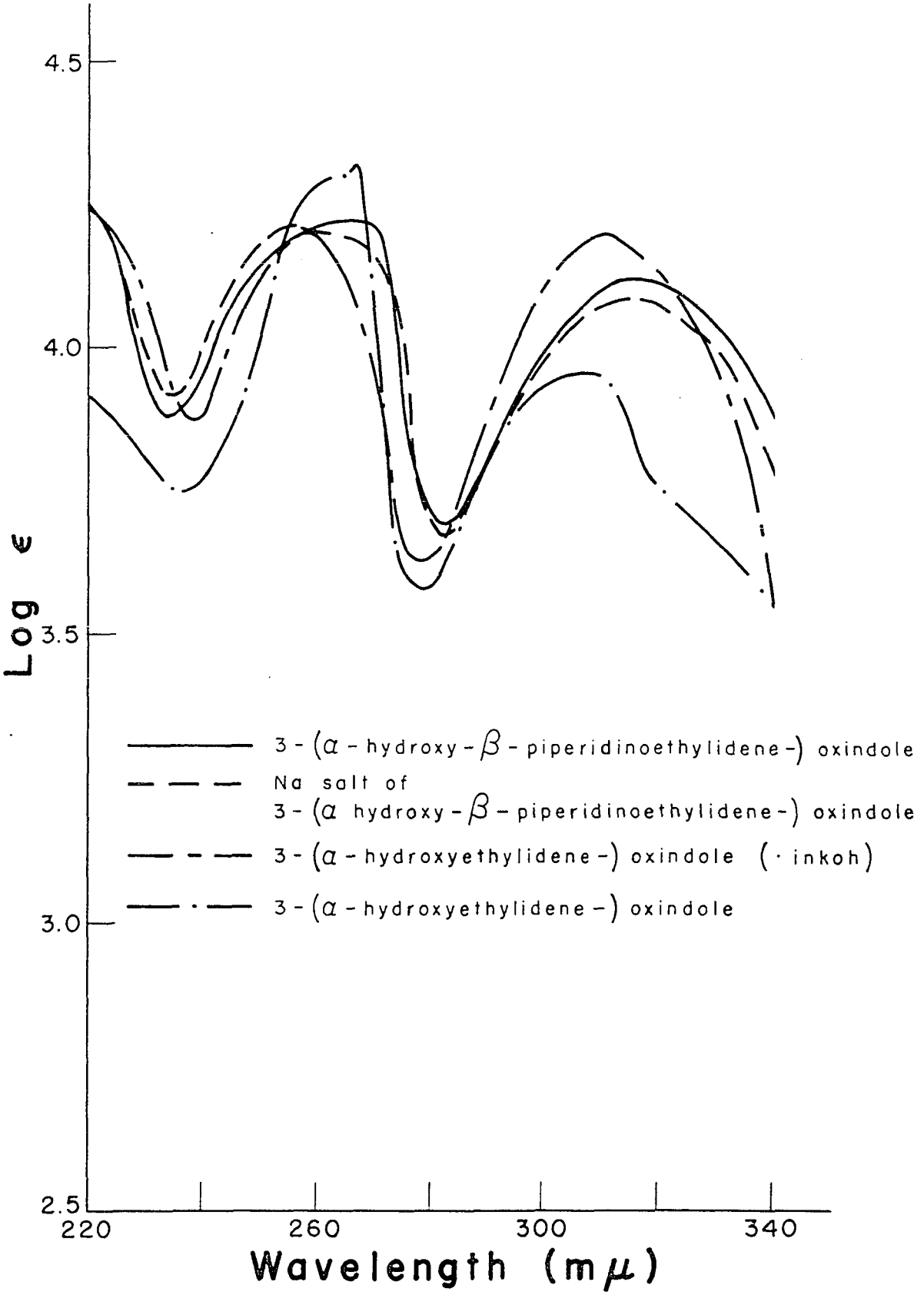
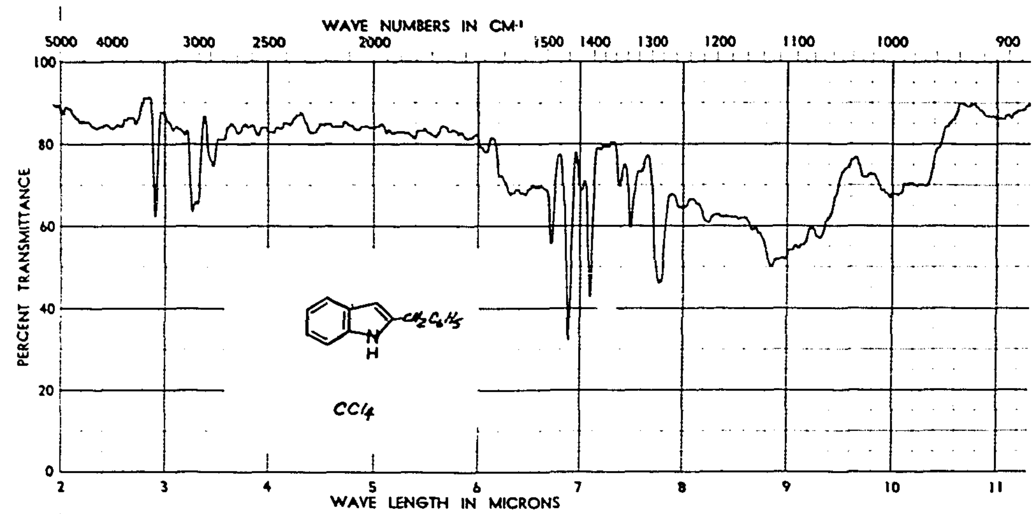
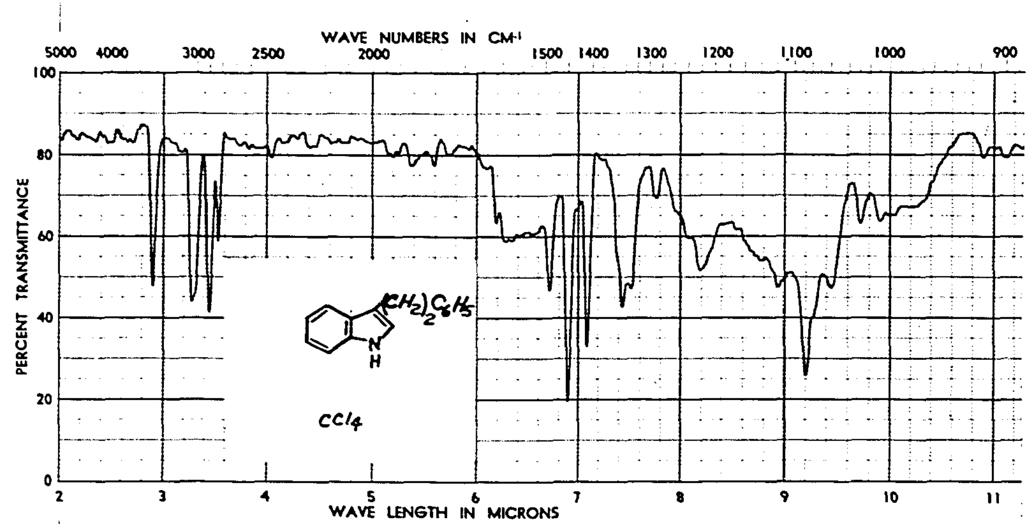

4.5
4.0
3.5
3.0
2.5
Log ε
220
260
300
340
Wavelength (mμ)
3-(α-hydroxy-β-piperidinoethylidene-) oxindole
Na salt of
3-(α hydroxy-β-piperidinoethylidene-) oxindole
3-(α-hydroxyethylidene-) oxindole (·inkoh)
3-(α-hydroxyethylidene-) oxindole

Figure 4. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
0 20 40 60 80 100
$CH_2C_6H_5$
N
H
CCl_4
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
0 20 40 60 80 100
$(CH_2)_2C_6H_5$
N
H
CCl_4
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS

