THE CHEMISTRY OF ISATIN

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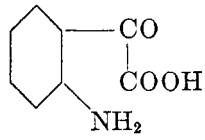
I. INTRODUCTION

In the course of studies of the action of various oxidizing agents on indigo, Erdmann (108, 109, 110) and Laurent (259, 260, 261, 262) in 1841 independently discovered an oxidation product which had the formula $C_8H_5NO_2$ and to which the name isatin was given. The preparation of the compound was best effected by the action of nitric acid or a mixture of nitric and chromic acids on indigo. When indigo was oxidized by chlorine, chloroisatin and dichloroisatin were obtained, while bromoisatin and dibromoisatin were prepared similarly through the agency of bromine. That the compound contained a benzene nucleus was shown by the fact that further action of chlorine on chloroisatin yielded chloranil.

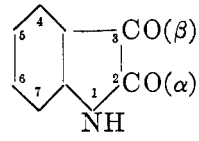
In 1845 Hofmann (209) found that heating isatin with strong alkali gave aniline and that similar treatment of chloroisatin yielded chloroaniline. Subsequently Hofmann (210) also showed that treatment of isatin with nitrous acid gave 5-nitrosalicylic acid.

In 1866 and 1868 Baeyer (15,24) published the results of his researches on the

reduction of isatin. Besides isatide, which had been obtained previously by Laurent (262, 265, 266) and by Erdmann (109), Baeyer obtained dioxindole, $C_8H_7NO_2$, and through further reduction of the latter compound oxindole, C_8H_7NO. Oxindole was further reduced to indole by passing its vapor over hot zinc oxide. Isatin was found to dissolve in alkali to give the salt of an acid, isatic (isatinic) acid. Kekulé (233) offered the suggestion that isatic acid was *o*-aminobenzoylformic acid and that isatin was its lactam, and thought that isatin might



Isatic acid



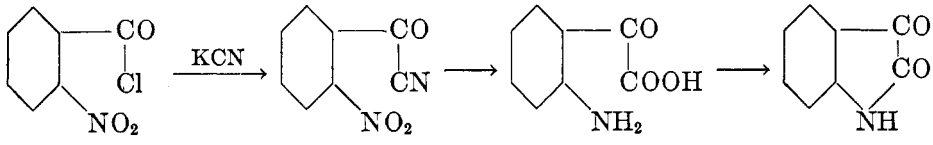
Isatin

be synthesized from *o*-aminophenylacetic acid. Baeyer quickly realized that Kekulé's suggestion was correct and also saw the relationship of dioxindole and oxindole to isatin (16, 17).

Current practice in isatin nomenclature is to number the positions as shown in the formula above. The 2- and 3-positions are also frequently referred to as the α- and β-positions, respectively. Other systems of numbering have been used at times by some workers (170, 344) but the system shown here is used generally at the present time.

II. SYNTHESES OF ISATIN AND OF ISATIN DERIVATIVES

The synthesis of isatin from *o*-nitrobenzoyl chloride by Claisen and Shadwell (77) furnished definite confirmation of the structure suggested by Kekulé. The work of Kolbe (245) furnished further confirmation of its structure.



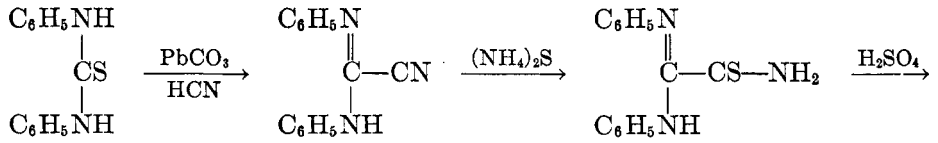
o-Nitrobenzoyl chloride

Isatin

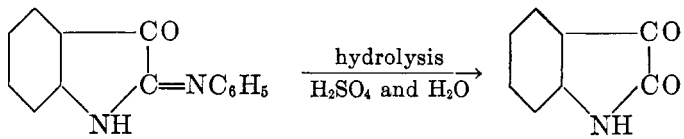
Isatin was also synthesized by Baeyer (20) and by Forrer (119) by the action of alkali on *o*-nitrophenylpropiolic acid.

