THE CHEMISTRY OF OXINDOLE

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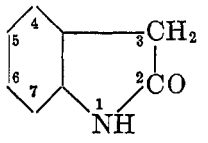
I. INTRODUCTION

In 1866 and 1868 Baeyer (4, 10) published the results of his researches on the reduction of isatin. In addition to isatide, which had been obtained previously by Laurent (128, 130, 131) and by Erdmann (49), Baeyer obtained dioxindole, $C_8H_7NO_2$, by the further reduction of which oxindole, C_8H_7NO, was prepared.

Baeyer (5) established the constitution of oxindole as the lactam of 2-aminophenylacetic acid through its synthesis by the reduction of 2-nitrophenylacetic acid with tin and hydrochloric acid.

Current practice in oxindole nomenclature is to number the positions as shown in the formula below. Other systems of numbering have been used at times by



some workers (28, 29, 30, 31, 33, 169), but the system shown here is employed generally at the present time. In the English and German literature oxindole is frequently called indolinone.

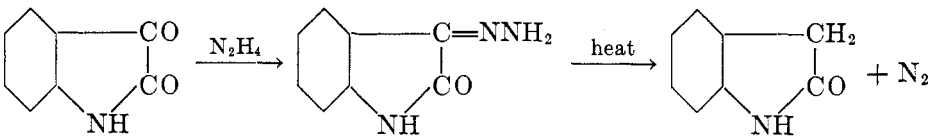
II. SYNTHESIS OF OXINDOLE AND OF OXINDOLE DERIVATIVES

Baeyer and Knop (10) found that when isatin is reduced with sodium amalgam in alkaline medium 3-hydroxyoxindole (dioxindole) is obtained. Further reduction of dioxindole with tin and mineral acids or by sodium amalgam in acid medium gave oxindole. One convenient procedure for preparing oxindole is that of

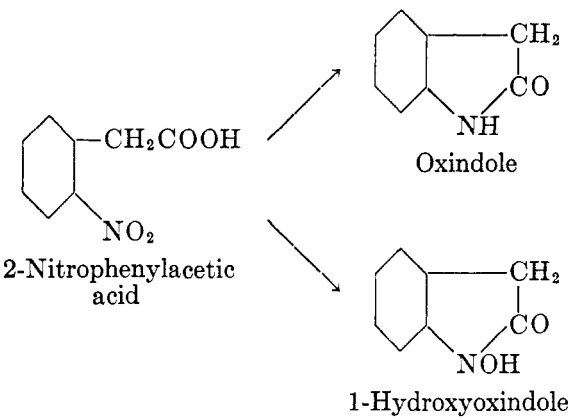
Marschalk (141, 142). In this procedure isatin is reduced to dioxindole through the agency of sodium hydrosulfite. Dioxindole is then reduced to oxindole by the action of sodium amalgam in a solution saturated with carbon dioxide. The reduction of a number of substituted dioxindoles to the corresponding derivatives of oxindole has been accomplished by Wahl and coworkers (204, 205).

v. Braun and Hahn (26) prepared dioxindole-4-carboxylic acid by reducing isatin-4-carboxylic acid with sodium amalgam. Dioxindole-4-carboxylic acid undergoes disproportionation when heated in alcohol solution, yielding oxindole-4-carboxylic acid and isatin-4-carboxylic acid in equivalent quantities. Oxindole-4-carboxylic acid can also be prepared by reducing dioxindole-4-carboxylic acid with sodium amalgam under proper conditions.

Isatin was also reduced to oxindole through the agency of hydrazine by Curtius and Thun (43).



The first synthesis of oxindole (other than by the reduction of isatin) and the one which established its constitution with certainty was by Baeyer (5) through the reduction of 2-nitrophenylacetic acid with tin and hydrochloric acid.



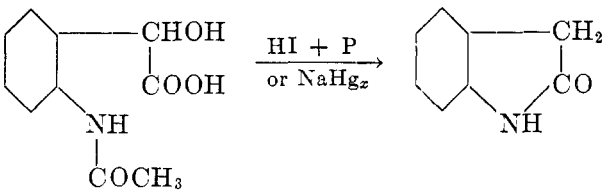
Reduction of 2-nitrophenylacetic acid with zinc and hydrochloric acid gives both oxindole and 1-hydroxyoxindole (also sometimes called 1,2-dioxindole) (163, 164, 165).

Substituted oxindoles have been prepared by the reduction of substituted derivatives of 2-nitrophenylacetic acid by Wispec (212), Smith and MacMullen (172), Wahl and Livovschi (138, 139, 207), Ruggli and Grand (166), Parks and Aldis (158), Wahl and Bagard (200), Hahn and Schulz (68), Hahn and Tulus (69), Trinius (196), Heller (78), and Gabriel and Meyer (56). König and Reissert (114) obtained oxindole and *o*-aminophenylacetanilide by the reduction of *o*-nitrophenylacetanilide.

Heller (77) found that reduction of *N*-acetoxyoxindole with zinc dust and acetic acid gave oxindole.

Di Carlo (44) found that catalytic reduction of *o*-nitrophenylacetic acid gave oxindole. Under certain conditions some 1-hydroxyoxindole was obtained as a by-product. The procedure given by Di Carlo seems to offer a convenient method for the synthesis of oxindole. Koelsch (113) has utilized a similar procedure for the synthesis of 5-methoxyoxindole.

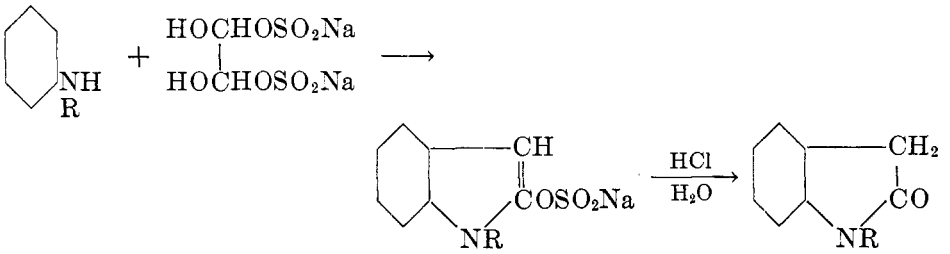
Oxindole was also prepared by Suida (183) through the reduction of 2-acetaminomandelic acid by either hydriodic acid and phosphorus or sodium amalgam.



Baeyer and Comstock (9) prepared oxindole from the barium salt of 2-aminophenylacetic acid by acidifying and then heating.

Pschorr and Hoppe (161) prepared oxindole from 2-aminobenzyl cyanide by treatment with aqueous sodium hydroxide and subsequent acidification.

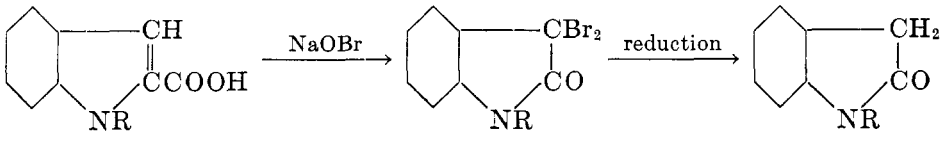
A procedure developed by Hinsberg (87, 88) serves for the preparation of *N*-alkyloxindoles. A secondary aromatic amine is condensed with the sodium



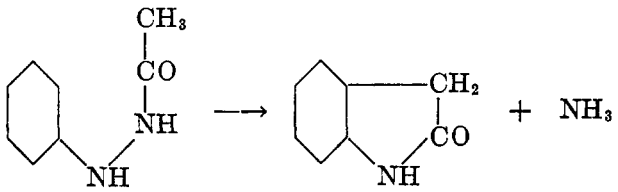
bisulfite addition compound of glyoxal. The resulting product gives an *N*-alkyloxindole on treatment with aqueous hydrochloric acid.

Oxindole was obtained by Mazzaro and Borgo (150) by steam distillation in the presence of hydrochloric acid of the product obtained when indole is treated with sulfuryl chloride.

N-Alkylindoles and *N*-substituted indole-α-carboxylic acids have been converted into the corresponding oxindoles by Colman (40) and by Michaelis (152). The *N*-alkylindole-α-carboxylic acid (or *N*-alkylindole) is treated with sodium hypobromite, giving a 1-alkyl-3,3-dibromoöxindole which on reduction gives the corresponding 1-alkyloxindole.

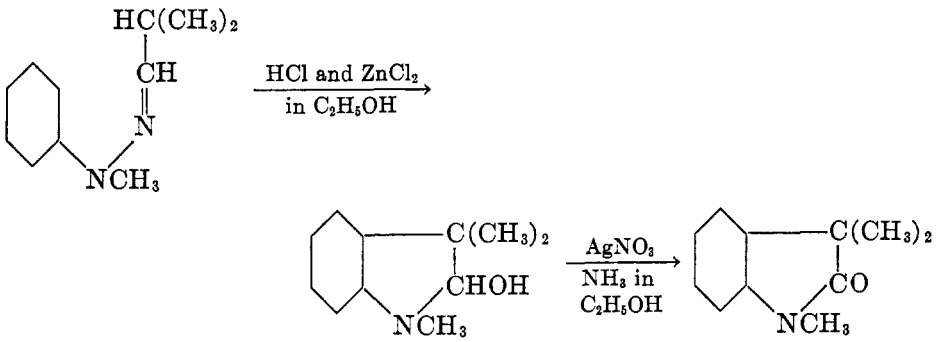


Brunner (29, 30, 33) prepared oxindole by heating β-acetylphenylhydrazine with lime at 200–220°C. This procedure has been extended by Brunner (34, 35,

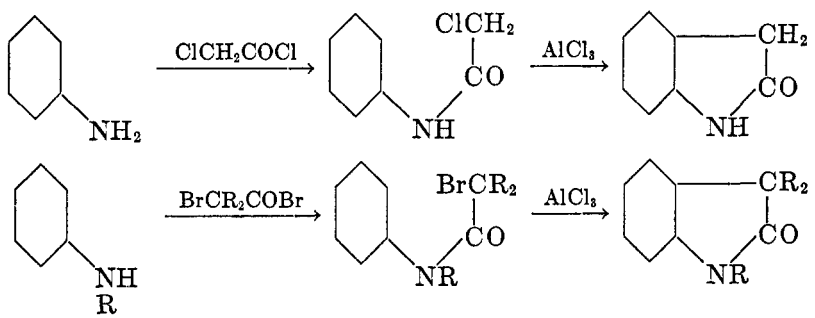


36) and by others (59, 60, 169, 195, 199) to the preparation of many substituted oxindoles, especially 3,3-dialkyl derivatives of oxindole.

A similar preparation of substituted oxindoles also due to Brunner (28, 31) is shown in the following scheme:

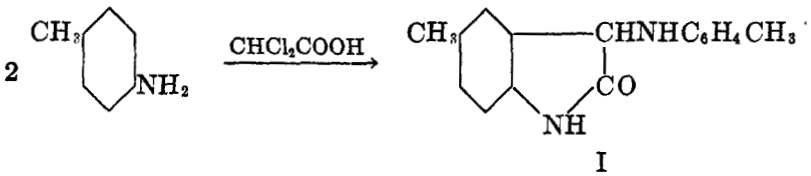


Another convenient and general method for the preparation of oxindole and of *N*-substituted oxindoles is that of Stollé (62, 63, 179, 180, 182). An α-halogenated acid chloride or bromide is condensed with an aromatic amine. Subsequent ring closure with aluminum chloride yields the corresponding oxindole.



The Stollé synthesis has also been utilized by a number of other investigators (98, 100, 107, 138, 139, 160, 207). Stollé found that *N*-benzylchloroacetanilide on treatment with aluminum chloride gave oxindole with the splitting out of the benzyl group (180).