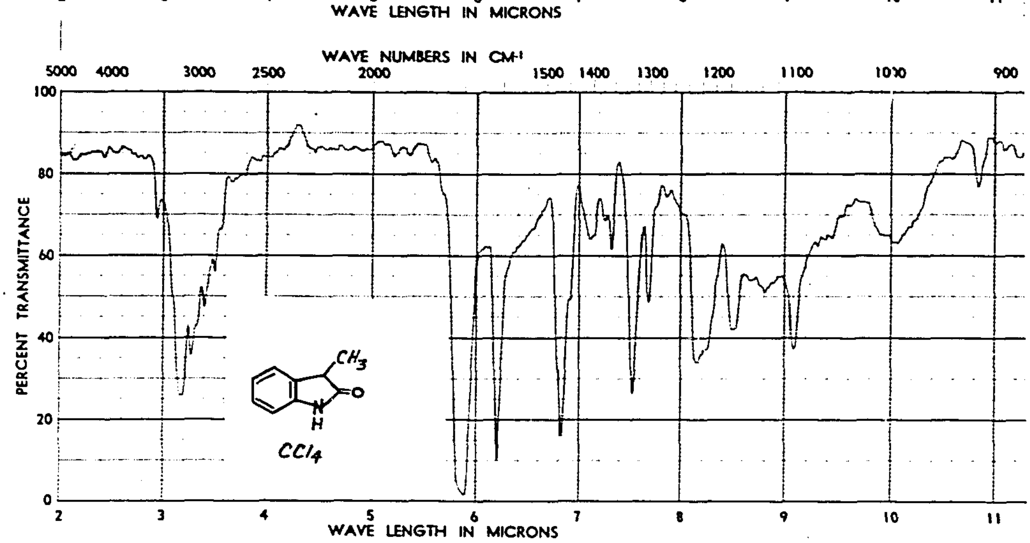
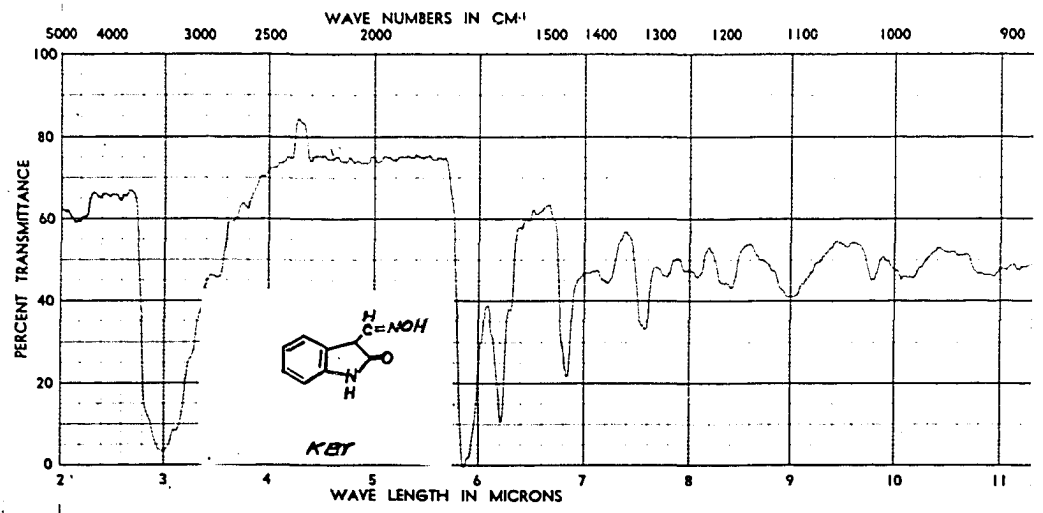
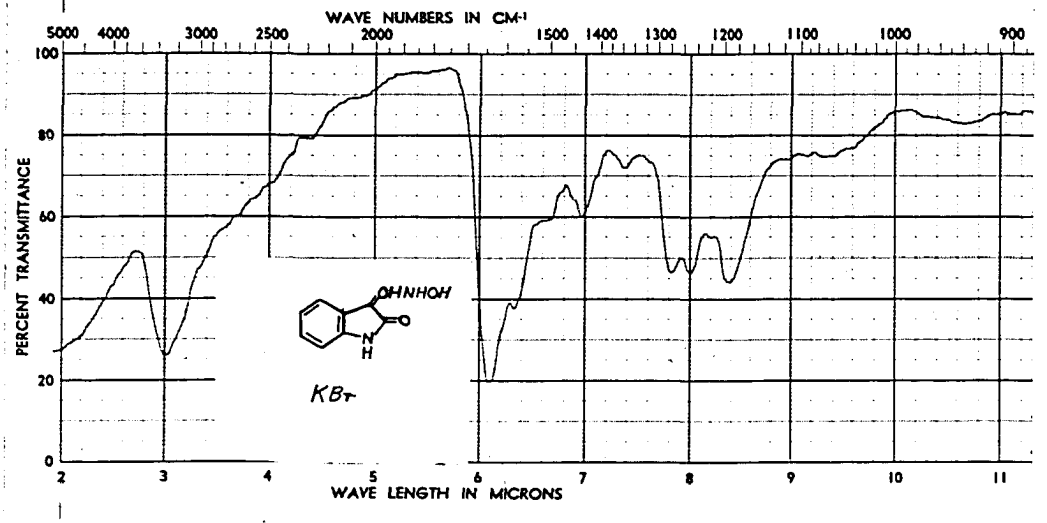

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
0 20 40 60 80 100
CH_3
O
N
H
CCl_4
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS

Figure 5. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
H
C=NOH
N
H
KBr


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
OHNHOH
N
H
KBr

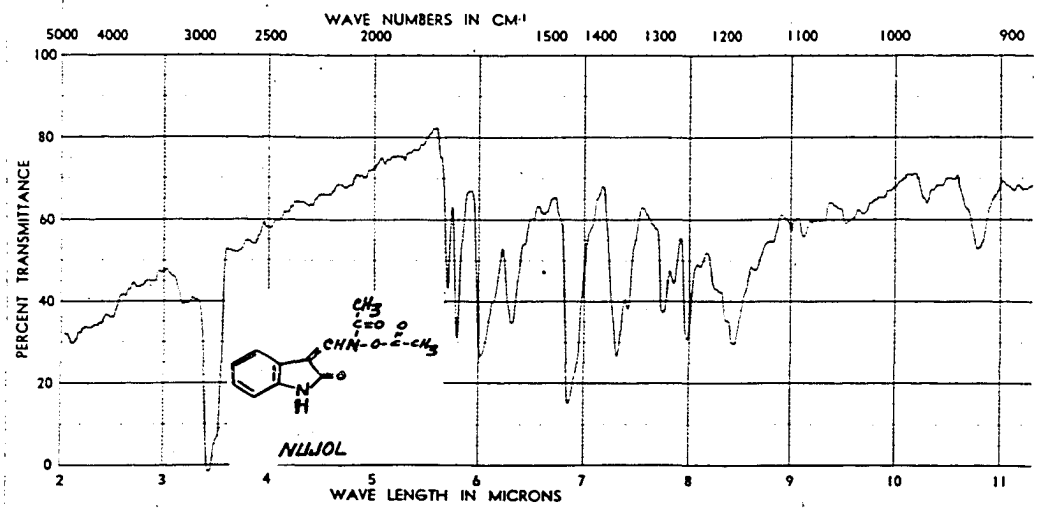
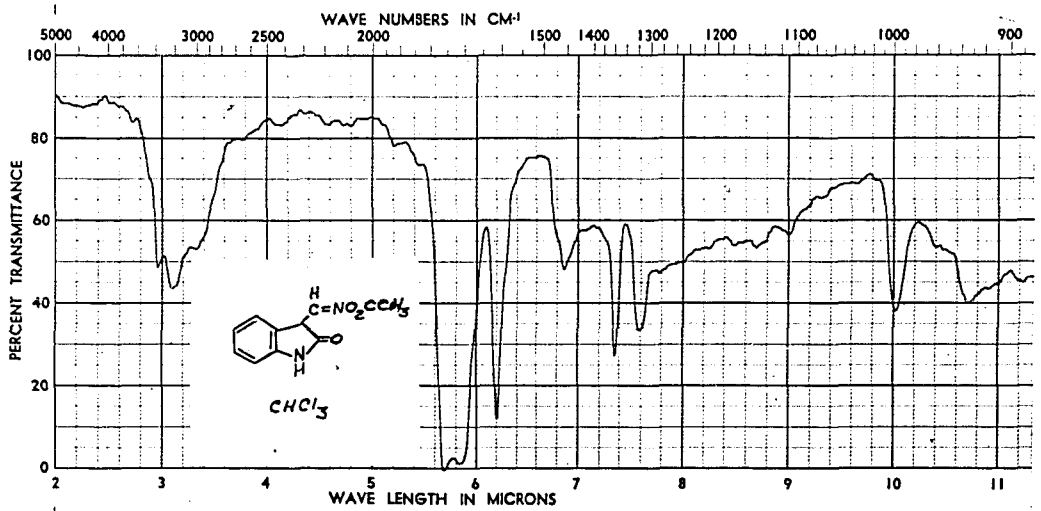
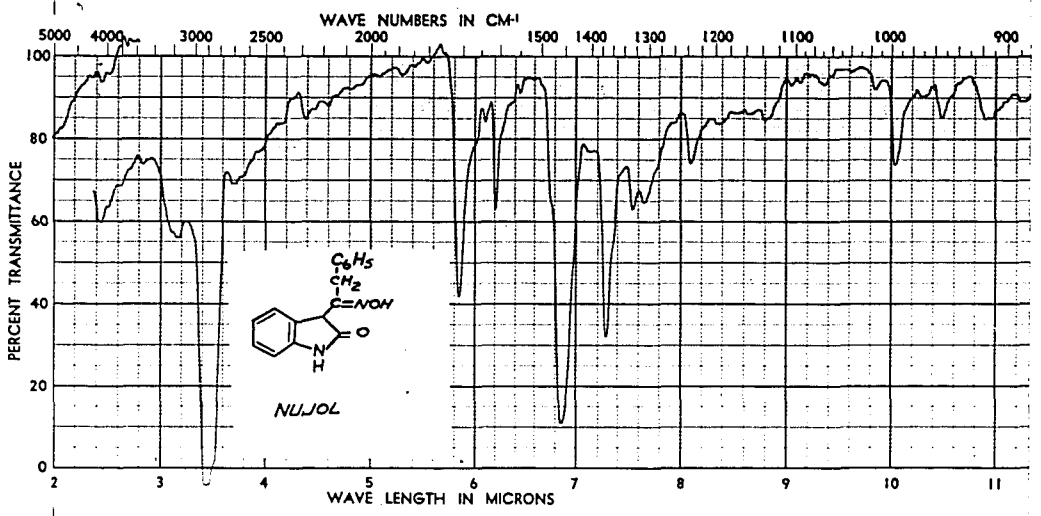