Baeyer (16) further synthesized oxindole by the reduction of *o*-nitrophenylacetic acid and later converted aminoöxindole into isatin (17).

The synthesis of isatin and of many isatin derivatives has been accomplished through the utilization of two procedures developed by T. Sandmeyer. One of these methods starts with thiocarbanilide and is carried out according to the following scheme (39, 113, 347):



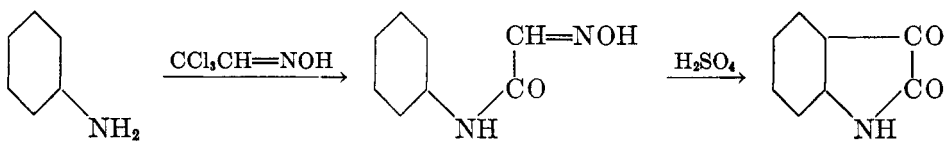
Thiocarbanilide



Isatin-α-anilide Isatin

The isatin-α-anilide can be hydrolyzed quite readily to isatin.

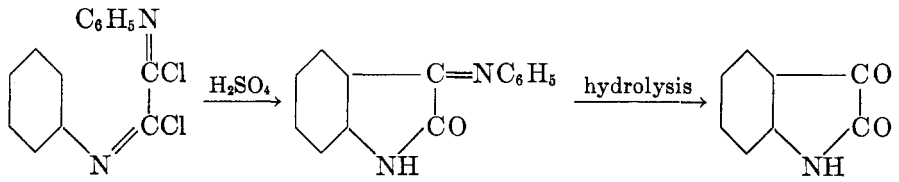
The second of Sandmeyer's procedures (348) depends on the formation of isonitrosoacetanilide from aniline, chloral hydrate, and hydroxylamine. The isonitrosoacetanilide is converted into isatin on treatment with concentrated sulfuric acid.



Isatin

This method of synthesis has been used for the preparation of many isatin derivatives (49, 52, 90, 91, 144, 219, 290, 293, 294, 305, 338, 339, 364, 408). The nitroanilines form the corresponding nitroisonitrosoacetanilides, but these fail to give the nitroisatins when treated with sulfuric acid (46, 344).

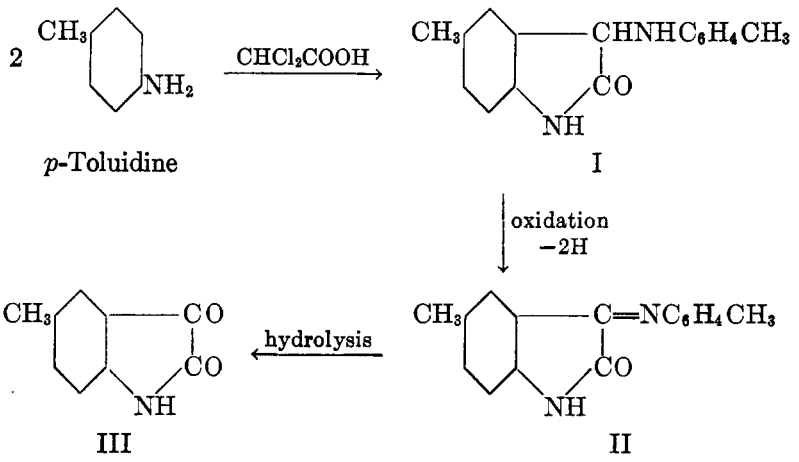
Isatin and nuclear-substituted isatins have been prepared by Bauer (30, 31, 32) by the action of sulfuric acid on substituted imide chlorides of oxalic acid. This method has also been applied by Ostromisslensky (313), who has likewise



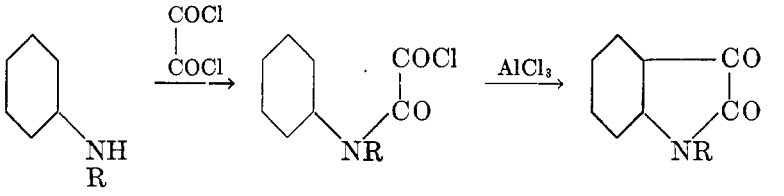
Isatin

synthesized substituted isatins from *o*-toluidine and *p*-toluidine and dichloroacetic acid, in a reaction discovered by P. J. Meyer (300) and subsequently studied by Duisberg (101), Heller (170, 187), and Paucksch (314). The procedure depends on heating dichloroacetic acid with arylamines and results in the intermediate formation of an oxindole derivative (I). This derivative is then

oxidized to the corresponding isatin anil (II), which on hydrolysis gives the substituted isatin (III).