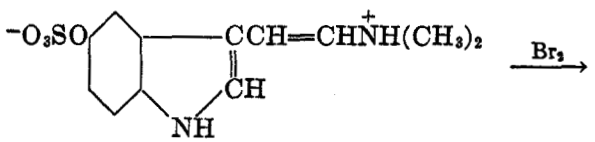
Oxindole derivatives of the type of I are obtained from arylamines and



I

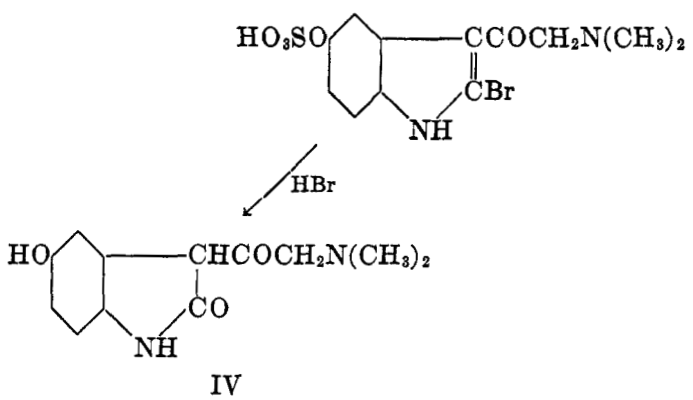
dichloroacetic acid in a reaction discovered by P. J. Meyer (151) and subsequently studied by Duisberg (46), Heller (79, 80), and Paucksch (159).

Wieland and Wieland (210) obtained the oxindole derivative IV from bufothionine (II) in the manner shown below:



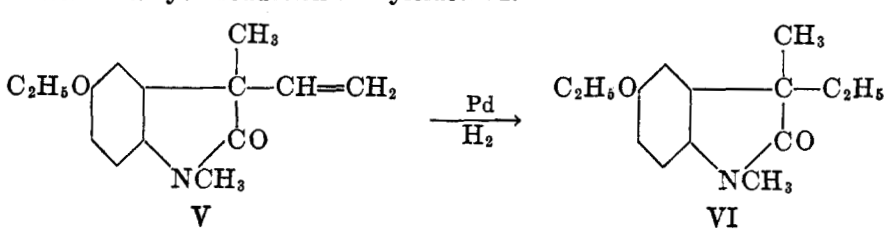
II

Bufothionine



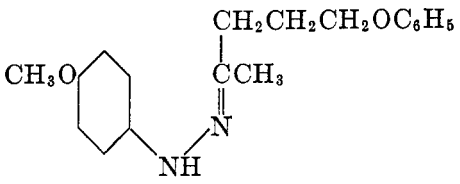
IV

Stedman and Barger (173), in the course of the investigation of the structure of physostigmine (eserine), obtained the oxindole derivative V as a degradation product. Catalytic reduction of V yielded VI.

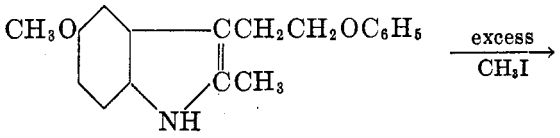


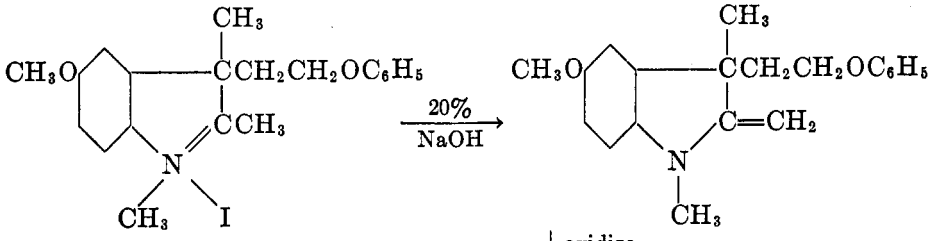
V VI

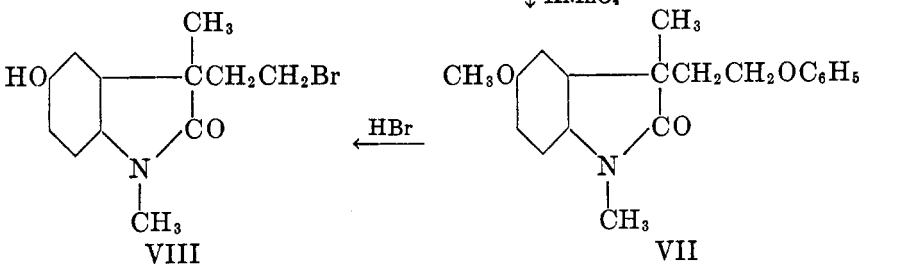
In a series of papers pointing to the synthesis of physostigmine, Robinson, Boyd-Barrett, and King (23, 24, 108, 109) developed syntheses of some interesting oxindole derivatives (VII, VIII, IX, X).



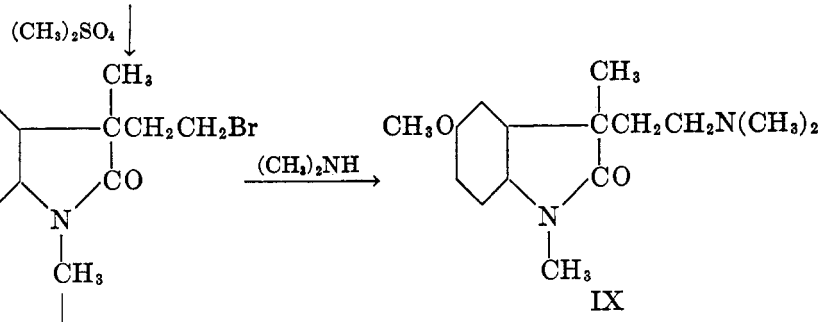
γ-Phenoxypropylacetone
p-methoxyphenylhydrazone





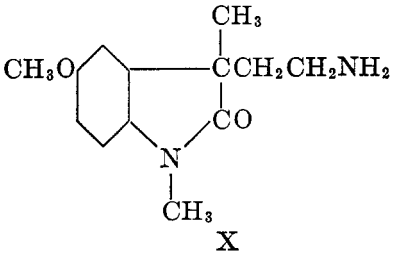


VIII VII



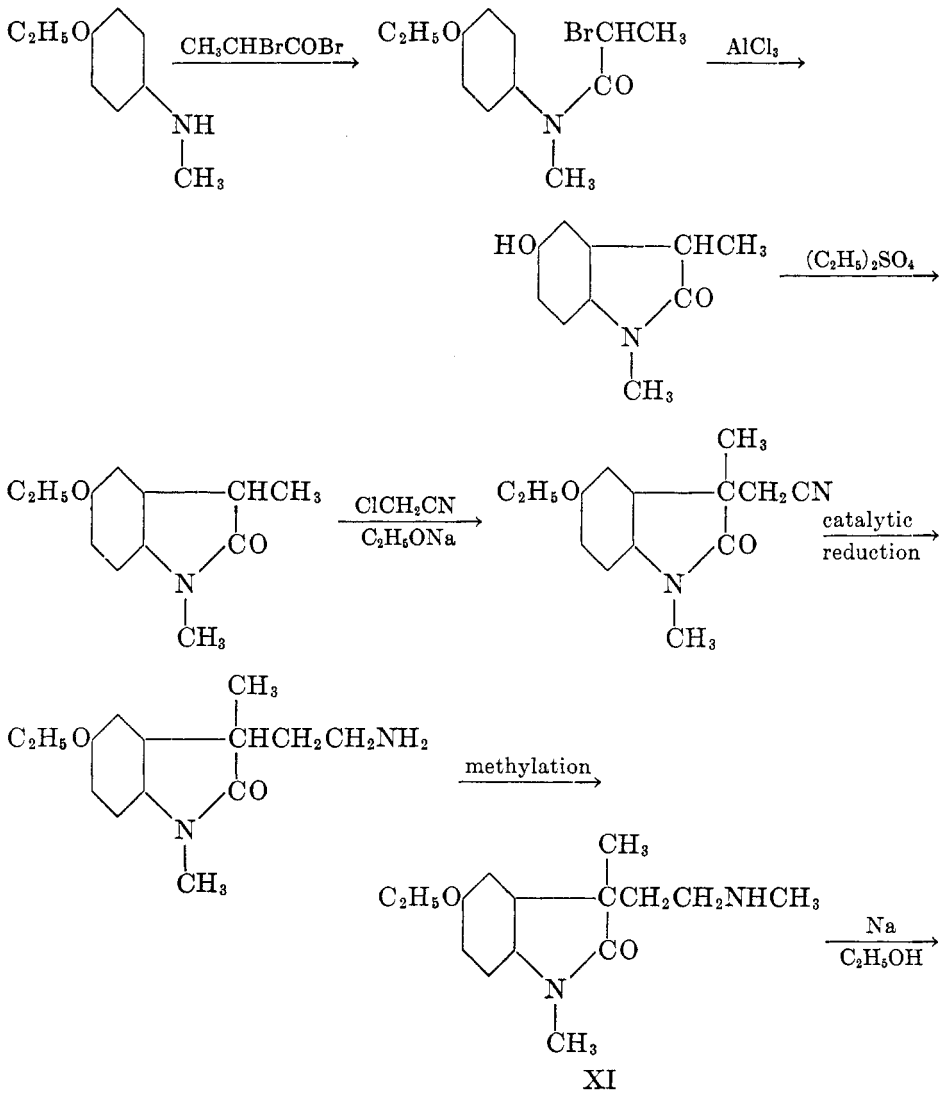
IX

potassium phthalimide
and subsequent hydrolysis

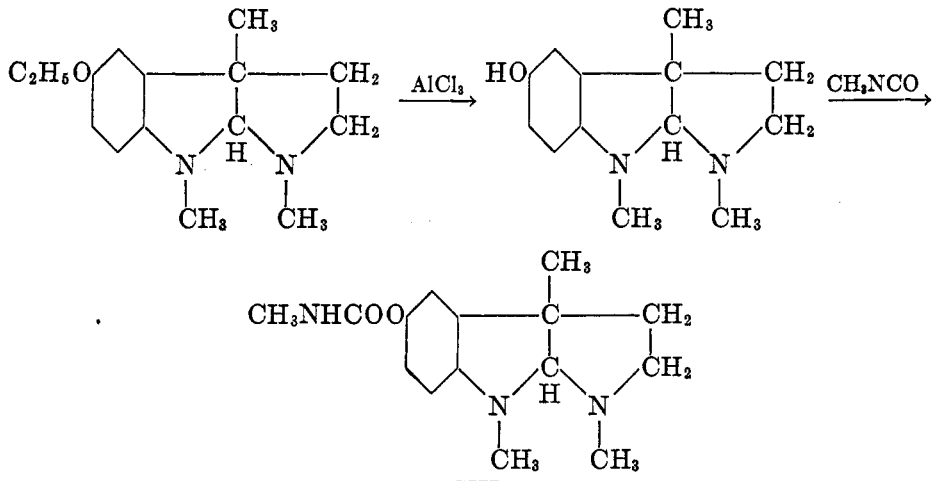


X

The total synthesis of physostigmine was accomplished by Julian and coworkers (98, 99) in a research involving some beautiful oxindole chemistry. The synthesis follows in outline:



XI

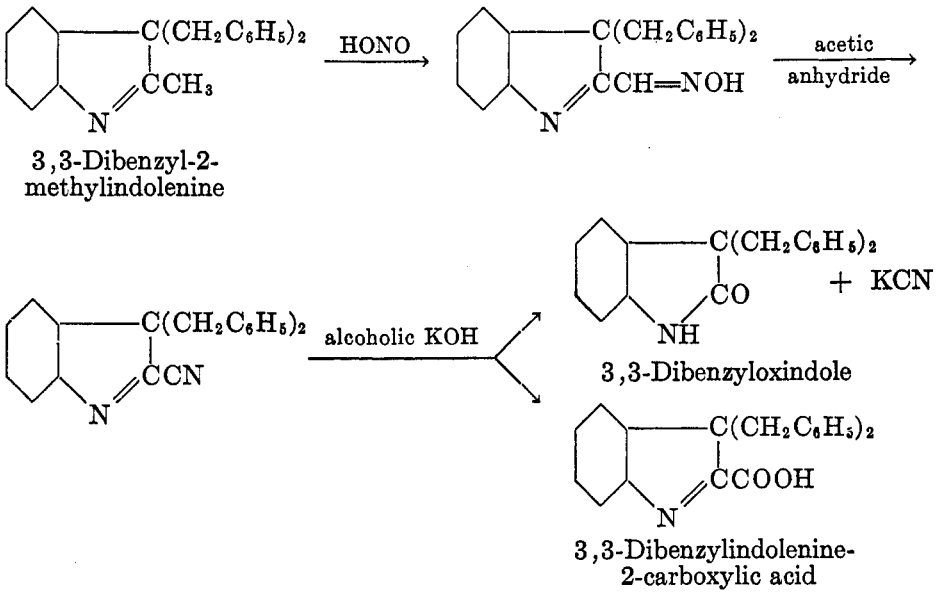


XII

dl-Physostigmine

Resolution of racemic XI and continuation of the synthesis with *l*-XI gave *l*-physostigmine, identical with the natural product.