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
CH3
C=O
CHN-O-C-CH3
O
N
H
NUJOL

Figure 6. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
C=NO2CCH3
CHCl3


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
C6H5
CH2
C=NOH
NUJOL

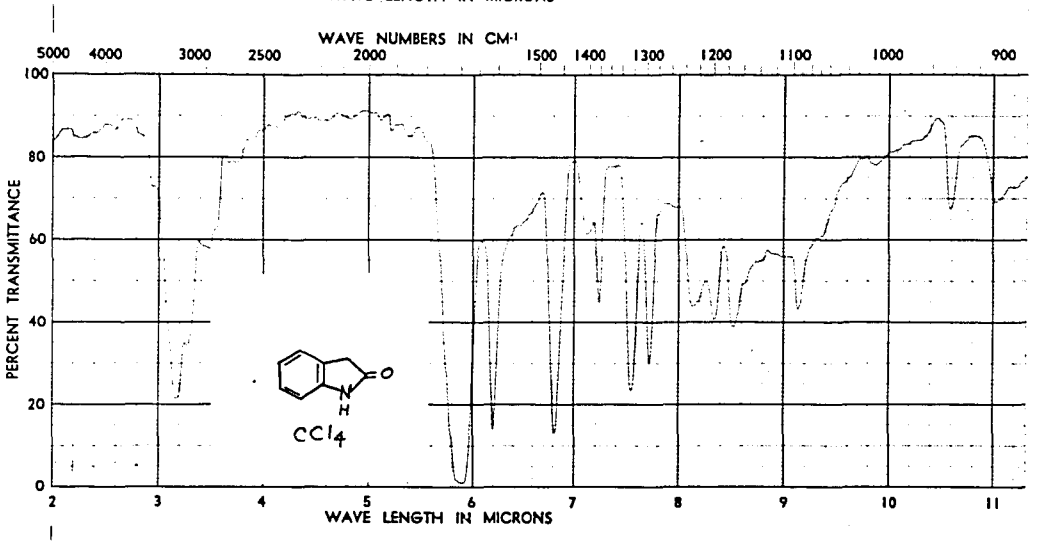

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
CCl4

Figure 7. Infrared spectra

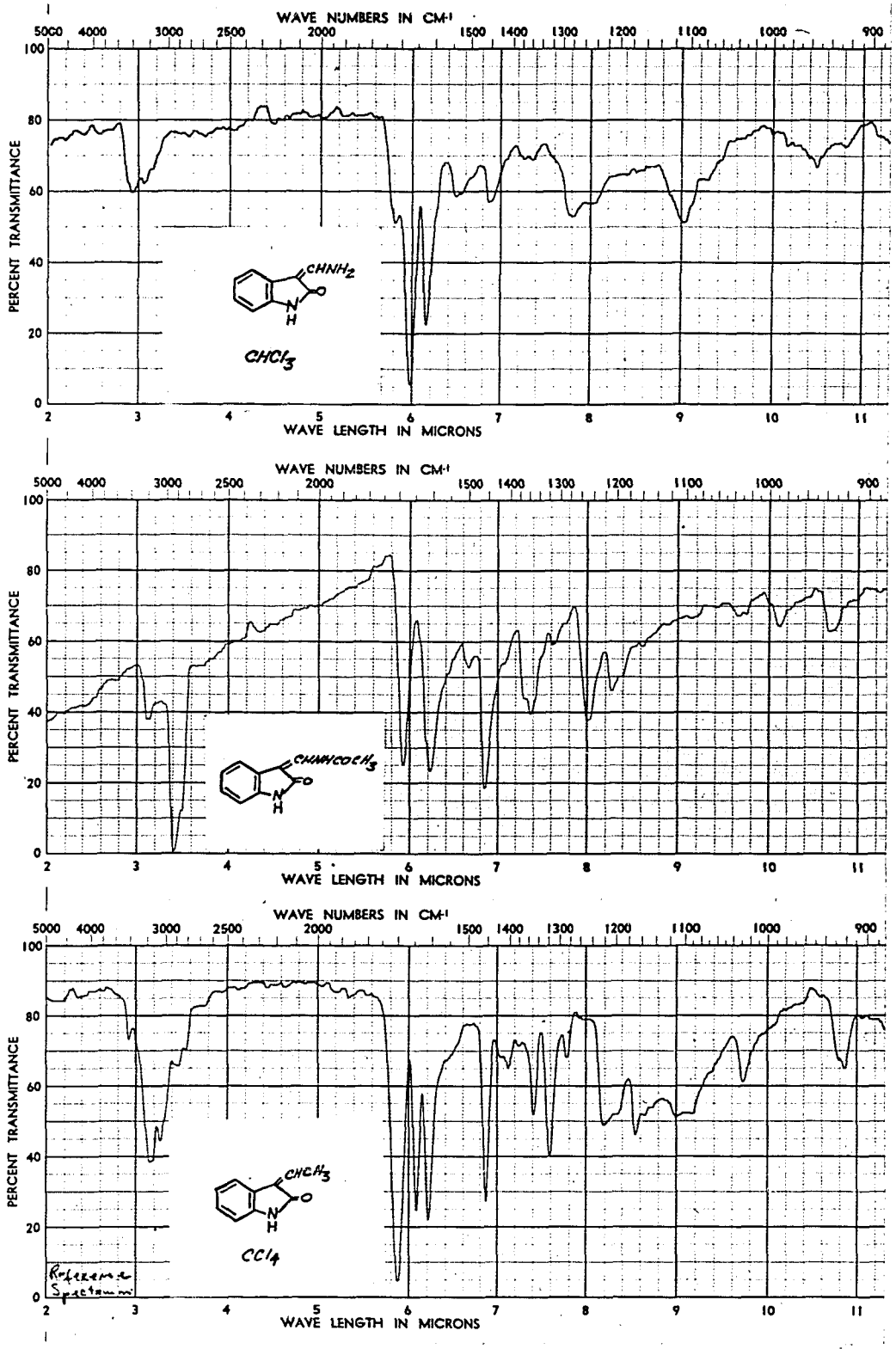
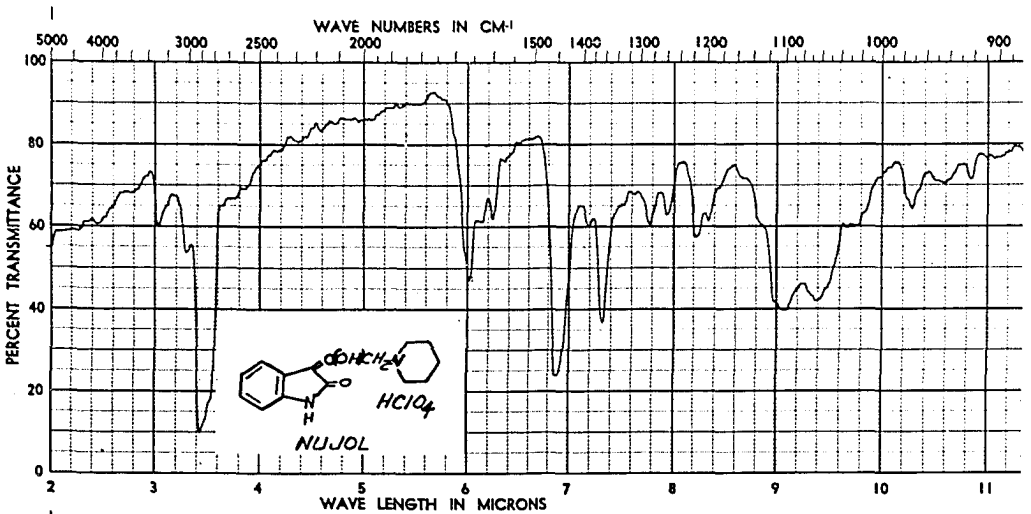
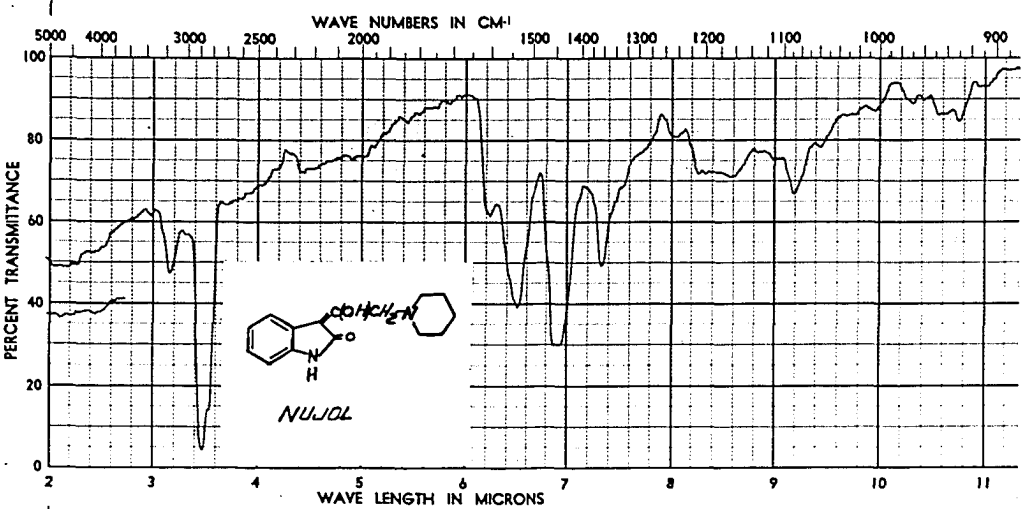