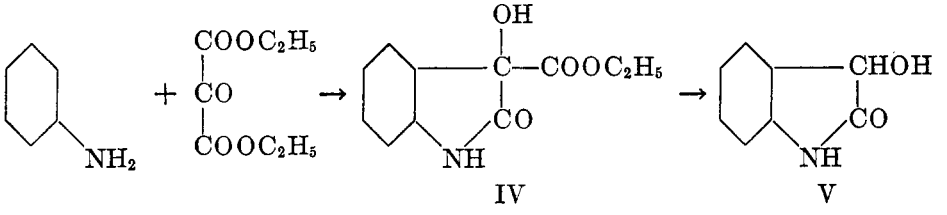


A method developed by Stollé (377, 378) provides a convenient procedure for the synthesis of many isatin derivatives (see also reference 253). In this synthesis an *N*-substituted aniline is treated with oxalyl chloride, and the resulting intermediate is converted into an isatin by treatment with anhydrous aluminum chloride.



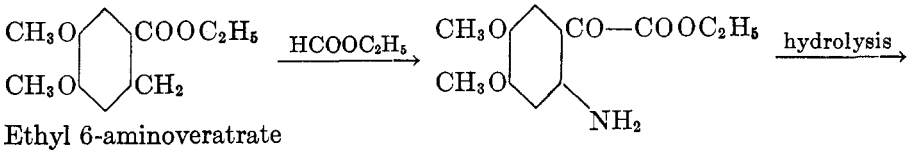
Cyanoformarylides also undergo similar ring closure on treatment with aluminum chloride or zinc chloride (53).

Another method for the synthesis of isatin derivatives is provided by a procedure developed by Martinet and coworkers (39, 146, 287, 288, 289, 292). Aniline or a substituted aromatic amine is condensed with the ethyl or methyl ester of oxomalonic acid. On treatment with alkali the resulting compound (IV) yields dioxindole (V) in the absence of oxygen. If the treatment with alkali takes place in the presence of air, isatin is obtained. This reaction has been

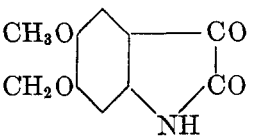


studied also by Kalb (229, 230) and by Halberkann (150). The method has been applied to the synthesis of α- and β-naphthisatins (207, 253, 287, 289).

Fetscher and Bogert (112) obtained 5,6-dimethoxyisatin from ethyl 6-aminoveratrate by means of the following series of reactions:

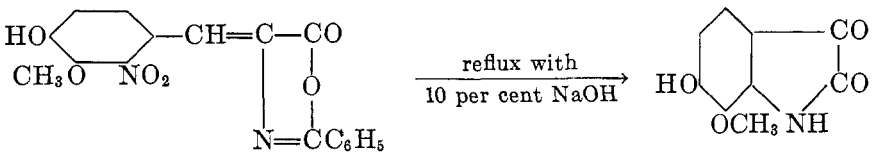


Ethyl 6-aminoveratrate



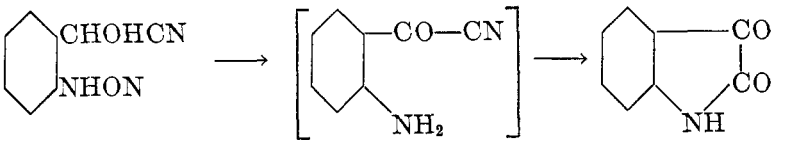
5,6-Dimethoxyisatin

Burton and Stoves (66) prepared isatin derivatives by treating the azlactones of certain *o*-nitrobenzaldehydes with alkali.



Succharda (383) obtained isatin-7-sulfonic acid by oxidizing quinoline-8-sulfonic acid with alkaline potassium permanganate.