Leuchs and Overberg (133) prepared 3,3-dibenzyloxindole from 3,3-dibenzyl-2-methylindolenine, as outlined below:

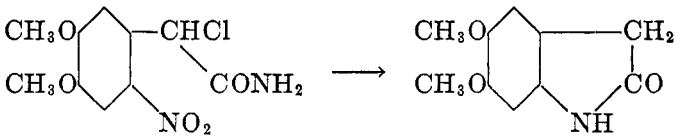


3,3-Dibenzyl-2-methylindolenine

3,3-Dibenzyloxindole

3,3-Dibenzylindolenine-2-carboxylic acid

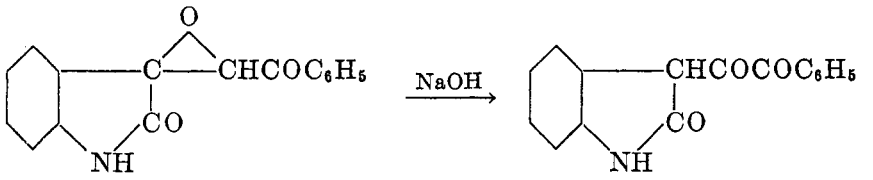
Hahn and Tulus (69) prepared several oxindole derivatives by the catalytic reduction of certain α-chloro-α-(*o*-nitroalkoxyphenyl)acetanilides. The reduction of XIII yielded 5,6-dimethoxyoxindole (XIV).



XIII XIV

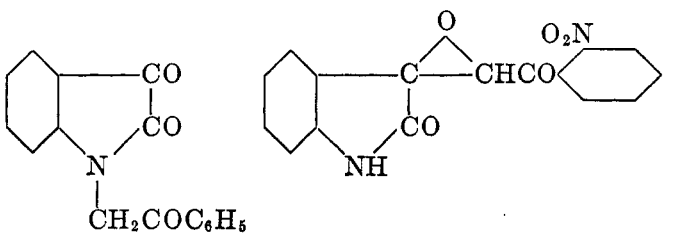
5,6-Methylenedioxyoxindole (XV) and 5-acetoxy-6-methoxyoxindole (XVI) were prepared in similar fashion. Under different catalytic conditions the reduction of XIII gives the hydrochloride of 2-amino-3,4-dimethoxyphenylacetamide as well as the dimethoxyoxindole (XIV).

Ainley and Robinson (2) found that 3-benzoylformyloxindole (XVII) is formed when isatylideneacetophenone oxide (XVIII) is treated with alkali. The latter compound (XVIII) is formed when the sodium salt of isatin is treated with



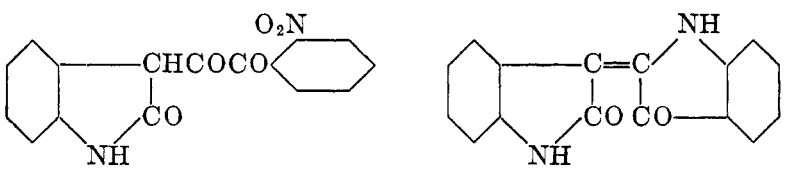
XVIII XVII

phenacyl bromide. Ainley and Robinson had expected that 1-phenacylisatin (XIX) would be the product in this reaction but found that XVIII was the actual substance obtained. In support of the structures assigned to this substance (XVIII) and to the rearrangement product (XVII), Ainley and Robinson found



XIX XX

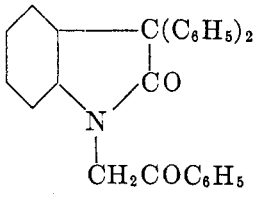
that isatylidene-*o*-nitroacetophenone oxide (XX) and *o*-nitrobenzoylformyloxindole (XXI) both yield indirubin (XXII) on reduction.



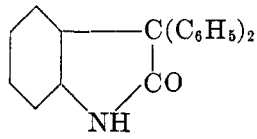
XXI XXII

Measurements of the absorption spectra of benzoylformyloxindole (XVII) have been reported by Bergstrom and Robinson (18).

A recent attempt (189) to prepare 1-phenacylisatin from isatin-1-acetyl chloride and benzene through the agency of aluminum chloride led to the preparation of 3,3-diphenyl-1-phenacyloxindole (XXIII) and not XIX as expected. This condensation with two molecules of benzene in the 3-position seems to be general in the isatin series, since 3,3-diphenyloxindole (XXIV) was obtained from isatin, benzene, and aluminum chloride (189).

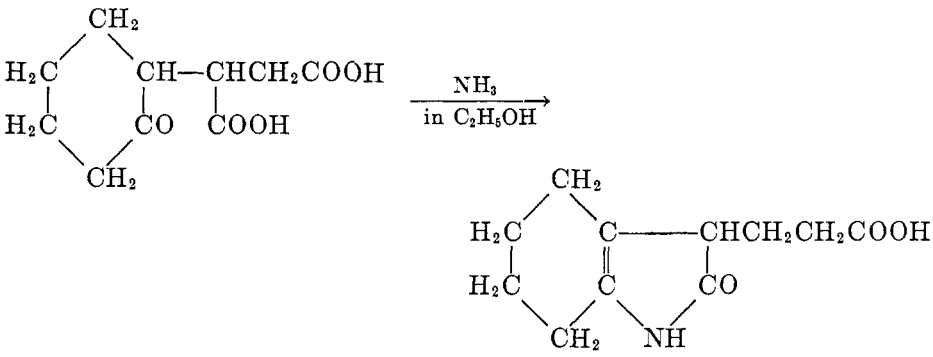


XXIII



XXIV

An interesting preparation of 4,5,6,7-tetrahydroöxindole-3-propionic acid from 2-ketocyclohexane-α-glutaric acid has been described by Kendall and coworkers (105, 106).



A number of brominated and iodinated derivatives of oxindole-3-propionic acid have been described by these workers. The structures suggested for several of these derivatives are somewhat unorthodox and, being supported by evidence which appears quite inadequate, must be regarded as far from established. The melting point given for their oxindole-3-propionic acid is quite different from that given elsewhere (64) for oxindole-3-propionic acid prepared by more conventional methods.

III. GENERAL PROPERTIES OF OXINDOLE

A. Physical properties

Oxindole crystallizes from water in colorless needles melting at 126–127°C. The substance boils at 195°C. at 17 mm. (202) and at 227°C. at 73 mm. (43). It is soluble in hot water, alcohol, benzene, ether, and acetic acid. It is more soluble in alkaline solutions than in water. The heat of combustion at constant volume has been found to be about 950.5 kg.-cal. per mole (19).

B. Salts

Oxindole forms a white silver salt, C_8H_6ONAg, on treatment of its aqueous solution with cold ammoniacal silver nitrate solution (10). On prolonged heating the silver nitrate is reduced by the oxindole.

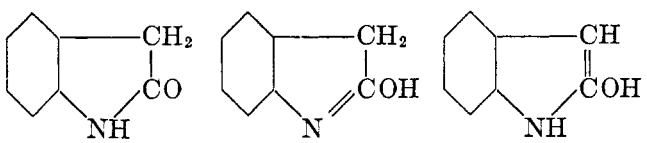
The sodium salt of oxindole is obtained from oxindole and sodium amalgam in warm benzene (209). This salt is also obtained by the treatment of oxindole with sodium ethoxide (78).

Heating oxindole with barium hydroxide solution at 150°C. gives the barium salt of 2-aminophenylacetic acid. The latter salt on acidification again yields oxindole (9, 141, 142).

Oxindole combines with hydrochloric acid to give a hydrochloride which is easily soluble in water (10).

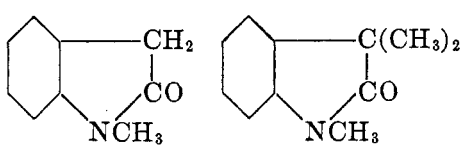
C. Tautomerism

Oxindole is usually regarded as the lactam (I) of *o*-aminophenylacetic acid. However, the lactim (II) and the enol (III) formulas represent possible structures.



I II III

Ramart-Lucas and Biquard (162) found the absorption spectra of oxindole to be quite similar to those of *N*-methyloxindole (IV) and 1,3,3-trimethyloxindole (V); since the latter compound can exist only in the lactam form, they consider



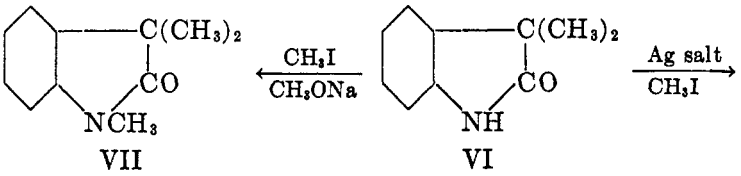
IV V

that I is probably the correct structure for oxindole.

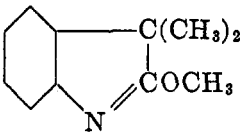
Julian (101) writes oxindole as the lactam (I) but found that in the Grignard machine two moles of reagent are consumed and two molecules of gas liberated. He feels that this indicates enolization of oxindole (I) in the sense represented by formula III rather than formula II. The reaction of 1-ethyloxindole with the Grignard reagent has been studied by Stollé (182).

Alkylation of oxindole with alkyl halides and sodium ethoxide gives the corresponding *N*-alkyloxindole (9). *O*-Alkyl ethers corresponding to the *O*-alkyl isatin derivatives have not been prepared from oxindole itself. The lactam and lactim ethers of certain 3,3-dialkyloxindoles have been prepared, however. Thus, Brunner (29) prepared 1,3,3-trimethyloxindole (VII) from 3,3-dimethyloxindole (VI) through the agency of methyl iodide and sodium methoxide, while

the lactim ether VIII resulted when the silver salt of VI was treated with methyl iodide.

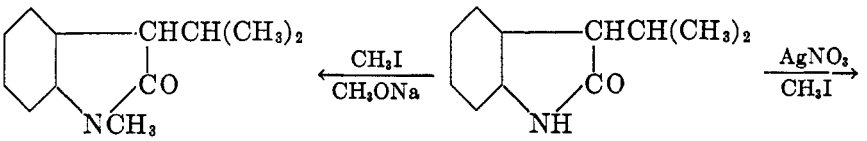


VII VI

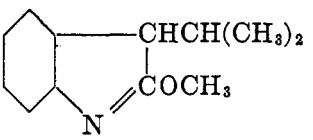


VIII

Schwarz (16) likewise obtained lactam and lactim ethers from 3-isopropyloxindole and methyl iodide.



Lactam ether



Lactim ether

D. Oxidation and reduction

Oxindole gives indole when its vapor is passed over hot zinc (7). On prolonged heating with ammoniacal silver nitrate solution oxindole reduces the silver nitrate to a mirror (10).

On prolonged contact with air an aqueous solution of oxindole is oxidized in part, yielding dioxindole (10).

Reduction of 1,3,3-trimethyloxindole with sodium and alcohol gives 1,3,3-trimethylindolinol-2 (28, 36).

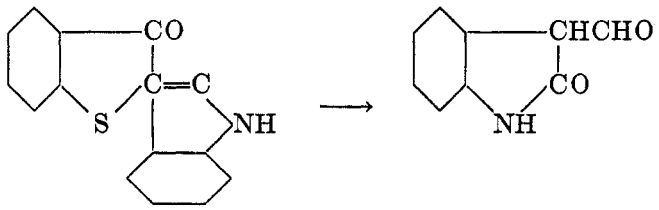
E. Acyl and alkyl derivatives of oxindole

Suida (184) prepared 1-acetyloxindole by the action of acetic anhydride on oxindole. 3-Methyloxindole and other oxindole derivatives similarly yield 1-acetyl derivatives (29, 30, 150, 165, 169, 199).

Treatment of the sodium salt of oxindole with one molecular proportion of benzoyl chloride yields 1-benzoyloxindole, while with excess benzoyl chloride 1,3,3-tribenzoyloxindole is formed (78).

3-Formyloxindole (oxindole-3-aldehyde) was first prepared by Friedlander and

coworkers (53, 54) by treatment of Thioindigo Scarlet R with alcoholic sodium hydroxide.