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
CHNH2
CHCl3
WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
CHNHCOCH3
WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
CHCH3
CCl4
Reference Spectrum

Figure 8. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
HClO4
NUJOL


WAVE NUMBERS IN CM-1
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PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
NUJOL

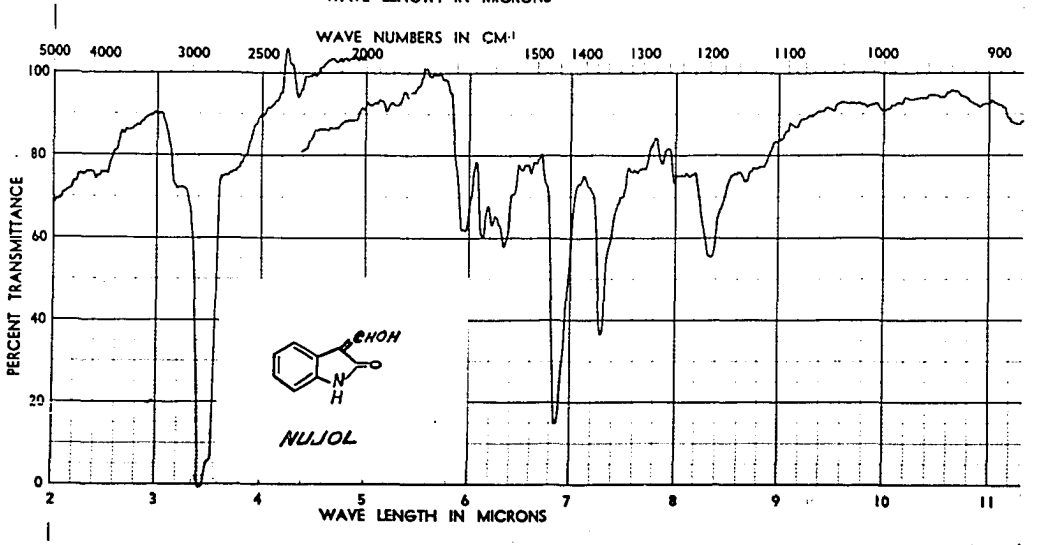
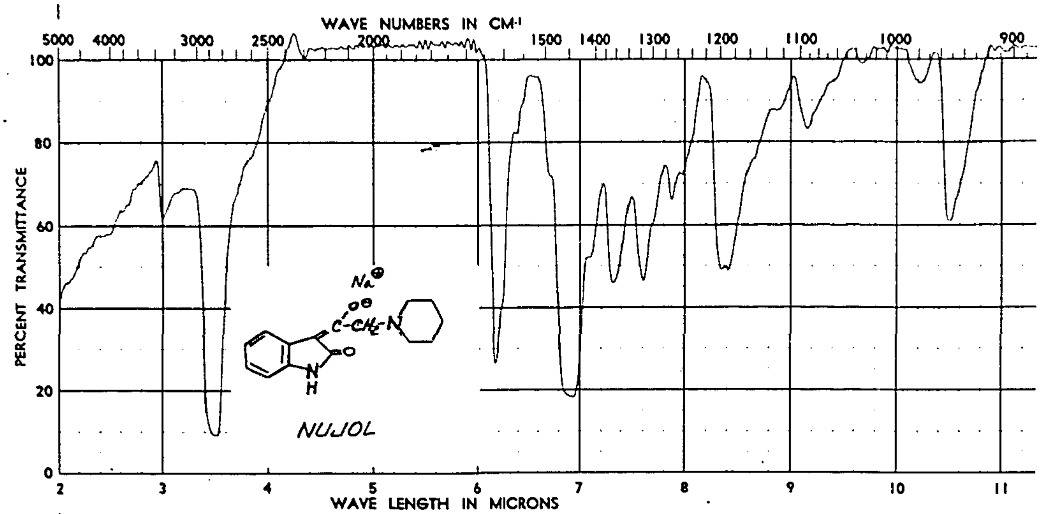
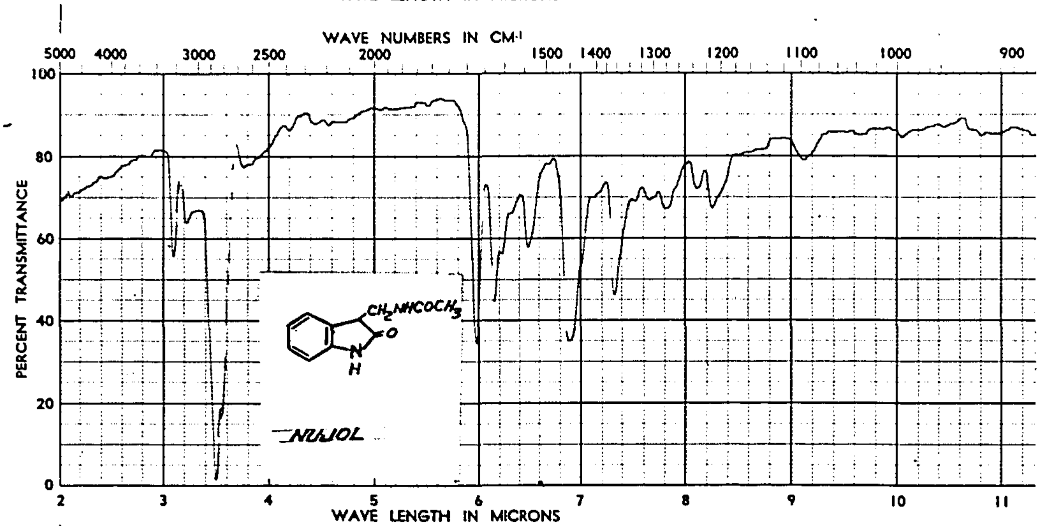

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
PERCENT TRANSMITTANCE
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11
WAVE LENGTH IN MICRONS
NUJOL