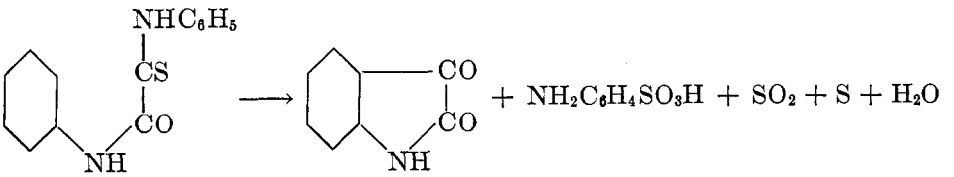
Heller (168) obtained isatin by heating *o*-hydroxylaminomandelic acid with hydrochloric acid.



o-Hydroxylaminomandelic acid

Isatin

A synthesis developed by Reissert (332) depends on heating thioöxanilide with concentrated sulfuric acid.



Thioöxanilide

Procedures have been developed by a considerable number of workers for preparing isatin and isatin derivatives by the oxidation of indigo or the appropriate indigo derivatives (93, 110, 119, 131, 201, 209, 230, 231, 235, 236, 250, 262, 326, 330, 391).

Böhm (38) has reported that isatin is formed in the body and excreted in the urine when *o*-nitrophenylglyoxylic acid is fed to rabbits. When *o*-nitromandelic acid is fed, dioxindole is found in the urine.

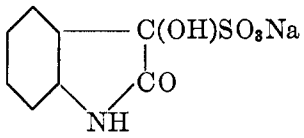
III. GENERAL PROPERTIES OF ISATIN

A. Physical properties

Isatin crystallizes from water, alcohol, or acetic acid in the form of red needles melting at 200–201°C. It is soluble in hot water, alcohol, acetic acid, and benzene but is sparingly soluble in ether. The substance is soluble in concentrated hydrochloric acid and in concentrated sulfuric acid. It dissolves in sodium or potassium hydroxide solution, forming the sodium or potassium salt of isatin. Heating the solution results in ring opening with the formation of the salt of isatic acid. Ring closure results when the solution is acidified, and isatin precipitates.

B. Salts of isatin

Laurent (264) and Schiff (349) found that isatin forms addition compounds with alkali bisulfites in a reaction typical of the β-carbonyl group.

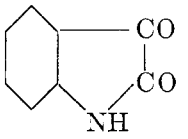


Isatin gives a stable perchlorate with perchloric acid (211). On the question of the constitution of the silver and alkali salts of isatin a lively controversy is found in the literature (76, 88, 153, 154, 169, 174, 176, 182, 183, 351). The sodium salt of isatin is obtained readily by the action of sodium ethylate on a solution of isatin in absolute alcohol. The potassium salt is prepared in similar fashion. The silver salt is prepared by adding the sodium salt of isatin to a solution of silver nitrate or by the action of silver acetate on a solution of isatin in alcohol.

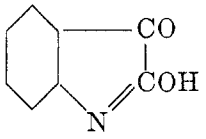
Peters (316) prepared the mercuric salt of isatin, while Hantzsch (157) prepared the mercurous salt. Of these metal salts the only ones of value in the synthesis of isatin derivatives are the silver salt (for *O*-alkyl derivatives) and the alkali salts (for *N*-derivatives).

C. Tautomerism

In 1882 Baeyer (22, 27) recognized the fact that isatin might be represented by either the lactam or the lactim structure.

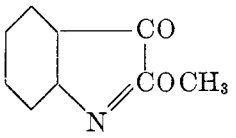


Lactam structure of isatin

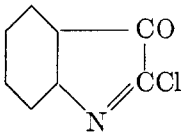


Lactim structure of isatin

Toward many reagents isatin behaves as though it were the lactam, but *O*-alkyl ethers can be prepared from its silver salt and alkyl halides. Furthermore, isatin reacts with phosphorus pentachloride in hot benzene solution to give isatin α-chloride (18). It is said that isatin presents the first recognized case of a tau-



O-Methylisatin

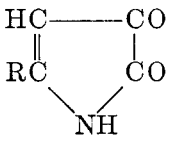


Isatin α-chloride

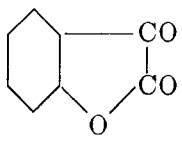
tomeric substance (366). Baeyer thought that isatin itself had the lactim form and termed the lactam "pseudoisatin." For a time it was thought that absorption-spectra measurements indicated that isatin was the lactam (86, 162, 247, 295, 306), but more recent work (7, 13, 80) leaves the question in doubt, since isatin and the lactam and lactim ethers have very similar absorption curves.