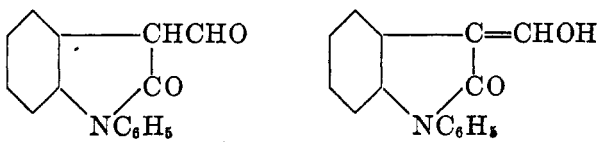


Thioindigo Scarlet R

3-Formyloxindole
(oxindole-3-aldehyde)

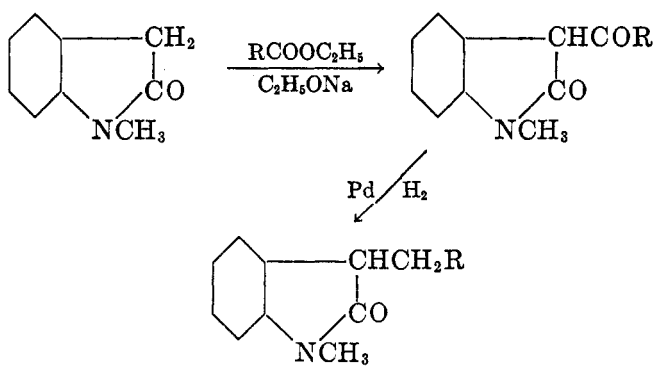
Friedlander also prepared the *N*-methyl analog from *N*-methyl Thioindigo Scarlet R. The procedure has also been employed by Kalb and Berrer (104) for the preparation of 3-formyl-5,7-diiodoöxindole.

In 1932 Stollé, Hecht, and Becker prepared 3-formyl-1-phenyloxindole (I) through the condensation of ethyl formate with 1-phenyloxindole. They formulated the compound as the tautomeric structure II.



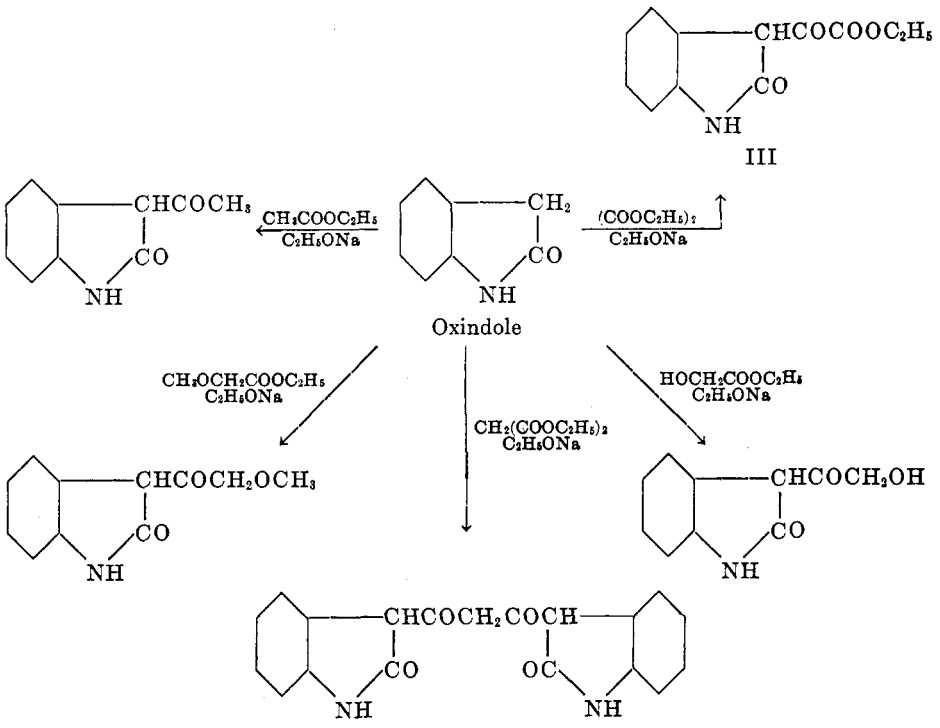
II

The reaction was developed independently by Julian (100) in 1934 and used for the preparation not only of 3-formyloxindoles but also of 3-acyloxindoles in general (101).



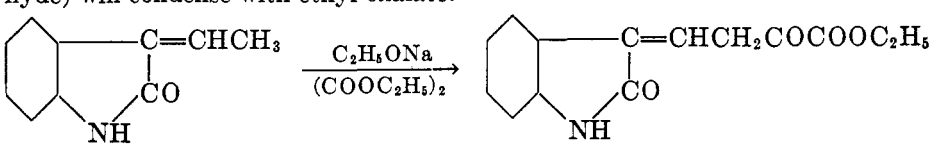
Catalytic reduction of the latter compounds affords a new synthesis of 1,3-dialkyloxindoles. On the other hand, Horner (89) has reported that 3-acyloxindoles without substituent groups on nitrogen could not be reduced to 3-alkyl derivatives.

This synthesis of 3-acyloxindoles was applied by Julian only in the case of the *N*-alkyl derivatives. Horner (89) extended the reaction to include the condensation of oxindole itself with various esters, as shown in the accompanying chart. The condensation of *N*-substituted oxindoles with esters has also been studied by



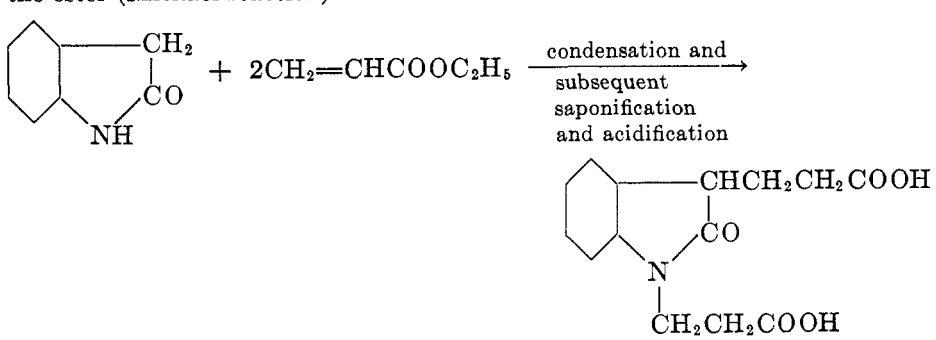
Porter, Robinson, and Weyler (160).

Horner (89) also found that 3-acetylideneoxindole (from oxindole and acetaldehyde) will condense with ethyl oxalate.



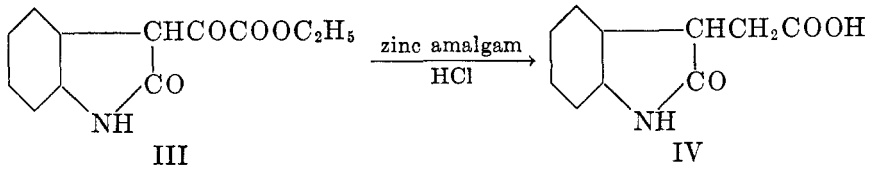
The condensation of 3-formyloxindole with malonic acid gives oxindole-3-acrylic acid, which on reduction gives oxindole-3-propionic acid (64).

Oxindole and ethyl acrylate (89) undergo an interesting reaction which involves addition of oxindole (positions 1 and 3) to the double bond in two molecules of the ester (Michael reaction).



A similar reaction between isatin (position 1) and acrylonitrile has recently been reported by Di Carlo and Lindwall (45).

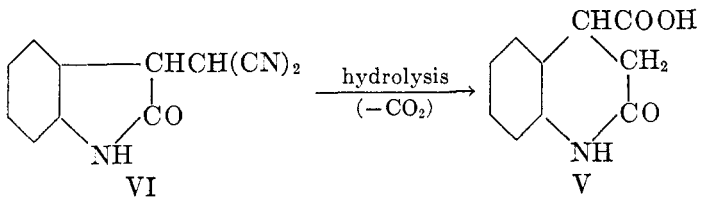
The reduction of ethyl oxindole-3-glyoxalate (III) under Clemmensen conditions has been studied by Horner (89). Reduction of III with zinc amalgam and hydrochloric acid gave a product melting at 217°C., which Horner described as oxindoleacetic acid (IV).



III IV

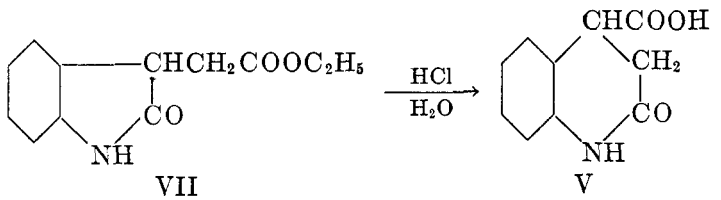
This reduction has been reinvestigated by Sumpter, Miller, and Hendrick (192), who found that Horner's "oxindoleacetic acid", like the "oxindoleacetic acid" of Gränacher (57, 58), is in reality 2-keto-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (V) (1, 82, 83).

The formation of V in the reduction and hydrolysis of III is quite in keeping with the results of Zrike and Lindwall (213), who obtained V in the hydrolysis of VI.



VI V

Horner (89) also reported that the reduction of III gave the ethyl ester of oxindoleacetic acid (VII) when zinc amalgam and acetic acid were employed. This has been confirmed by Sumpter, Miller, and Hendrick (192), who further found that hydrolysis of VII yielded V.



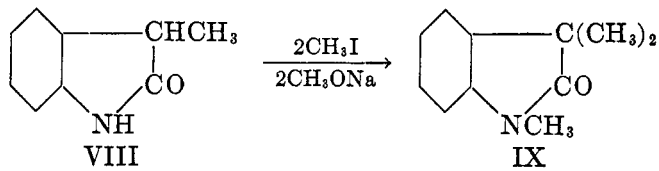
VII V

It has been stated (143) that the Clemmensen reduction of α-keto acids and esters always gives the corresponding α-hydroxy acid or ester rather than the completely reduced acid. Obviously the preparation of V and of VII through the Clemmensen reduction of III constitutes an exception to this rule.

Alkyl derivatives of oxindole have been prepared by many workers (23, 24, 28, 29, 30, 31, 33, 34, 35, 36, 40, 62, 63, 79, 80, 87, 88, 107, 108, 109, 133, 134, 138, 139, 152, 173, 179, 180, 182, 202) and by a variety of procedures. A number of these general methods have already been discussed in section II of this paper.

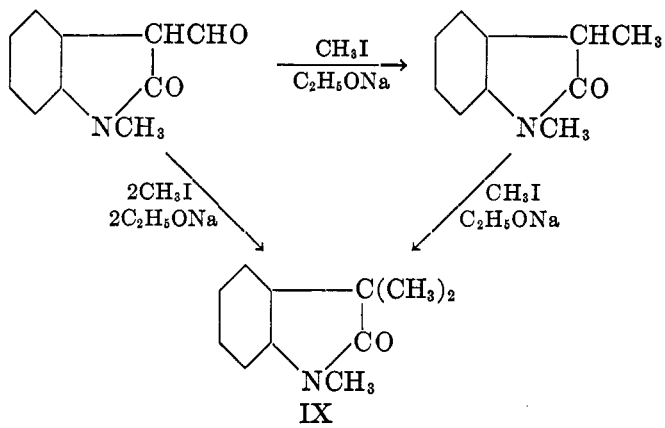
Direct alkylation of oxindole and of *N*-alkyloxindoles has been accomplished

by Brunner (30) and by Julian (98, 100, 101). Julian seemingly overlooked the work of Brunner, for he stated, "The literature records no efforts at direct alkylation of oxindoles." On the contrary, Brunner (30) had recorded the alkylation of 3-methyloxindole by the action of methyl iodide.