Figure 9. Infrared spectra


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
NUJOL


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
CH₂NHCOCH₃
NUJOL

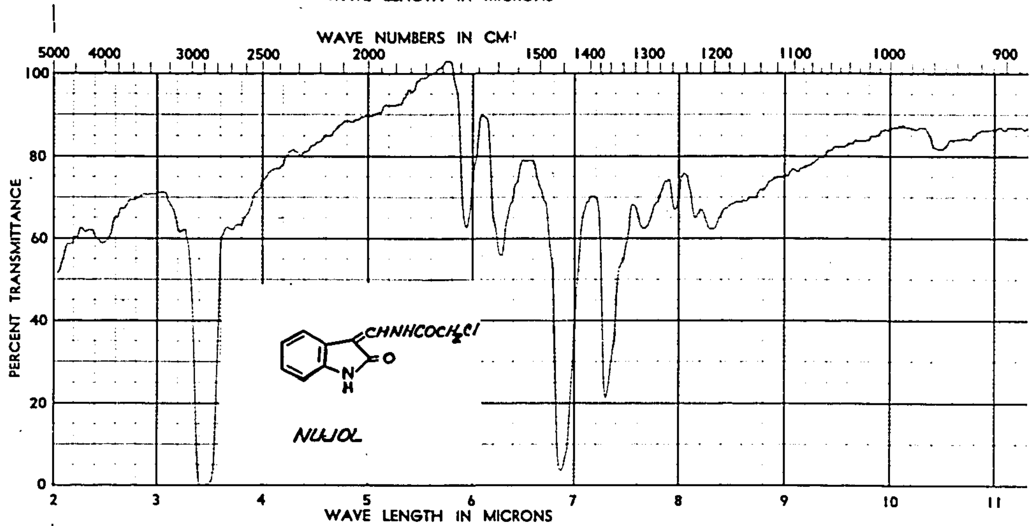
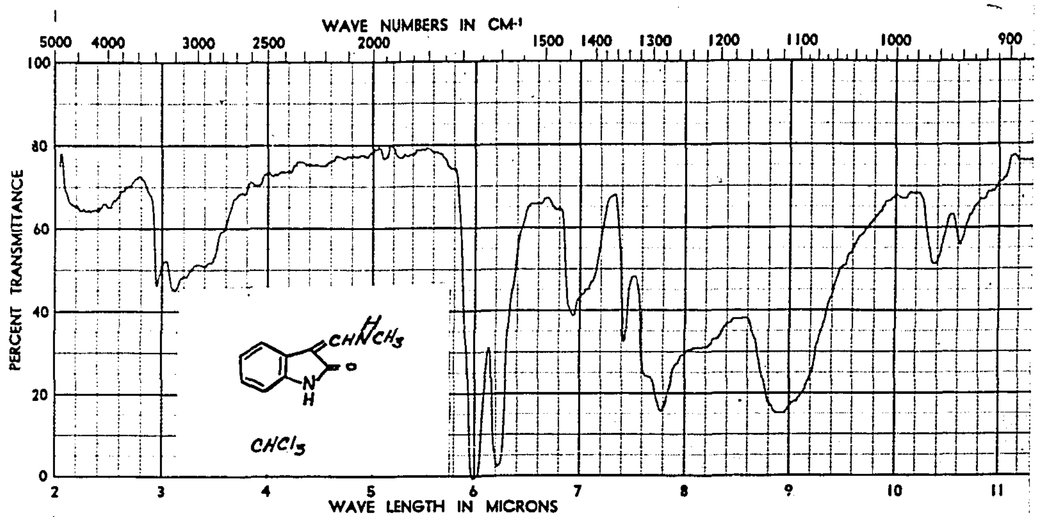

WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
CHNHCOCH₂Cl
NUJOL

Figure 10. Infrared spectra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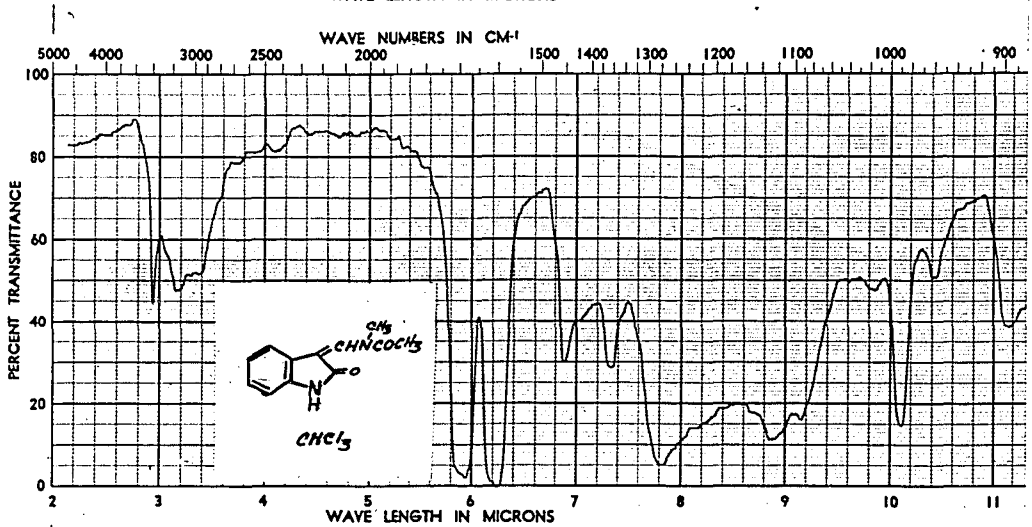
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
CHCl3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PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
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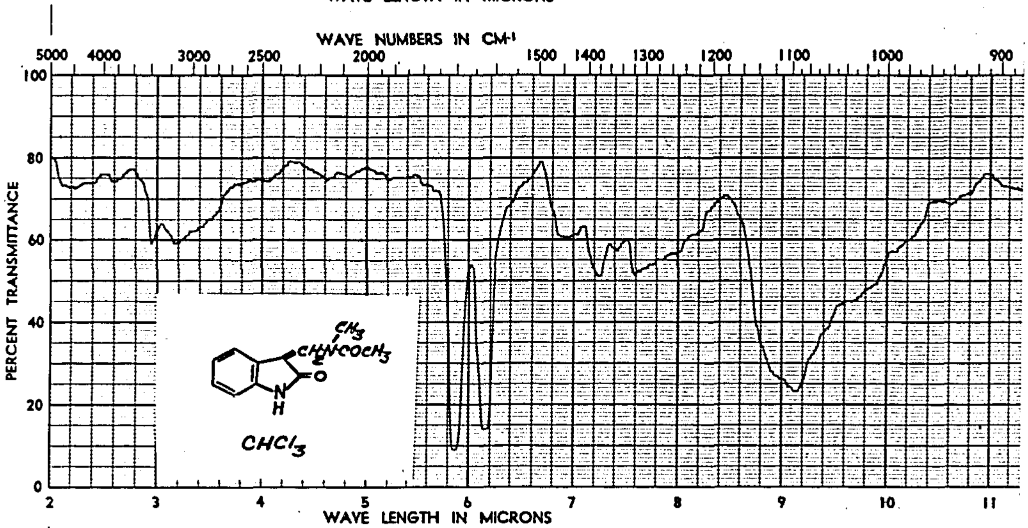
WAVE NUMBERS IN CM-1
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS
CHCl3

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed by Strauss and Weiler Microanalytical Laboratory, Oxford, England, and Midwest Microlab, Indianapolis, Indiana.

Adsorbants for chromatography

Activated alumina, 80-200 mesh, was allowed to stand with ethyl acetate for 48 hours, then washed with water and methanol, and dried at 50° for 48 hours.

Oxindole (Ib)

The method of Di Carlo (51) was followed.

1-Methyloxindole (Ia)

To a solution of 15.56 g. of oxindole and 4.80 g. of sodium hydroxide in 100 ml. of water, 11.3 ml. of dimethyl sulfate was added dropwise. The resulting heterogeneous mixture was allowed to be stirred for one hour, after which time Ia precipitated out. Crystallization from petroleum ether yielded white crystals, m.p. 89° [lit. value (52): m.p. 89°]. Kondo reported the same reaction (40) after it was carried out in this laboratory.

1-Methyl-3-hydroxymethyleneoxindole (IIf)

The method of Julian (I) was followed.

1-Methyl-3-(α-hydroxyethylidene-)oxindole (IId)

Julian's method (II) led to a 77% yield of IId.

1-Methyl-3-(α-hydroxy-β-phenylethylidene-)oxindole (IIc)

Bernstein's method (8) was followed.

3-Hydroxymethyleneoxindole (IIe)

The procedure of Wenkert (15) was followed.

3-(α-Hydroxyethylidene-)oxindole (IIb)

Horner's procedure (5) modified by the use of continuous stirring of the reaction mixture, gave a 72% yield of IIe, m.p. 205° lit. value (5): m.p. 203° .

Ultraviolet spectrum. (INKOH) $\lambda_{max.}$ 258 mμ (log.ϵ 4.22) and 310 mμ (log.ϵ 4.20).

3-(α-Hydroxy-β-phenylethylidene-)oxindole (IIa)

The method of Wenkert (6) was followed.

3-(α-Hydroxy-β-piperidinoethylidene-)oxindole (LCIa)

A slurry of 4 g. of oxindole (Ia) and 6 g. of ethyl piperidinoacetate was added to a warm sodium ethoxide solution, prepared from 1 g. of sodium and 5 ml. of absolute ethanol. The mixture was refluxed for two hours at which time a precipitate of the sodium salt of LCIa appeared. Separation by filtration and neutralization of the sodium salt yielded a white solid, m.p. 255-60°. Crystallization from ethanol gave white crystals, m.p. 260°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.80; H, 6.98; N, 10.85. Found: C, 69.99; H, 7.30; N, 10.9.

Ultraviolet spectrum. $\lambda_{max.}$ 268 mμ (log.ϵ 4.22) and 317 (log.ϵ 4.13).

LCIa perchlorate. Crystallized from ethanol, m.p. 245°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$-$HClO_4$: C, 50.25; H, 5.31; N, 7.81; Found: C, 49.84; H, 5.25; N, 7.81.

Ultraviolet spectrum. $\lambda_{max.}$ 256 mμ (log.ϵ 4.22) and 318 mμ (log.ϵ 4.08).

Sodium salt of LCIa $\lambda_{max.}$ 256 mμ (log.ϵ 4.22) and 315 mμ (log.ϵ 4.08).