Claims have been made by G. Heller that numerous di- and tri-molecular isomers of isatin exist (174, 175, 176, 177, 178, 179, 181, 182, 183, 192, 194, 195, 196, 197). The claims of Heller have been disputed by Hantzsch and others (71, 153, 154, 155, 157, 158, 160). The details of this prolonged controversy can be found in the original papers and in part in Heller's own review (165).

Mumm and coworkers (307) have pointed out that 2,3-diketopyrrolines (I) are quite like isatin in appearance and properties and have suggested that these derivatives be regarded as mononuclear isatins. The oxygen analog of isatin



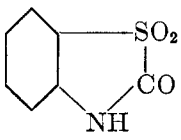
I



II

(II) has been studied by Stoermer (376) and by Fries (126) and coworkers.

Claascz (75) has prepared compound III, which he calls sulfurylisatin.

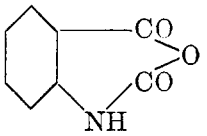


III

Sulfurylisatin

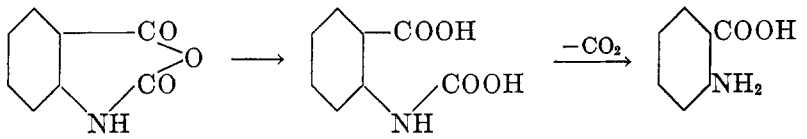
D. Oxidation and reduction

Kolbe (245) found that oxidation of isatin by chromic acid in acetic acid solution gave isatoic anhydride, a substance also obtained by Erdmann (107)



Isatoic anhydride

from anthranilic acid and phosgene (see also Friedlander and Wleugel (125)). Isatoic anhydride is converted into anthranilic acid by heating with mineral

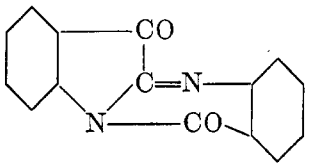


Isatoic anhydride Anthranilic acid

acids. On the other hand, *N*-acetylisatin is converted directly into *o*-acetaminobenzoic acid by oxidation with chromic acid. Nuclear-substituted isatins are converted into the corresponding isatoic acid anhydrides by chromic acid oxidation (36, 279, 315, 344).

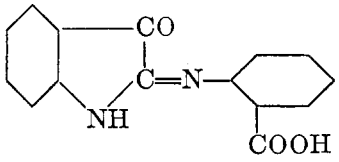
Friedlander and Roschdestwensky (124) found that oxidation of isatin with potassium permanganate gave a compound designated as anhydroisatin-α-anthranilide, which was also obtained by Machemer (278) by the oxidation of indigo or isatin in pyridine by atmospheric oxygen in the presence of copper salts as catalysts.

The same compound is obtained by condensing isatin-α-anilide or isatin-α-chloride with anthranilic acid (95) or from the reaction of indoxyl and *o*-nitrosobenzoic acid.



Anhydroisatin-α-anthranilide

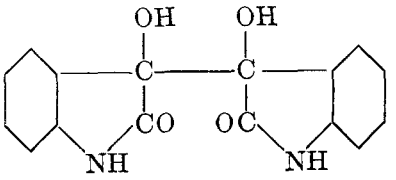
O-Methylisatin and anthranilic acid condense (189), giving isatin-α-anil-*o*-carboxylic acid



which on heating in acetic acid solution readily changes to anhydroisatin-α-anthranilide. Derivatives of anhydroisatin-α-anthranilide have also been prepared (195, 199).

Oxidation of isatin with alkaline hydrogen peroxide gives anthranilic acid, while substituted isatins similarly give the corresponding substituted anthranilic acids (230, 388, 391, 392).