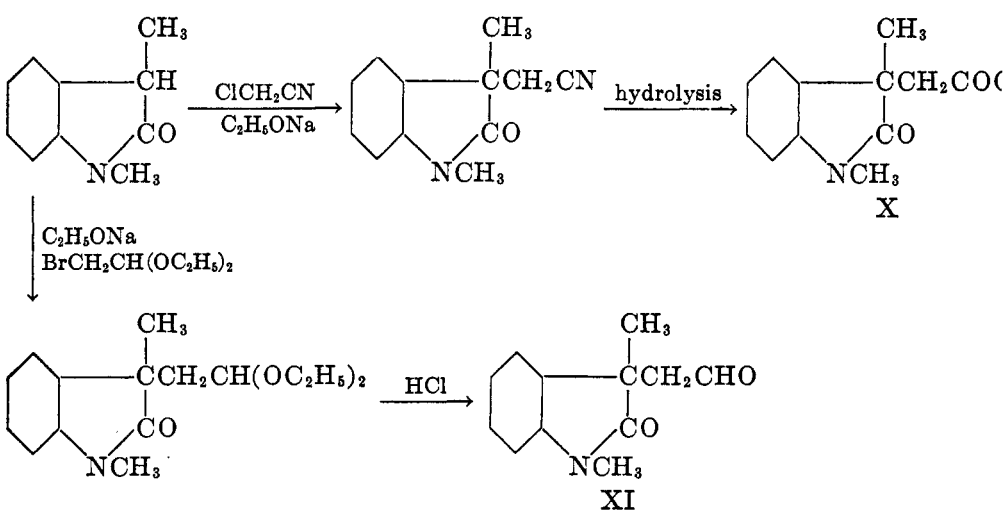
VIII IX

Julian found that IX was formed when 1-methyl-3-formyloxindole was methylated by the action of methyl iodide and sodium ethoxide.



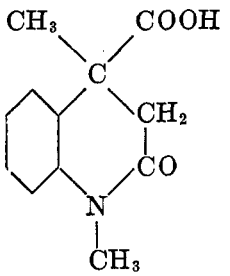
IX

This same technique has been applied by Julian in the synthesis of 1,3-dialkyloxindole-3-acetic acid derivatives (X) and derivatives of 1,3-dialkyloxindole-3-acetaldehyde (XI).



X XI

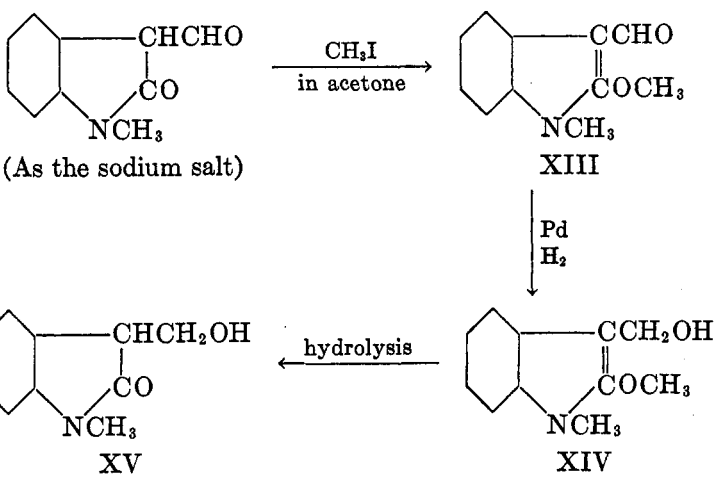
In view of the non-existence of "oxindoleacetic acid" (1, 57, 58, 83, 192), it seems entirely possible that Julian's X has been incorrectly formulated and that the compound may be the quinoline derivative XII. This point has not been investigated.



XII

Julian was unable to effect alkylation in position 3 in the case of oxindole itself or of 1-methyloxindole. Apparently it is necessary that there be either an alkyl or an acyl group in position 3 for further alkylation in this position to be accomplished.

Treatment of the sodium salt of 1-methyl-3-formyloxindole with methyl iodide in acetone results in the formation of the *O*-methyl derivative (XIII) (101). Reduction of this *O*-methyl ether gives the alcohol (XIV), which on



(As the sodium salt)

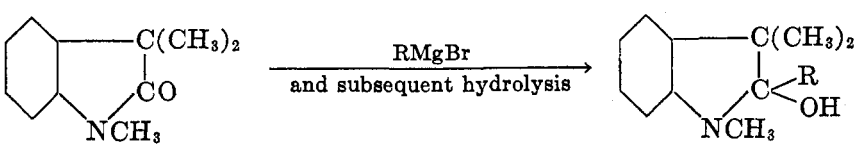
XIII

XV

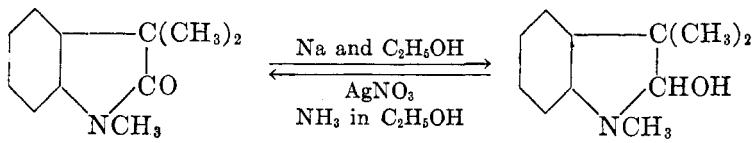
XIV

hydrolysis yields 1-methyl-3-hydroxymethyloxindole (XV).

1,3,3-Trialkyloxindoles react with the Grignard reagent to give indolinol derivatives (32, 97).

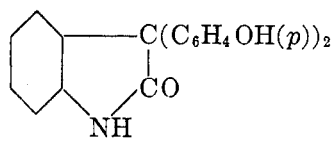


The reduction of 1,3,3-trialkyloxindoles yields indolinol derivatives in a reaction which can be reversed (28, 31, 39).

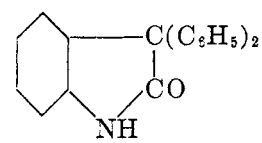


F. 3,3-Diaryl derivatives of oxindole

Baeyer and Lazarus (11, 12) and subsequently Liebermann and Danaila (135) found that isatin condenses with toluene, phenol, resorcinol, anisole, α-naphthol, and secondary and tertiary aromatic amines to give oxindole derivatives of the type of phenolisatin (3,3-bis(4′-hydroxyphenyl)oxindole) (I).



I



II

In general it was assumed, in agreement with Baeyer, that these condensation products were 3,3-derivatives of oxindole (on the other hand compare Sen (170)), but it remained for Inagaki (90, 91, 92, 93, 94, 95) to establish definitely their structure. Inagaki synthesized the parent compound of the series (II) by treating a benzene solution of 3,3-dichloroöxindole with aluminum chloride. The method had been employed by Inagaki and by others (154, 186, 193) for the synthesis of other members of the series. Other 3,3-diaryl derivatives of oxindole have been prepared by Candea (71), Steopoe (177), and Gabel and Zubarovski (55).

3,3-Diphenyloxindole (II) has also been prepared from 3,3-dibromoöxindole and benzene through the agency of aluminum chloride (193). It has also been found that the same compound (II) is formed through the action of benzene and aluminum chloride on isatin (189).

Phenolisatin and its diacetyl derivative, isacene, have found use pharmacologically as mild purgatives (17, 27, 38, 65, 171, 208). A number of halogenated derivatives of phenolisatin have also been described (135, 185). Certain sulfonated members of the series are said to be of value as mothproofing agents (62).

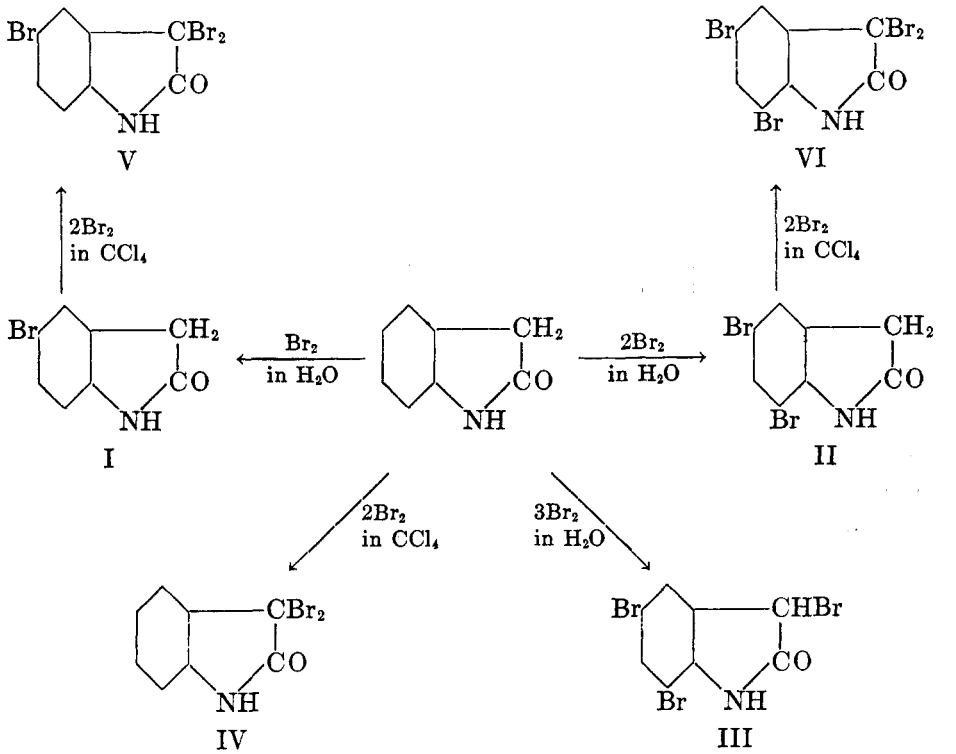
G. Halogenation, nitration, and sulfonation

In their first paper on oxindole and dioxindole Baeyer and Knop (10) described several substituted derivatives of oxindole. Since this work was done before the true structures of oxindole, dioxindole, and isatin were known, the structures of these derivatives were not determined. It also appears that in at least some cases the physical properties reported by Baeyer and Knop were seriously in error (82, 190, 193, 194), and it is doubtful that their products were obtained in a pure state.

The bromination of certain *N*-substituted oxindoles was investigated by Stollé

and coworkers (180). These investigators found that the bromination of *N*-substituted oxindoles in aqueous solution yielded derivatives with bromine substituted in position 5 when one molecular proportion of bromine was employed and in positions 5 and 7 when two molecular proportions of bromine were used. On the other hand, the bromination of *N*-substituted oxindoles in anhydrous carbon tetrachloride gave the 3,3-dibromo derivatives.

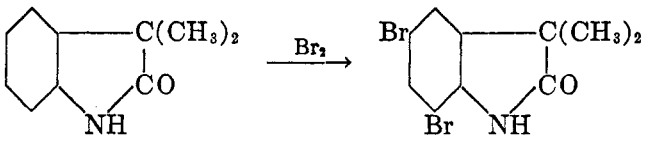
Baeyer and Knop (10) reported the preparation of a monobromoöxindole through the action of bromine water on an aqueous solution of oxindole, and reported the melting point of this derivative as 176°C. The preparation was repeated by Henze and Blair (77), who found the melting point to be 220–221°C. but did not determine the structure of the compound. The entire problem of the bromination of oxindole was recently investigated by Sumpter, Miller, and Hendrick (193), who found that this monobromoöxindole was 5-bromoöxindole (I). The use of two molecular proportions of bromine results in the preparation of 5,7-dibromoöxindole (II), while with three molecular proportions of bromine



3,5,7-tribromoöxindole (III) is obtained. When the bromination is carried out with two molecular proportions of bromine in anhydrous carbon tetrachloride, 3,3-dibromoöxindole (IV) is obtained. The bromination of I and II under similar conditions yields V and VI, respectively.

Brunner and coworkers (34) obtained a dichloro derivative of 3,3-dimethyl-

oxindole (VII) by the direct chlorination of the parent compound. The assumed that this was the 5,7-derivative, from analogy with the dibrom derivative (VIII) obtained from VII by the action of bromine. The structu of compound VIII was definitely established by its synthesis from 2,4-dibrom



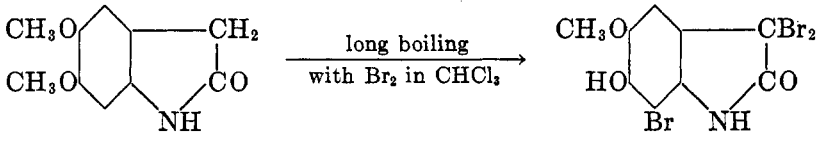
VII VIII

phenylhydrazine and isobutyraldehyde. Brunner also synthesized the 4,7 dibromo derivative of VII from 2,5-dibromophenylhydrazine.

The iodination of VII through the agency of iodine, potassium iodide, an potassium iodate in acetic acid gave the 5-iodo derivative (IX) (34). The struc ture of IX was established through its synthesis from the 5-amino derivative (X by diazotization and replacement of the diazonium group by iodine.