1-Methyl-3-(α-hydroxy-β-piperidinoethylidene-)oxindole (LCIb)

Using the procedure above, 2.3 g. 74% of LCIb was obtained. Crystallization from ether-chloroform combination, m.p. 170°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.60; H, 7.36; N, 10.30; Found: C, 70.32; H, 7.20; N, 10.15.

Ultraviolet spectrum. $\lambda_{max.}$ 270 mμ (log.ϵ 4.24) and 310 mμ (log.ϵ 4.14).

3-Phenylacetyloxindole oxime (VIa)

The method of Wenkert (6) was followed.

3-Acetyloxindole oxime (VIb), 1-methyl-3-phenylacetyloxindole oxime (VIc), 1-methyl-3-acetyloxindole oxime (VId) and 1-methyl-3-formyloxindole (VIf)

Bernstein's procedure (7) was followed.

3-Formyloxindole oxime (VIe)

An absolute ethanol solution of a mixture of 4 g. of IIe, 2 g. of hydroxylamine hydrochloride, and 4 g. of potassium acetate was refluxed for one hour. After removal of the inorganic salts, vacuum concentration of the filtrate, and an

addition of a small quantity of water to the latter, 2.5 g. of VIe appeared as an amorphous powder, m.p. 221-222°.

Ultraviolet spectrum. $\lambda_{shoulder}$ 240-260 mμ (log. ∈ 3.75-3.65).

A benzene extract of the mother liquor was concentrated and chromatographed on alumina. Elution with petroleum ether yielded 140 mg. of indole, m.p. 54°. No m.p. depression was observed on admixture of an authentic sample.

3-Hydroxylaminomethyleneoxindole (LXXXI)

The above conditions for VIe except for a five reaction time were followed. A light green product was obtained which was crystallized from tetrahydrofuran, m.p. 160°. Solidification of the melt took place at 165° and remelting at 220°.

Ultraviolet spectrum. $\lambda_{max.}$ 250 mμ (log. ∈ 4.10) and 276 mμ (log. ∈ 4.10).

3-Formyloxindole oxime acetate (LXXXIIIa)

A mixture of 650 mg. of VIc and 5 ml. of acetic anhydride was warmed for two minutes, colled, hydrolyzed with a saturated sodium bicarbonate solution and extracted with chloroform. Removal of solvent after drying left a white solid, m.p. 168-170°.

Ultraviolet spectrum. $\lambda_{shoulder}$ 235-245 mμ (log.ϵ 3.85-3.90) and $\lambda_{max.}$ 290 mμ (log.ϵ 3.10).

1-Methyl-3-formyloxindole oxime acetate (LXXXXIIIb)

Bernstein's procedure (7) was followed.

3-Diacetylhydroxylaminomethyleneoxindole (LXXXIV)

One gram of LXXXI was dissolved in 10 ml. of acetic anhydride by gentle heating for two minutes and on cooling gave yellow crystals, m.p. 215°. Crystallization from methanol gave LXXXIV, m.p. 220°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: N, 10.78; Acetyl, 33. Found: N, 10.9; Acetyl, 30.95.

Ultraviolet spectrum. $\lambda_{max.}$ 280 mμ (log.ϵ 4.19).

Catalytic hydrogenation of oximes over platinum and acetic acid

An acetic acid solution of the oxime (1.00 g. in 50 ml.) was hydrogenated over platinum (10%, by weight, of the oxime) at atmospheric pressure. When hydrogen uptake had ceased, the catalyst was filtered, the filtrate neutralized with saturated sodium bicarbonate solution, and extracted with chloroform. After washing with water and drying over sodium

sulfate, the chloroform was removed to give a residue which was chromatographed on alumina.

Hydrogenation of 3-phenylacetyloxindole oxime (VIa)

Reduction of 250 mg. of VIa led to 30 mg. (15%) of 2-benzylindole (LXIXc), m.p. 84° (eluted with petroleum ether), identical in m.p., mixed m.p., and infrared spectrum with an authentic sample prepared by the method of Clemo (46).

Hydrogenation of 3-acetyloxindole oxime (VIb)

Hydrogenation of 500 mg. of VIb yielded 30 mg. (8%) of 2-methylindole (LXIXd), m.p. 61° (eluted with petroleum ether) identical in m.p., mixed m.p., and infrared spectrum with an authentic sample prepared by a Fischer indole synthesis, and 300 mg. (66%) of 3-(α-aminoethylidene-)oxindole (XXXb), m.p. 225°, identical in m.p. with that of Bernstein (7).

Hydrogenation of 1-methyl-3-acetyloxindole oxime (VId) and 1-methyl-3-phenylacetyloxindole oxime (VIc)

The procedure of Bernstein (7) was followed.

Hydrogenation of 3-(α-hydroxy-β-piperidinoethylidene-) oxindole (LCIa)

From 2.3 g. of the sodium salt of LCIa was obtained 1.4 g. of an oil which on alumina chromatography yielded semi-solid fractions which failed to give picrate derivatives and characteristic oxindole ultraviolet spectra.

Hydrogenation of 1-methyl-3-(α-hydroxy-β-piperidinoethyi-dene-)oxindole (LCIb)

From 1.000 g. of LCIb was obtained .8 g. of brown oil which showed on oxindole-type ultraviolet spectrum but gave no picrate derivatives.

3-(β-Phenylethyl-)indole (LXIXa)

Two grams of 3-phenylacetyloxindole enol (IIa) in 100 ml. of glacial acetic acid was hydrogenated over 150 mg. of platinum oxide. When the reduction had stopped after a 250 ml. uptake of hydrogen, the catalyst was filtered, the filtrate neutralized with 10% sodium bicarbonate solution, extracted three times with chloroform, and the extracts dried over anhydrous sodium sulfate. Removal of the solvent left a semi-solid residue, which gave a positive ferric chloride test, and whose benzene washings were concentrated and

chromatographed on alumina. Elution with 1:1 benzene ether gave a clear oil whose 252 mμ ultraviolet spectrum maximum agreed well with the one expected for 3-(β-phenylethyl-) oxindole (XVIIa).

One gram of sodium was added in several small portions to a n-butanol solution (25 ml.) of 275 mg. of XVIIa. After dissolution of all sodium the mixture was cooled, water added, the butanol removed under vacuum, and the aqueous residue extracted with ether. Removal of the solvent after drying of the ether extracts over sodium sulfate gave 100 mg. (39%) of residue which crystallized on standing, m.p. 116-118°. Recrystallization from dilute ethanol produced pure 3-(β-phenylethyl-)indole (LXIXa), m.p. 119-120°, identical in m.p., mixed m.p. and infrared spectrum with an authentic sample prepared in 86% yield by the Snyder method (43).

3-Ethyloxindole (XVIIc)

Two grams of 3-acetyloxindole enol (IIb) in 50 ml. of absolute ethanol was hydrogenated over 1 g. of 5% palladium-charcoal. After cessation of hydrogen uptake, filtration of the catalyst and concentration of the filtrate in vacuo, the oily residue was chromatographed on alumina. Benzene elution gave 1.5 g. (82%) of a yellow solid, m.p. 130-132°. Crystallization from benzene gave 3-ethylideneoxindole (XXIII), m.p. 142° [lit. value: (5) m.p. 140°].

Ultraviolet spectrum. $\lambda_{max.}$ 246 mμ (log.ϵ 4.47), 255 mμ (log.ϵ 4.50) and 288 mμ (log.ϵ 3.70).

A solution of 100 mg. of (XXIII), 40 mg. of hydroxylamine hydrochloride and 88 mg. of potassium acetate in 25 ml. of absolute ethanol was refluxed for three hours. After filtration of the inorganic salts, the solvent was removed in vacuo and the residue chromatographed on alumina. Elution with ether gave 40 mg. of a crystalline solid. Crystallization from benzene-petroleum ether yielded 3-ethyl oxindole (XVIIc), m.p. 104° [lit. value (5) m.p. 104°].

Similar runs, however, with adjustment of pH to approximately 10 by addition of solid sodium hydroxide or by acidification by the addition of acetic acid and a trace of p-toluenesulfonic acid, led to similar results.

Oxime hydrolyses

A solution of the oxime and an equal weight of potassium acetate in ethanol was refluxed for six hours. After filtration of the inorganic salts, the solution was concentrated and the dark gummy residue chromatographed on alumina.

Hydrolysis of 3-phenylacetyloxindole oxime (VIa)

Hydrolysis of VIa in 35 ml. gave 100 mg. (25%) of 2-benzylindole (LXIXc), m.p. 84°, (eluted with petroleum

ether), identical with an authentic sample.

Hydrolysis of 1-methyl-3-phenylacetyloxindole oxime (VIc)

Hydrolysis of VIc gave a 14% yield of 1-methyl-2-benzylindole (LXIXe), m.p. 60° [lit. value (44): m.p. 60°] ; picrate, m.p. 97° [lit. value (44): m.p. 97°] .