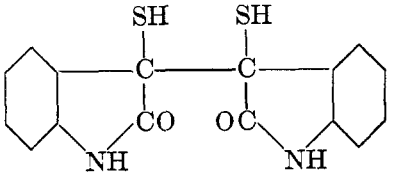
The first product obtained in the reduction of isatin is isatide (I) (19, 24, 110, 167, 259, 262, 265, 266, 399, 400, 401). This substance is also obtained by the



I

Isatide

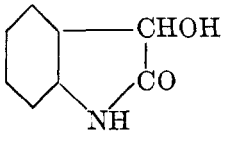
condensation of isatin and dioxindole in the presence of piperidine (152, 167, 399, 405). When isatin is reduced with hydrogen sulfide in alcoholic solution, the product is isatin thiopinacol (disulfisatide) (II) (260, 346, 397, 401, 402, 403, 404).



II

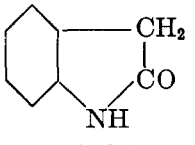
Isatin thiopinacol

Baeyer and Knop (15, 24) found that when isatin is reduced in acid solution the product is isatide. Further reduction by sodium amalgam gives 3-hydroxy-oxindole (dioxindole), which was also obtained by reducing isatin with sodium amalgam in alkaline medium. The further reduction of dioxindole by tin and



Dioxindole

mineral acids or by sodium amalgam and acid gave oxindole.

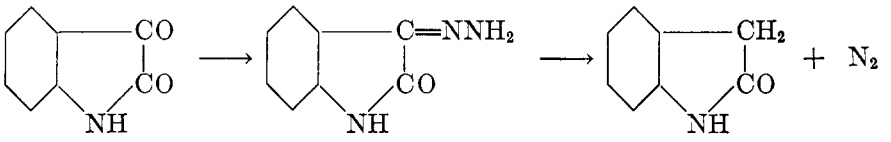


Oxindole

Isatin has also been reduced to dioxindole by Heller (167), using zinc and acetic acid, and by Marshalk (284, 285) and Kalb (229), using sodium hydrosulfite as the reducing agent. The procedure of Marshalk seems to offer the most satisfactory method for the preparation of dioxindole. Marshalk has further reduced dioxindole to oxindole through the action of sodium amalgam on an aqueous solution of dioxindole saturated with carbon dioxide.

The reduction of 1-methylisatin and of 1-ethylisatin by zinc and hydrochloric acid gives 1-methyldioxindole (78,390) and 1-ethyldioxindole (303), respectively. Sodium hydrosulfite can also be employed to convert other isatin derivatives to the corresponding dioxindoles (205, 390).

Curtius and Thun (84, 85) obtained oxindole from isatin through the agency of hydrazine. This reaction has also been studied by Borsche and Meyer (44)



Isatin Oxindole

and by Shapiro (363).

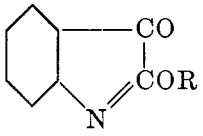
E. Acylation and alkylation

Suida (384) obtained *N*-acetylisatin by heating isatin with acetic anhydride. The same derivative was described by Liebermann and Krauss (270) and was also prepared by Heller (177) from the sodium salt of isatin and acetyl chloride. *N*-Benzoylisatin was prepared by Schwartz (361), Schotten (355), Liebermann and Krauss (270), and Heller (166, 169, 196). The compound is best prepared by the action of benzoyl chloride on the sodium salt of isatin or on a solution of isatin in pyridine. A number of other acyl derivatives of isatin and of substituted isatins have been described (299).

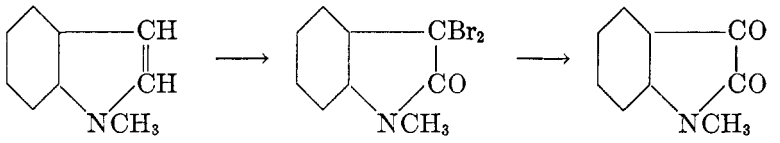
N-Benzenesulfonylisatin has been prepared by Heller (178), while Aeschlimann (2) prepared *N*-phenylacetylisatin by treating the sodium salt of isatin with phenylacetyl chloride.