VII IX X

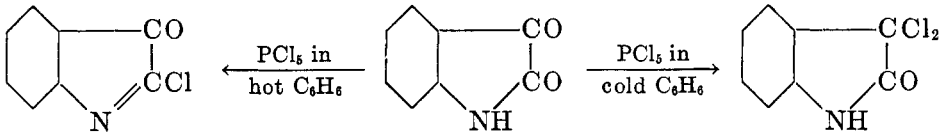
The bromination of 5,6-dimethoxyoxindole has been studied by Hahn anc Tulus, who found that prolonged treatment with bromine in chloroform resultec in substitution in positions 3 and 7. The methyl group was removed from the



methoxyl in position 6 also.

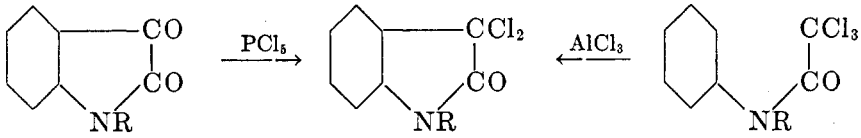
It thus seems clear that halogen substitution in the oxindole series takes place in positions 5 and 7, respectively (34, 116, 147, 180, 190, 193, 194), and that under certain conditions the halogen can be directed to position 3. In several earlier papers Brunner (28, 30) and Schwarz (169) described bromo derivatives of 3,3-dialkyloxindoles. While the structures of these derivatives were not determined, the editors of Beilstein's *Handbuch* have assumed in several cases (16) that these compounds were the 5- and 5,7-derivatives. In the light of the evidence reviewed above this assumption seems to be justified.

The 3,3-dichloro derivatives of *N*-alkyloxindoles were prepared by Stollé (180) through the action of calcium hypochlorite on the oxindole. The 3,3-dichloroöxindoles are also prepared quite readily from the corresponding isatin through the agency of phosphorus pentachloride. Isatin itself gives either isatin-α-chloride (XI) or 3,3-dichloroöxindole (XII), depending on the reaction conditions (6, 72).

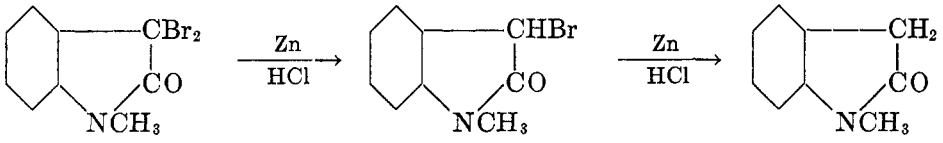


XI XII

The 1-alkyl(or aryl)-3,3-dichloroöxindoles may be prepared from the corresponding isatins or through the Stollé synthesis from the appropriate trichloroacetyl-*N*-alkylanilide.

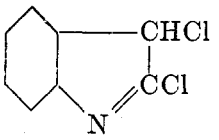


The 3,3-dibromo and 3,3-dichloro derivatives of 1-ethyloxindole, 1-methyloxindole, and 1-propyloxindole were prepared by Michaelis (152) and by Colman (40) and Fischer and Hess (52) by treating the appropriate 1-alkylindole or 1-alkylindole-2-carboxylic acid with sodium hypochlorite. Colman (40) found that reduction of 1-methyl-3,3-dibromoöxindole with zinc dust and hydrochloric acid gave 1-methyl-3-bromoöxindole and 1-methyloxindole.



The preparation of 3,3-dichloroöxindole derivatives by the combined action of chlorosulfonic acid and hydrochloric acid on isatin and isatin derivatives has been reported (66). In a subsequent patent (198) the same worker reported that the 3,3-dichloroöxindole derivatives so obtained contained at least one sulfonyl chloride grouping in the oxindole nucleus. It has been found in this laboratory (189) that the product obtained when isatin is dissolved in chlorosulfonic acid and the solution then treated with sodium chloride is not 3,3-dichloroöxindole, as reported in the first patent (66), but a compound containing sulfur. While this compound was not investigated further, this finding is in keeping with the second patent (198).

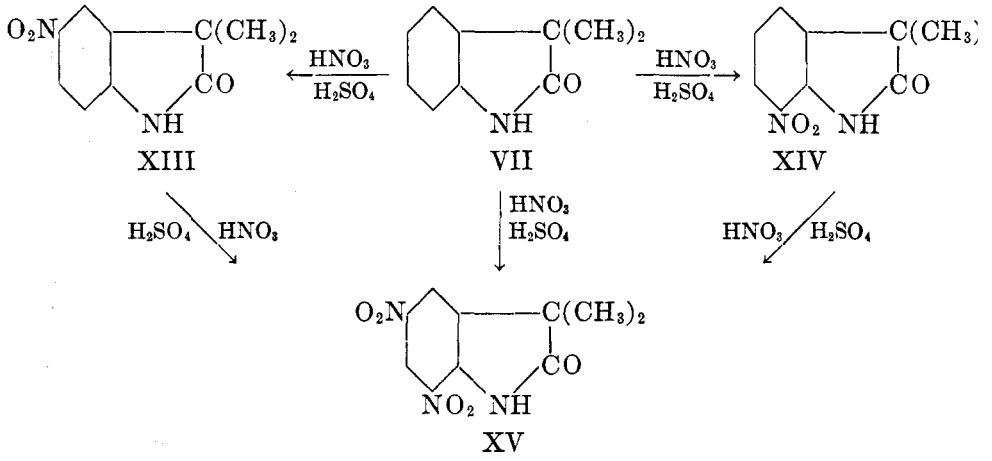
Baeyer (6) found that oxindole reacts with phosphorus pentachloride, yielding a product designated as chloroöxindole chloride. This same substance is obtained when dioxindole is treated with phosphorus pentachloride.



Chloroöxindole chloride

Oxindole was converted into a nitro derivative by Baeyer (8), who did not determine its structure. Borsche, Weussmann, and Fritzche (22) reported that the compound was 6-nitroöxindole but gave no proof other than the claim that the compound on treatment with nitrous acid gave a nitroisatin oxime supposedly different from that obtained from 5-nitroisatin and hydroxylamine. The work of Baeyer and of Borsche was repeated by Sumpter, Miller, and Magan (194), who found the work of Borsche in error. The product obtained by nitrating oxindole was definitely shown to be the 5-nitro derivative, as would be expected. 1-Methyloxindole was nitrated by Porter, Robinson, and Weyler (160). These workers were uncertain, in view of Borsche's paper (22), whether the resulting compound should be formulated as the 5-nitro or as the 6-nitro derivative. In view of the work of Sumpter, Miller, and Magan (194) on the nitration of oxindole, there seems little doubt that the product of Porter, Robinson, and Weyler was analogously 1-methyl-5-nitroöxindole.

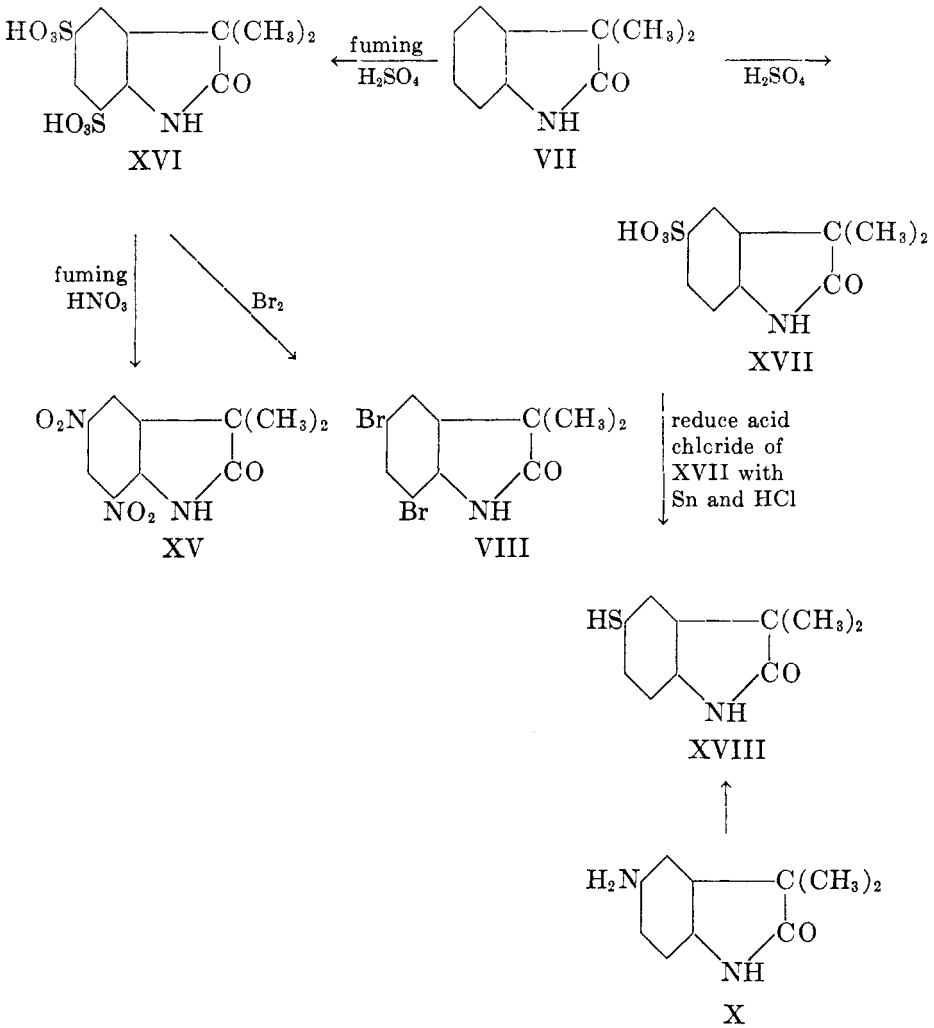
Brunner and coworkers (34) found that 3,3-dimethyloxindole (VII) with nitric acid gave two mononitro derivatives, which were identified as the 5-nitro derivative (XIII) and the 7-nitro derivative (XIV), respectively.



These two derivatives (XIII and XIV) were also synthesized from the corresponding nitrophenylhydrazines by methods which leave no doubt as to their structure. The 5,7-dinitro derivative (XV) was prepared by the nitration of VII and also by further nitration of XIII and XIV. In the light of the evidence outlined above it seems reasonable to assume that the nitration of certain other oxindole derivatives by Brunner also yielded the 5-nitro and the 5,7-dinitro

derivatives. This assumption has been made by the editors of Beilstein's *Handbuch* (16) in designating certain nitro derivatives as the 5- and 5,7-derivatives.

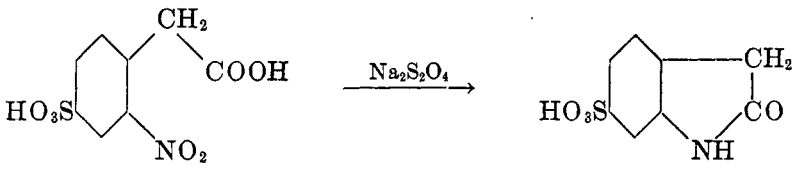
The only study of the direct sulfonation of an oxindole derivative is that made by Brunner (35). 3,3-Dimethyloxindole (VII) was sulfonated through the agency of sulfuric acid and of fuming sulfuric acid. The corresponding 5- and 5,7-disulfonic acid derivatives of VII were obtained.



The structure of the disulfonic acid (XVI) follows from its conversion into the dinitro derivative (XV) and the dibromo derivative (VIII), respectively. The structure of XVII was shown by its conversion to XVIII, which was also prepared from X through the diazonium salt.

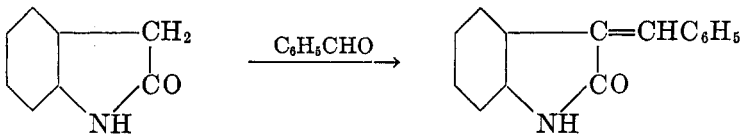
The direct sulfonation of oxindole does not seem to have been attempted.

Oxindole-6-sulfonic acid was prepared by Martinet and Dornier as indicated below (149) (compare also reference 61):



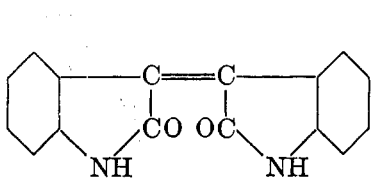
H. Condensation with aldehydes and ketones

Wahl and Bagard (200, 201, 202) found that oxindole condenses readily with benzaldehyde and with substituted benzaldehydes in the presence of piperidine to give benzaloxindoles.