Hydrolysis of 3-acetyloxindole oxime (VIb)

A solution of 6.0 g. of 3-acetyloxindole enol (IIb), 3.0 g. of hydroxyloxime hydrochloride and 6.0 g. of potassium acetate in 100 ml. of ethanol was refluxed for 15 hours. After the usual work up of an oximination reaction the brown oily product was chromatographed on alumina, giving 1.5 g. (34%) of 2 methylindole, (LXIXd), m.p. 60°, (eluted with petroleum ether) identical with the authentic sample.

Hydrolysis of 3-(α-hydroxyethylidene-)oxindole (IIb)

A mixture of 1 g. of IIb and 15 ml. of 5% HCl solution was refluxed for two hours. After cooling of the reaction mixture, the entire starting material was recovered.

A solution of 1 g. of IIb in 15 ml. of 5% aqueous sodium hydroxide was refluxed for two hours. Cooling of the solution

and neutralization with dilute HCl gave 700 mg. (92%) of oxindole (Ia) m.p. 126°.

Attempted preparation of 1-o-nitrophenyl-2-propanone (LXXVb)

A solution of 5 g. of o-nitrophenylacetic acid in 20 ml. of a 50:50 mixture of acetic anhydride and pyridine was heated for five minutes. The resulting red solution was slowly added to ice water, neutralized, and extracted with chloroform. The residue left after solvent removal was chromatographed on alumina giving no ketonic fractions.

Attempted preparation of 1-o-nitrophenyl-3-phenyl-2-propanone (LXXVc)

A similar procedure using phenylacetic anhydride gave no ketonic materials.

3-Chloromethyleneoxindole (LXXXII)

The method of Behringer (17) was followed.

3-Aminomethyleneoxindole (XXXe)

Ammonia gas was passed into an ice cooled solution of 1 g. of LXXXII in 100 ml. of ethanol. After sitting for

three hours, the solution was concentrated in vacuo and a small amount of water added, giving 800 mg. (89%) of XXXe. Crystallization from ethyl acetate yielded white crystals, m.p. 220°.

3-Methylaminomethyleneoxindole (XVIe)

A mixture of 1 g. of LXXXII and 40 ml. of 25% methylamine in water was allowed to sit overnight. Vacuum concentration and addition of water gave 900 mg. (92%) of tan solid; crystallized from dil. ethanol, m.p. 235°. No depression was observed on admixture with an authentic sample.

Ultraviolet spectrum. $\lambda_{max.}$ 275 mμ (log.ϵ 4.27) and 342 mμ (log.ϵ 4.12).

3-Dimethylaminomethyleneoxindole (XVIa)

A mixture of 1 g. of LXXXII and 40 ml. of 25% dimethylamine in water was allowed to set overnight. Vacuum concentration and addition of water gave 950 mg. of tan solid. Crystallization from ethanol gave XVIb, m.p. 185° lit. value (9): 185° .

Ultraviolet spectrum. $\lambda_{max.}$ 275 mμ (log.ϵ 4.24) and 345 mμ (log.ϵ 4.14).

3-Acetamidomethyleneoxindole (LXXXVIa)

One g. of XXXe was dissolved in a mixture of 30 ml. of acetic anhydride and 5 ml. of pyridine by gentle heating for two minutes and on cooling gave 1 g. (80%) of light-green needles, m.p. 245°. Crystallization from ethanol gave crystalline LXXXVIa, m.p. 251°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.40; H, 4.95; N, 13.85. Found: C, 66.02; H, 4.90; N, 13.70.

Ultraviolet spectrum. $\lambda_{max.}$ 273 mμ (log.ϵ 4.36) and 320 mμ (log.ϵ 4.23).

3-(N-methylacetamidomethylene-)oxindole (LXXXVIb)

The procedure for LXXXVIa was followed. One g. of LXXXVIb yielded 900 mg. (73%) of light yellow solid. Crystallization from ethanol gave yellow-green crystals m.p. 185°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.75; H, 5.61; N, 12.95. Found: C, 66.21; H, 5.56; N, 12.65.

Ultraviolet spectrum. $\lambda_{max.}$ 275 mμ (log.ϵ 4.27) and 342 mμ (log.ϵ 4.12).

3-Chloroacetamidomethyleneoxindole (LXXXVIII)

A mixture of 500 mg. of chloroacetyl-chloride and 1 g. of anhydrous potassium carbonate in 50 ml. dry acetone was

refluxed for 30 minutes. The deep red mixture was filtered and the solvent removed in vacuo. Red residue was taken up in ethanol and allowed to be recrystallized three or four times, giving 450 mg. (60%) of yellow orange crystals of LXXXVIII.

Anal. Calcd. for $C_{11}H_9N_2O_2Cl$: C, 56.00; H, 3.81; N, 11.85. Found: C, 55.70; H, 3.91; N, 11.95.

3-Carboethoxymethylaminomethyleneoxindole (LC)

A solution of 3.5 g. of 3-hydroxymethyleneoxindole and 2.8 g. of ethyl glycinate hydrochloride was dissolved in pyridine and allowed to set for 16 hours. After vacuum distillation of the pyridine, 95% ethyl alcohol was added to the oily residue, inducing solidification, m.p. 175-180°. Recrystallization from ethanol gave white crystals of LC, m.p. 197°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.69; N, 11.38. Found: C, 63.55; H, 5.28; N, 11.40.

Ultraviolet spectrum. $\lambda_{max.}$ 274 mμ (log.ϵ 4.32) and 318 mμ (log.ϵ 4.12).

Attempted alkylation of 3-aminomethyleneoxindole (XXXe)

A mixture of 1 g. of XXXe, 1.3 g. of ethylene bromide, 2 g. of anhydrous potassium carbonate in 50 ml. of dry acetone

was allowed to reflux for two hours. Removal of the salt by filtration and of the solvent in vacuo, led to a recovery of starting material.

Attempted alkylation of 3-acetamidomethyleneoxindole (LXXXVIa)

A mixture of 500 mg. of LXXXVIa, 500 mg. of ethylene bromide, 1.000 g. of dry potassium carbonate, in 60 ml. of dry acetone was refluxed for 48 hours. The usual work-up led to recovery of starting material.

Attempted cyclization of 3-chloroacetamidomethyleneoxindole (LXXXVIII)

A mixture of 70 mg. of LXXXVIII, 100 mg. of dry potassium carbonate, and 20 ml. of dry acetone was refluxed for three hours. The usual work-up gave starting material.

Sodium ethoxide treatment of LXXXVIII

To a sodium ethoxide solution, prepared from 10 mg. of sodium in 15 ml. of absolute ethanol, was added 100 mg. of LXXXVIII. After refluxing for three hours, the solution was neutralized with dilute hydrochloric acid and extracted with chloroform. Following a sodium bicarbonate and water washing, and drying over sodium sulfate, removal of the solvent led to

50 mg. (73%) 3-aminomethyleneoxindole (XXXe), m.p. 220°, identical with an authentic specimen.

Neutralization and chloroform extraction of the sodium bicarbonate layer gave 10 mg. of an acidic substance, m.p. 63-4°.

Tert.-butoxide treatment of 3-acetamidomethyloxindole (LXXXVa)

To a nitrogen blanketed tert.-butoxide solution prepared from .800 g. of potassium in 125 ml. of tert.-butyl alcohol, containing 2 g. of LXXXVa, 1 ml. of ethylene bromide was slowly added. After setting overnight, the deep orange-red mixture was refluxed for four hours and cooled. After addition of 100 ml. of water and acidification, the solution was extracted with chloroform and the extract dried over sodium sulfate. Evaporation of the solvent gave a glassy solid whose alumina chromatographic fractions were also glassy.

Tert.-butoxide of treatment 3-aminomethyleneoxindole (XXXe)

A similar reaction involving 1 g. of XXXe and .55 ml. of ethylene bromide in a tert.-butoxide solution prepared from .500 g. of potassium in 75 ml. of tert.-butyl alcohol, was refluxed for 48 hours. After the usual work-up, sodium bicarbonate washing of the chloroform extract gave, after acidification, 3-hydroxymethyleneoxindole (IIe).

Sodium hydroxide hydrolysis of 3-acetamidomethyloxindole (LXXXVa)

A solution of 100 mg. of LXXXVa in 30 ml. of 5% sodium hydroxide solution was refluxed for one hour. Neutralization of the mixture, followed by extraction with chloroform and drying over sodium sulfate, led to a glassy solid after removal of the solvent.

Catalytic hydrogenation of oxindole derivatives over palladium-charcoal in ethanol

An ethanol solution of the oxindole compound (1.00 g. in 50 ml.) was hydrogenated over palladium-charcoal (10%, by weight, of the compound) at atmospheric pressure. When hydrogen uptake had ceased, the catalyst was filtered, the solvent evaporated at low temperature and the residue chromatographed on alumina, when necessary.

Hydrogenation of VIa

Reduction of 1.00 g. of VIa led to 200 mg. (26%) of 2-benzylindole (LXIXc), m.p. 84° (eluted with petroleum ether), identical in m.p., mixed m.p., and infrared spectrum with authentic sample prepared by the method of Clemo (46), and to 375 mg. (40%) of 3-(α-amino-β-phenylethylidene-)

oxindole (XXXa), m.p. 181-182° (eluted with chloroform). Crystallization of the latter from dilute ethanol gave colorless crystals, m.p. 195°.