The ethyl ester of isatin-*N*-carboxylic acid is obtained by treating the sodium salt of isatin with ethyl chloroformate (156, 177, 193, 196, 328). The sodium salt similarly reacts with ethyl chlorooöxalate to give ethyl isatin-1-glyoxalate (177). Putochin (329) prepared ethyl isatin-1-acetate and diethyl isatin-1-malonate by treating the sodium salt of isatin with ethyl chloroacetate and ethyl chloromalonate, respectively. Isatin-1-acetic ester was also studied by Langenbeck (252) and by Ainley and Robinson (3).

Baeyer and Oekonomides (27) found that the silver salt of isatin reacted with alkyl halides to give *O*-alkyl derivatives of isatin (169).



On the other hand, the sodium and potassium salts of isatin react with alkyl halides and with alkyl sulfates to give *N*-alkyl derivatives (22, 28, 118, 169). *N*-Methylisatin was first prepared (78) from *N*-methylindole, which was converted by alkali hypobromite into 3,3-dibromo-*N*-methyloxindole. The latter compound was then hydrolyzed to *N*-methylisatin. This method is of importance because it establishes beyond doubt the position of the methyl



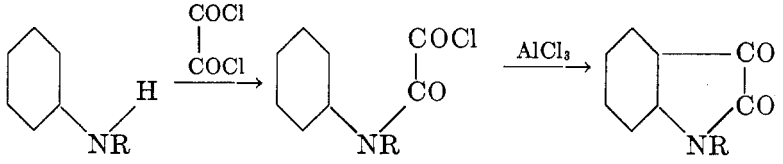
N-Methylindole *N*-Methylisatin

group.

The *O*-alkyl derivatives of isatin are easily hydrolyzed, while the *N*-alkyl derivatives are not. *O*-Methylisatin is stable when kept in a tightly stoppered bottle and protected from air and moisture; otherwise it changes rapidly to "methylisatoid".

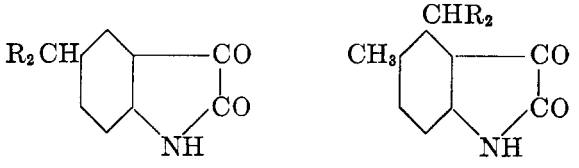
N-Methylisatin and *N*-ethylisatin can be prepared most conveniently by alkylating isatin by means of methyl sulfate and ethyl sulfate, respectively (43, 122, 242, 244).

The method of Stollé also provides a convenient preparation for the *N*-substituted isatins (378, 380, 381).



The metal salts of both *O*-methylisatin and *N*-methylisatin have been studied by Schlenk and Thal (351).

Reitzenstein and Breuning (337) have reported that tetramethyldiaminobenzohydrol condenses with isatin in the presence of concentrated sulfuric acid to give a compound of type I (R = $p(CH_3)_2NC_6H_4$—). In those cases where position 5 is occupied, the condensation is said to take place in position 4, yielding compounds of the type of II.



I II

F. N-Hydroxyisatin

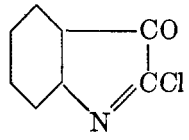
N-Hydroxyisatin and a number of its derivatives were prepared by Reissert (331, 333, 335), by Alessandri (5), and by Heller (168, 171, 200). The compound

is best prepared by the procedure developed by Arndt, Eistert, and Partale (11) through the action of benzoyl chloride on diazomethane. A product ($C_8H_5O_3N_3$) is obtained which gives *N*-hydroxyisatin when treated with dilute sulfuric acid. *N*-Hydroxyisatin is a red crystalline substance having the same melting point as isatin itself, 200–201°C. The compound was also obtained by Arndt, Eistert, and Partale (12) by treating *o*-nitrobenzoylcarbinol with sodium hydroxide.

Unsuccessful attempts have been made by Neber and Keppler (312) and by Stollé (379) to prepare *N*-aminoisatin. Several derivatives of the compound have been described.

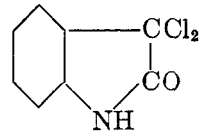
G. Halogenation, sulfonation, and nitration

Isatin reacts with phosphorus pentachloride in hot benzene solution to give isatin α-chloride (I) (18, 232). On the other hand, when isatin and phosphorus



I

Isatin α-chloride



II

3,3-Dichloroöxindole

pentachloride are allowed to react slowly at room temperature the product is 3,3-dichloroöxindole (II) (153). *N*-Alkyl derivatives of isatin react with phosphorus pentachloride to give the 1-alkyl-3,3-dichloroöxindoles (78, 118, 241, 244, 303, 378).