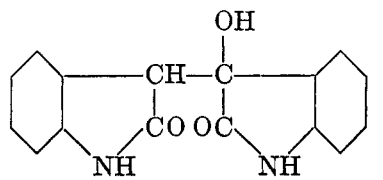
Similar condensations have been effected by Borsche (21), Wahl and Faivret (204), Wahl and Ferecean (205), Windaus and Eickel (211), Neber (155), Kliegl and Schmalenbach (112), Neber and Röcker (157), Armit and Robinson (3), Kirchner (110), Stollé (180), and Horner (89).

Isatin and oxindole condense in acid media (50, 71, 122, 138, 156, 200, 201, 203, 204, 205, 206) to give isoindigo (I) and in the presence of pyridine to give isatane (II) (71, 128, 132, 138, 156, 204, 206).



I

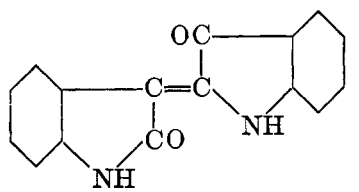
Isoindigo



II

Isatane

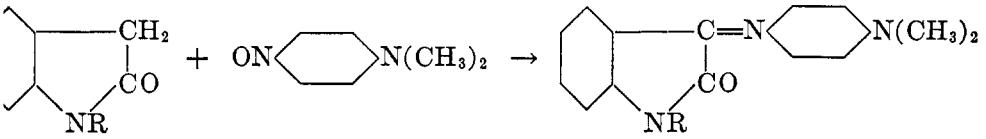
Oxindole and isatin chloride condense readily to give indirubin (III).



III

Indirubin

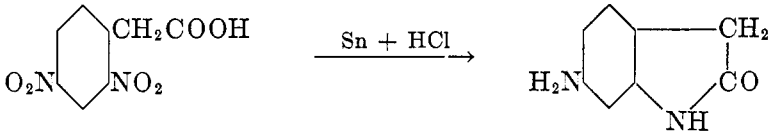
Oxindole and nuclear-substituted oxindoles condense with nitrosobenzene (156) and with *p*-nitrosodimethylaniline (156, 180) to give derivatives of isatin-3-anil.



Many derivatives of oxindole have been prepared through the condensation of isatin and isatin derivatives with compounds containing active methylene groups. These reactions have already been summarized in two reviews (74, 188).

I. Amino derivatives of oxindole

6-Aminoöxindole (II) was prepared by Gabriel and Meyer (56) by the reduction of 2,4-dinitrophenylacetic acid (I) with tin and hydrochloric acid. This method was also utilized by Parks and Aldis (158). The compound (II) was also prepared by Kishi and condensed with various aldehydes, condensation products

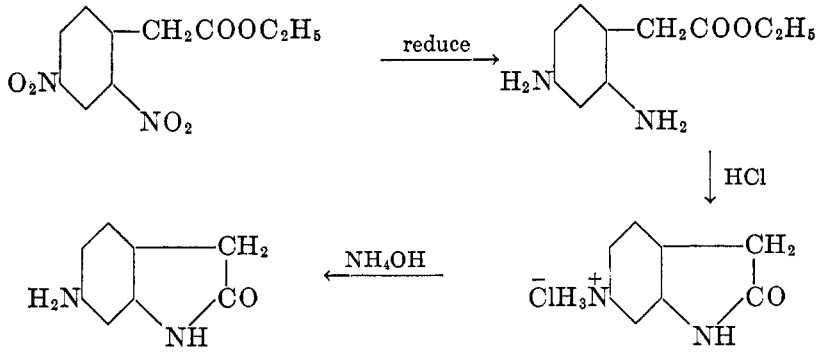


I II

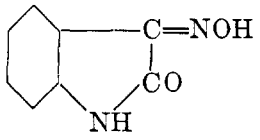
of types A and B being obtained under different experimental conditions.

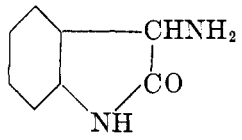
A B

6-Aminoöxindole (II) was also prepared by Ruggli and Grand (166), as shown in the following scheme:



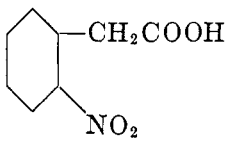
3-Aminoöxindole was first prepared by Baeyer (5, 10) by the reduction of the β-isatin oxime obtained by the action of nitrous acid on oxindole or of hydroxylamine on isatin.



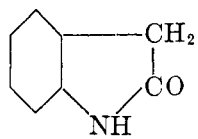


A number of 3-amino derivatives of oxindole and of substituted oxindoles have been prepared in this way by Langenbeck and his coworkers (124, 125, 126), while the method has also been used by Di Carlo and Lindwall (45).

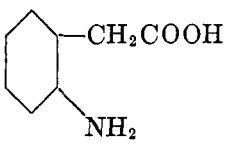
It has been shown by P. W. Neber (155, 156) that while the reduction of *o*-nitrophenylacetic acid (III) ordinarily gives oxindole (IV) through ring closure, under proper conditions *o*-aminophenylacetic acid (V) can be obtained. When the latter compound is diazotized and reduced by stannous chloride and the product (VI) quickly distilled, 1-aminoöxindole (VII) is obtained.



III

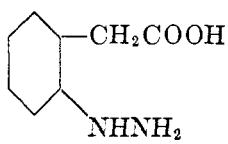


IV

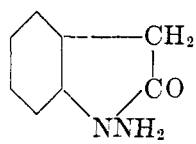


V

diazotize
reduce

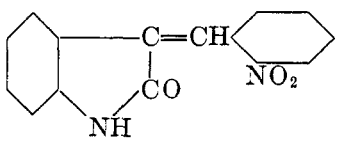


VI

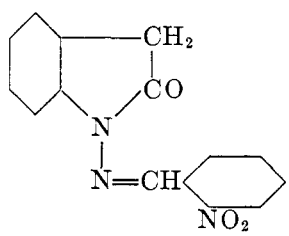


VII

Compound V condensed with *o*-nitrobenzaldehyde to give what Neber thought was a quinoline derivative, but the product was shown by Kliegl and Schmalenback (112) to be 3-(*o*-nitrobenzal)oxindole (VIII) (m.p. 226–227°C.). On the other hand, VI and *o*-nitrobenzaldehyde condense to give IX (m.p. 170°C.).



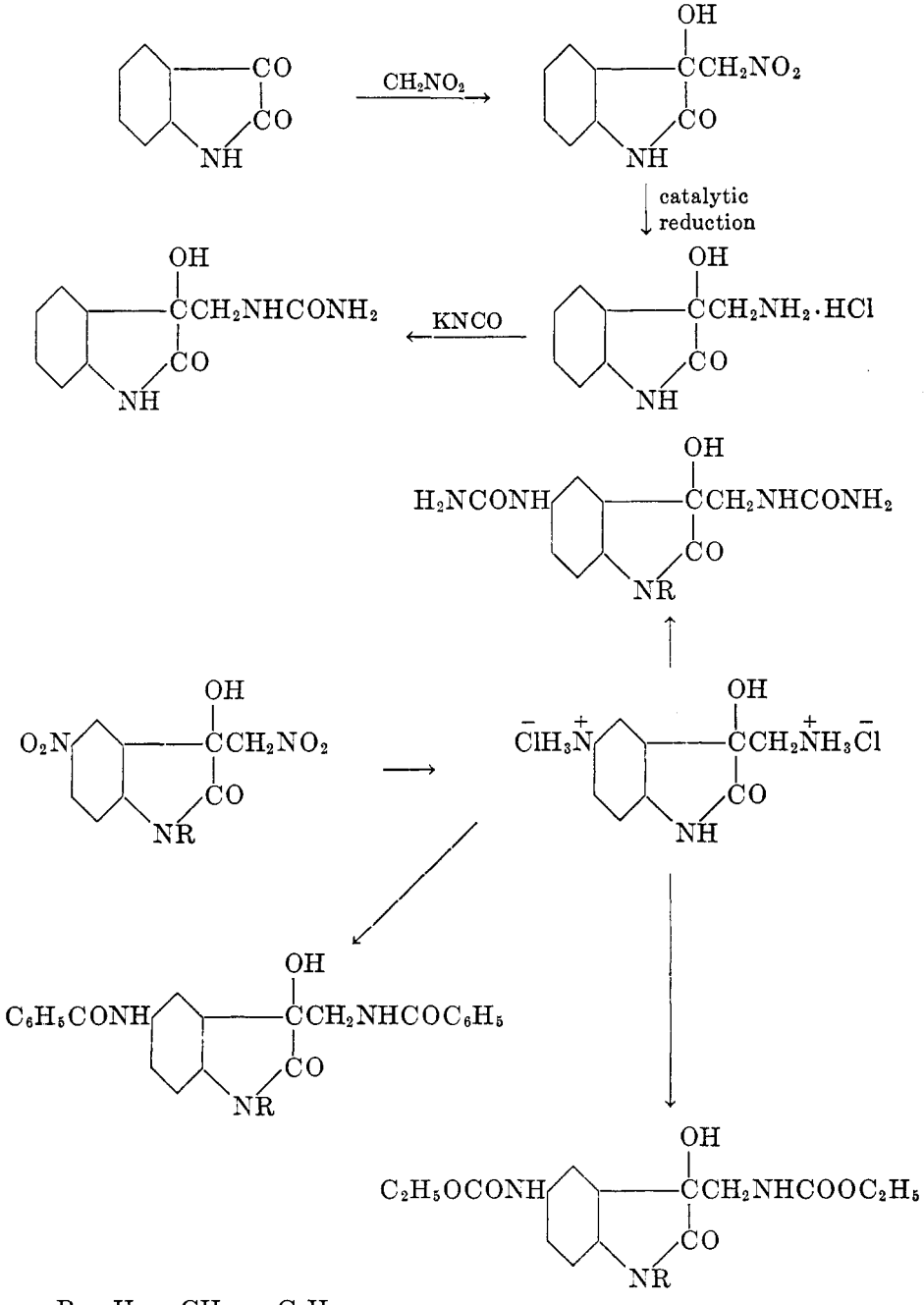
VIII



IX

A number of derivatives of 1-aminoöxindole were prepared by Neber and Keppler (156).

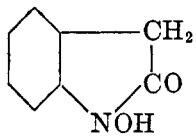
Other amino derivatives of oxindole were prepared by Lindwall and coworkers (41, 42) by condensing members of the isatin series with nitromethane and reducing the condensation product to the amine.



R = H—; CH_3—; C_2H_5—

J. Hydroxy derivatives of oxindole

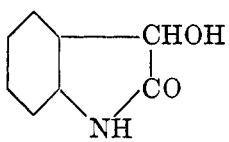
1-Hydroxyoxindole was obtained by Reissert (163, 164) by the reduction of



1-Hydroxyoxindole

o-nitrophenylacetic acid with zinc and hydrochloric acid. Oxindole was also obtained in the same reduction. Di Carlo (44) found that catalytic reduction of *o*-nitrophenylacetic acid under certain conditions gave 1-hydroxyoxindole, along with oxindole. 1-Hydroxyoxindole was converted to 1-acetoxyoxindole through the action of acetic anhydride and to 1-methoxyoxindole through the agency of methyl sulfate (76, 164). 1-Acetoxyoxindole was reduced to oxindole by the action of zinc dust and acetic acid (78).

3-Hydroxyoxindole (dioxindole) was first prepared by Baeyer and Knop (10) through the reduction of isatin by the action of sodium amalgam in alkaline medium. Reduction of isatide by sodium amalgam also yielded dioxindole (10). Isatin has also been reduced to dioxindole, by Heller (75), using zinc and acetic



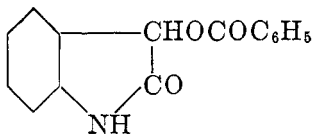
Dioxindole

acid, and by Marschalk (144, 142) and Kalb (102), using sodium hydrosulfite as the reducing agent.

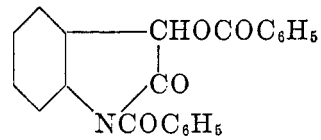
Isatin-4-carboxylic acid is reduced by sodium amalgam to dioxindole-4-carboxylic acid. The latter compound disproportionates in boiling alcoholic solution, yielding isatin-4-carboxylic acid and oxindole-4-carboxylic acid (26).