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.91; H, 5.33; N, 11.09.

Ultraviolet spectrum. $\lambda_{max.}$ 274 mμ (log.ϵ 4.24) and 338 mμ (log.ϵ 4.10).

Hydrogenation of VIb

Hydrogenation of 100 mg. of VIb yielded 15 mg. (21%) of 2-methylindole (LXIXd), m.p. 61° (eluted with petroleum ether) identical with an authentic sample, and 60 mg. (66% of 3-(α-aminoethylidene-)oxindole (XXXb), m.p. 225°.

Hydrogenation of VIc

Reduction of 500 mg. of VIc gave 450 mg. (96%) of colorless 1-methyl-3-(α-amino-β-phenylethylidene-)oxindole (XXXc), m.p. 176°, identical to the sample of Bernstein (7).

Hydrogenation of VId

Hydrogenation of 50 mg. of VId resulted in 40 mg. (90%) of 1-methyl-3-(α-aminoethylidene-)oxindole (XXXd), m.p. 205°, identical to the sample of Bernstein (7).

Hydrogenation of 3-formyloxindole oxime (VIe)

Reduction of 180 mg. of VIe gave 150 mg. (84%) of 3-methyloxindole (XVIIe), m.p. 122° [lit. (5) value: 124°].

Hydrogenation of 1-methyl-3-formyloxindole oxime (VIf)

Hydrogenation of 350 mg. of VIf yielded 200 mg. (66%) of 1,3-dimethyloxindole (XVIIg), m.p. 54° [lit. (15) value: 54°].

Hydrogenation of hydroxylaminomethyleneoxindole (LXXXI)

Reduction of 1.000 g. of LXXXI led to 850 mg. (95%) of 3-aminomethyleneoxindole (XXXe). Crystallization from ethyl acetate gave crystals, m.p. 220°. Solidification took place at 240° without remelting below 300°. No depression in m.p. was observed on admixture with a sample prepared by amination of 3-chloromethyleneoxindole.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.35; H, 5.10; N, 17.25.

Ultraviolet spectrum. $\lambda_{max.}$ 268 mμ (log.∈4.30), 272 mμ (log. ∈ 4.30) and 315 mμ (log. ∈ 4.10).

Hydrogenation of 3-formyloxindole oxime acetate (LXXXIIIa)

Hydrogenation of 200 mg. of LXXXIIIa yielded 150 mg. of an oil which was sublimed to give 100 mg. of 3-aminomethyleneoxindole (XXXe), crystallized from ethyl acetate, m.p. 220°.

Hydrogenation of diacetylhydroxylaminomethyleneoxindole (LXXXIV)

Reduction of 500 mg. of LXXXIV gave after chromatography 150 mg. (53%) of 3-methyloxindole (XVIIe), m.p. 124° (eluted with ether) and 125 mg. (32%) of 3-acetamidomethyloxindole (LXXXVa), m.p. 220°, (eluted with chloroform) identical in m.p. and mixed m.p. with an above sample.

Hydrogenation of 1-methyl-3-formyloxindole oxime (LXXXIIIb)

Reduction of LXXXIIIb gave an oily material which solidified on scratching to 300 mg. (80%) of 1-methyl-3-aminomethyleneoxindole. Crystallization from ether-chloroform combination, m.p. 145°.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.00; H, 5.75; N, 16.10. Found: C, 69.20; H, 5.89; N, 15.95.

Ultraviolet spectrum. $\lambda_{max.}$ 272 mμ (log. ϵ 4.30), 276 mμ (log. ϵ 4.31), and 315 mμ (log. ϵ 4.10).

Hydrogenation of 3-hydroxymethyleneoxindole (IIe)

Reduction of 1 g. of (IIe) led to 800 mg. (88%) of 3-methyloxindole, m.p. 122°.

Attempted hydrogenation of 3-aminomethyleneoxindole (XXXe)

Attempted reduction of 100 mg. of XXXe led to recovery of starting material.

Hydrogenation of 3-methylaminomethyleneoxindole (XVIe)

Hydrogenation of 200 mg. of XVIa led to 150 mg. of 3-methyloxindole, m.p. 124°.

Hydrogenation of 3-dimethylaminomethyleneoxindole (XVIa)

Reduction of 40 mg. of XVIb gave 25 mg. (80%) of 3-methyloxindole, m.p. 124°.

Hydrogenation of 3-acetamidomethyleneoxindole (LXXXVIa)

Hydrogenation of 760 mg. of LXXXVIa yielded 700 mg. (92%) of 3-acetamidomethyloxindole (LXXXVa), m.p. 215-219°. Crystallization from ethanol gave fluffy white crystals, m.p. 220°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.75; H, 5.88; N, 13.72. Found: C, 64.38; H, 5.96; N, 13.60.

Ultraviolet spectrum. $\lambda_{max.}$ 250 mμ (log.ϵ 3.90) and $\lambda_{shoulder}$ 272-285 mμ (log.ϵ 3.10-3.15).

Hydrogenation of 3-(N-methylacetamidomethylene-)oxindole (LXXXVIb)

Reduction of 400 mg. gave a clear oil which, on vigorous scratching, was induced to solidify. Crystallization from dilute ethanol gave 320 mg. (80%) of LXXXVb.

Hydrogenation of 3-(α-hydroxy-β-piperidiniumethylidene-) oxindole perchlorate (LCIa)

Hydrogenation of 900 mg. of LCIa gave an oil which, on scratching, solidified. Crystallization from acetone yielded 400 mg. (47%) of 3-(-piperidiniumethyl-)oxindole perchlorate m.p. 170°.

Ultraviolet spectrum. $\lambda_{max.}$ 252 mμ (log.ϵ 4.37) and 296 mμ (log.ϵ 3.68).

3-Cyanomethyloxindole (LCVI)

A mixture of .5 g. of 3-(α-hydroxyethylidene-)oxindole (IIb), 1.0 ml. of chloroacetonitrile and 1 g. of potassium

carbonate were refluxed for 6 hours in 60 c.c. of acetone (potassium carbonate dried). A red color developed during the course of the reaction. Water was added to the cooled reaction mixture and acetone removed in vacuo. Ether extracts were dried over anhydrous sodium sulfate. Removal of ether left a red oil which, after dissolving in dilute ethanol, yielded .25 g. (50%) of 3-cyanomethyloxindole, m.p. 160-2°. Crystallization from dilute ethanol, m.p. 163° [lit. value (53): m.p. 162-165°] .

3-Methyloxindole (XVIIe)

A mixture of 5 g. of 3-(∝-hydroxyethylidene-)oxindole (IIb), 2 ml. of methyl iodide and 10 g. of potassium carbonate was refluxed in 100 ml. of acetone (potassium carbonate dried) for four hours. Water was added to the cooled reaction mixture and the acetone removed in vacuo. The aqueous residue was extracted with ether, dried over anhydrous magnesium sulfate. Removal of the ether left a red oil which was chromatographed on alumina. Elution with ether yielded 2 g. (48%) of 3-methyloxindole, m.p. 115-120°. Crystallized from ether-petroleum ether, m.p. 124°.

Further elution with chloroform yielded .1 g. of solid material, m.p. 135-145°; crystallized from ethyl acetate, gave 3,3-dimethyloxindole, m.p. 150° [lit. value (54: m.p. 152-3°].

3-Isopropyloxindole (LCVIII)

A mixture of 3 g. of 3-(α-hydroxyethylidene-)oxindole (IIb), excess isopropyl bromide and 6 g. of potassium carbonate were allowed to reflux in 60 ml. of acetone (potassium carbonate dried) for 30 hours. The reaction mixture was worked up as above and chromatographed. Elution with ether yielded .5 g. (16.5%) of 3-isopropyloxindole, m.p. 110° [lit. value (14): m.p. 107-108°] .

Further elution .3g of a solid substance, m.p. 180°, which was not investigated further.

Acidification of the aqueous layer and extraction with ether yielded 2 g. of IIb.

Attempted preparation of 3-(β-phthalimidoethyl-)oxindole

A mixture of 3 g. of IIb, excess N-(2-bromoethyl-) phthalimide under the above conditions yielded starting materials after 36 hours.

SUMMARY

The catalytic hydrogenation of 3-acyloxindole oximes has been shown to give 3-(α-aminoalkylidene-)oxindoles (XXX) and 2-alkylindoles (LXIX). Reduction of the corresponding N-methyloxindoles in ethanol solution over palladium charcoal gave only XXX. The indoles were also produced by a potassium acetate treatment of the oximes. The mechanism of this reaction was portrayed.

The hydrogenation of oximes of 3-hydroxymethyleneoxindole and its N-methyl analogous gave 3-methyloxindoles, while their oxime acetates gave 3-aminomethyleneoxindoles.

Use of the hydrogenation products of 3-substituted oxindoles as intermediates in oxindole alkaloid synthesis was attempted.

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