The reduction of 1-methylisatin and 1-ethylisatin by zinc and hydrochloric acid gives the corresponding 1-alkyldioxindole (40, 152, 189). Sodium hydrosulfite can also be used for the reduction of various isatin derivatives to the corresponding dioxindoles (85, 189, 190, 204). The isolation of the *d*- and *l*-enantiomorphs of dioxindole, which is obtained as the racemic dioxindole in all of the above preparations, has been effected by McKenzie and Stewart (140). Measurement of the oxidation potential of dioxindole has been made by Fieser (51).

Dioxindole reacts with benzoyl chloride to give a benzoyl derivative (m.p. 134°C.), which has been shown by Heller (75, 81) and by McKenzie and Stewart (140) to be 3-benzoyldioxindole (I). 1,3-Dibenzoyldioxindole (II) (m.p. 170°C.) was prepared by Heller (75) and by McKenzie and Stewart through the Schotten–Baumann reaction.

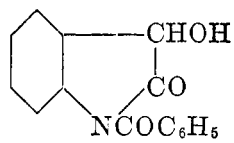


I



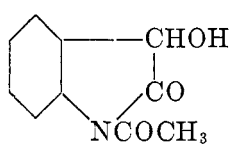
II

An isomer of I (m.p. 104°C.) was prepared by Hill and Sumpter (85) through the action of benzoyl chloride on the sodium salt of either dioxindole or isatide. The molecular weight of the substance corresponds to that of a benzoyl derivative of dioxindole and not to that of an isatide derivative (189). It is possible that this compound is 1-benzoyldioxindole (III), although definite proof of structure is lacking as yet.

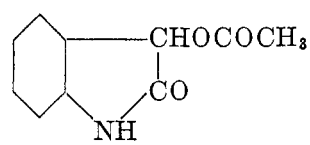


III

3-Acetyldioxindole (V) (m.p. 127°C.) was prepared by Suida (183, 184) through the action of acetic anhydride on dioxindole. The compound was described by Suida as being the 1-acetyl derivative (IV). Heller later reported that Suida's



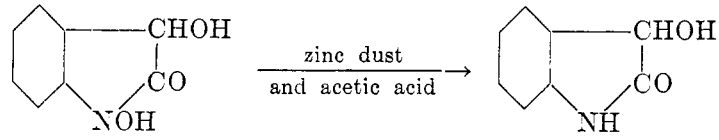
IV



V

acetyldioxindole was the 3-acetyl derivative (V) (references 74 (page 18) and 81). 1-Acetyldioxindole (IV) (m.p. 127°C.) was prepared by Sumpter (189) through the reduction of 1-acetylisatin with sodium hydrosulfite. While the melting points of IV and V are identical, the preparations are not identical, as is shown by the fact that a mixture of the two exhibits a marked depression in melting point. Since the method of preparation of IV leaves little doubt of its structure, it follows that Heller (74, 81) and McKenzie and Stewart (140) were correct in their conclusion that Suida's acetyldioxindole is V and not IV. An acetyldioxindole (m.p. 127°C.) was obtained by Bamberger and Lindberg (14) and described by these workers as "possibly 1-acetyldioxindole". From the method of preparation and physical properties this substance might have been either IV or V. This point can only be settled by the repetition of the work of Bamberger and Lindberg. The acetyl derivatives of a number of 1-alkyldioxindoles have been described by Stollé and Merkle (181).

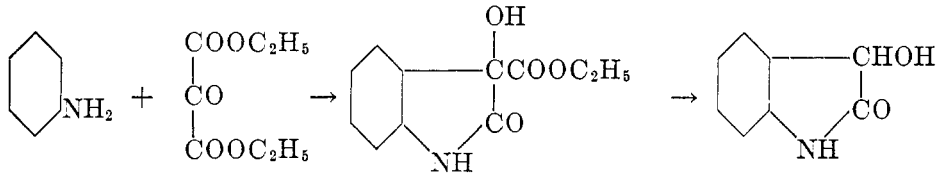
1-Hydroxydioxindole was prepared by Heller (77) through the reduction of *o*-nitromandelic acid by zinc dust and ammonium hydroxide. This compound (VI) is reduced to dioxindole by the action of zinc dust and acetic acid.



VI

Through the reduction of their "6-nitroisatin" by hydrogen in the presence of nickel catalyst, Rupe and Apotheker (167) obtained a compound which they regarded as being 6-aminodioxindole. Since Sumpter and Jones (191) demonstrated that Rupe's 6-nitroisatin was in reality 5-nitroisatin, it follows that the hydrogenation product was probably 5-aminodioxindole. The latter compound was also prepared by Hartmann and Pannizzon (73).

Another method for the synthesis of dioxindole and its derivatives is provided by a procedure developed by Martinet and coworkers (20, 67, 144, 145, 147, 149). Aniline or a substituted aromatic amine is condensed with the ethyl or methyl ester of oxomalonic acid. On treatment with alkali the resulting compound (VIII) gives dioxindole (VII) in the absence of oxygen. In the presence of oxygen isatin results through oxidation of VII. The reaction has also been studied

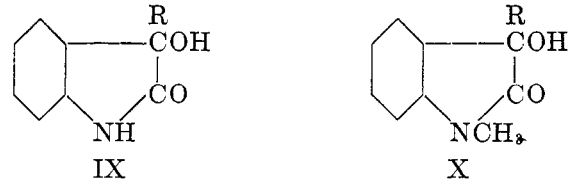


VIII VII

by Kalb (102, 104), by Halberkann (70), by Hinsberg (86), and by Langenbeck (122, 123). Heller (80a) found that VIII could also be prepared by the hydrolysis and esterification of the product obtained by the condensation of isatin with hydrocyanic acid.

Dioxindole is converted into isatin β-phenylhydrazone by heating with phenylhydrazine (75, 146).

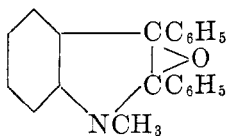
3-Alkyl-3-hydroxyoxindoles (IX) are readily prepared by the action of Grignard reagents on isatin (85, 115, 116, 119, 120, 121, 154, 174, 175, 176, 182, 186, 187). (For other syntheses of 3-phenyl-3-hydroxyoxindole see references 13 and



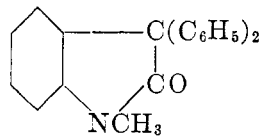
IX X

103.) Kohn (120) found that when phenylmagnesium bromide and *N*-methylisatin were allowed to react in equimolecular proportions, the analogous 1-methyl-3-phenyl-3-hydroxyoxindole (X) was obtained. On the other hand, when *N*-methylisatin was treated with excess Grignard reagent Kohn found that both

carbonyl groups in the isatin molecule reacted, yielding XI. It was subsequently found by Myers and Lindwall (154) that Kohn's product was in reality a mixture of XI and the rearrangement product XII. The latter substance was also obtained by Reeves and Lindwall (162a) by the action of phenylmagnesium bro-



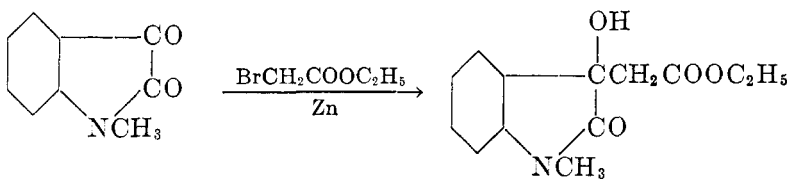
XI



XII

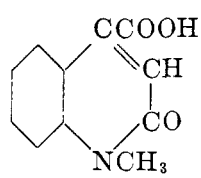
mide on *N*-methyl benzoylformanilide. The reactions of *N*-substituted isatins with Grignard reagents have also been studied by Inagaki (96), by Stollé (182), and by Sumpter (186, 187).

The Reformatsky reaction was employed by Myers and Lindwall (153) to obtain the ethyl ester of 3-hydroxy-1-methyloxindolyl-3-acetic acid (XIII). Hydrolysis of this ester brings about ring opening and subsequent closure to give



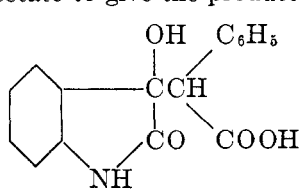
XIII

the quinoline derivative (XIV).



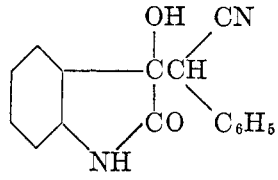
XIV

Isatin undergoes an aldol type of reaction with many compounds containing active methylene groups, yielding 3-hydroxy derivatives of oxindole (reference 188, page 413). For example, Zrike and Lindwall (213) found that isatin condenses with ethyl phenylacetate to give the product XV.

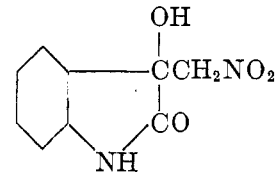


XV

Hill and Samachson (84) found that phenylacetonitrile condensed with isatin to give compound XVI.



XVI

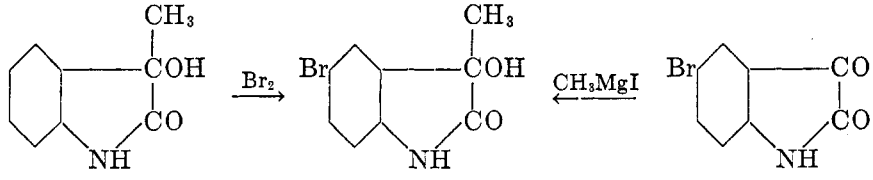


XVII

Similar aldol-like condensation products (XVII) were obtained by Lindwall and coworkers when isatin and substituted isatins were condensed with nitromethane and nitroethane. Other 3-hydroxyoxindole derivatives were prepared by Lindwall and coworkers (25, 47, 48, 136, 213), by Baumen (15), and by Schönberg, Schütz, Arend, and Peter (168).

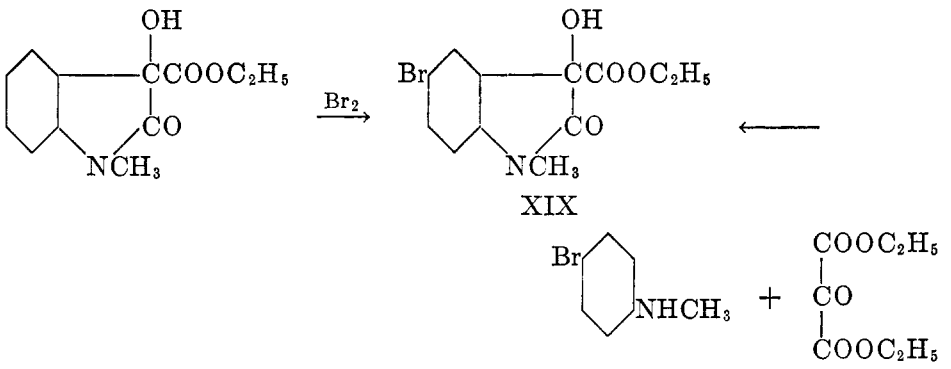
Baeyer and Knop (10) described the preparation of a number of substituted dioxindoles by direct substitution. Most of these preparations have not been repeated. The preparation of the monobromodioxindole of Baeyer and Knop (10) has been repeated in this laboratory (190) and the melting point reported by Baeyer found to be far too low. That the product of this bromination is 5-bromodioxindole has been shown by the preparation of the same compound by the reduction of 5-bromoisatin with sodium hydrosulfite. Further proof of structure was provided by the fact that the bromodioxindole yielded 5-bromoisatin phenylhydrazone when heated with phenylhydrazine. It was further found that the dibromo derivative (from dioxindole and two molecular proportions of bromine) was the 5,7-dibromo derivative. This was established by its preparation from 5,7-dibromoisatin through reduction as well as its conversion to 5,7-dibromoisatin phenylhydrazone through the agency of phenylhydrazine.

Kohn (116) found that the 3-alkyl-3-hydroxyoxindoles brominate in position 5. 5-Bromo-3-methyl-3-hydroxyoxindole (XVIII) was prepared equally well by the action of bromine on 3-methyl-3-hydroxyoxindole and from the Grignard complex resulting from the action of methylmagnesium iodide on 5-bromoisatin.



XVIII

Martinet (147) found that ethyl 5-bromo-3-hydroxy-1-methyloxindole-3-carboxylate (XIX) could be prepared by the bromination of the parent compound or by the condensation of ethyl oxomalonate with *N*-methyl-*p*-bromoaniline.



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