The direct chlorination of isatin gives 5-chloroisatin (89, 108, 109, 110, 209, 232, 259, 270, 280, 401) and 5,7-dichloroisatin (87, 89, 135, 136, 183, 228, 232). Chlorination of isatin or of 5-chloroisatin in aqueous suspension in the presence of potassium iodide or by addition of sodium hypochlorite to a suspension of isatin in 10 per cent hydrochloric acid gives 1,5-dichloroisatin (97). This substance when treated with sodium bisulfite and then acidified gives 5-chloroisatin, while heating with concentrated sulfuric acid converts it to 5,7-dichloroisatin. 5-Bromoisatin similarly gives 1-chloro-5-bromoisatin.

Bromination of isatin in alcohol in the cold gives 5-bromoisatin, while with the calculated quantity of bromine in hot solution 5,7-dibromoisatin is obtained (27, 89, 98, 134, 209, 219, 270, 274).

Isatin can be iodinated directly through the agency of iodine monochloride, the product being 5-iodoisatin (47, 230, 308). It has been claimed (357) that 5,7-diiodoisatin and a tetraiodoisatin can be obtained by the action of iodine monochloride on a solution of isatin in concentrated hydrochloric acid. It has been found, however, that such is not the case and that the sole product is 5-iodoisatin (391). It is apparently impossible to introduce an atom of iodine directly into the isatin nucleus in position 7 (388, 391).

5,7-Diiodoisatin and 5,6,7-triiodoisatin have both been prepared by indirect methods (230, 231, 391).

Isatin-5-sulfonic acid is obtained readily when isatin is treated with fuming sulfuric acid (291, 353).

The first nitration of isatin was effected by Baeyer (19) through the action of potassium nitrate on a solution of isatin in concentrated sulfuric acid. Baeyer reported that the compound melted at 226–230°C. and assumed that it was 5-nitroisatin. Liebermann and Krauss (270) employed essentially the same procedure and reported the melting point as 245°C. Rupe and Stocklin (345) reported that 6-nitroisatin was obtained when isatin was nitrated by the action of nitric acid in sulfuric acid solution. Calvery, Noller, and Adams (69) used a procedure essentially that of Rupe and Stocklin and obtained a product melting at 254–255°C. which they assumed to be Baeyer's 5-nitroisatin (compare also German patent 221,529). Rupe and Kersten (344) presented evidence purporting to show that Baeyer's product was 5-nitroisatin and that Rupe's nitroisatin was 6-nitroisatin.

The work of Baeyer, of Rupe, and of Calvery, Noller, and Adams was repeated by Sumpter and Jones (392), who found that the same product was obtained in each case and that it had been correctly characterized by Calvery, Noller, and Adams. The structure was established as 5-nitroisatin by oxidation in alkaline solution with hydrogen peroxide to 5-nitroanthranilic acid, which had been described previously by Bogert and Scatchard (37). 1-Methyl-5-nitroisatin was prepared by Borsche, Weussmann, and Fritzsche (46) by nitrating 1-methylisatin.

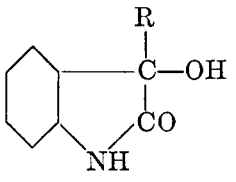
5-Nitroisatin was reduced catalytically to 5-aminodioxindole by Hartmann and Pannizzon (163). The acetyl derivative of the latter compound was oxidized to 5-acetaminoisatin, which on hydrolysis gave 5-aminoisatin. 5-Aminoisatin was converted to 5-hydroxyisatin by diazotization. It has also been reported (392a) that 5-nitroisatin can be reduced directly to 5-aminoisatin.

5,7-Dinitroisatin was prepared by Menon, Perkin, and Robinson (298) and by Guha and Basu-Mallic (142) through the action of potassium nitrate on isatin in sulfuric acid solution. The same compound is obtained when a solution of isatin in concentrated sulfuric acid is treated with two molecular proportions of nitric acid (390).

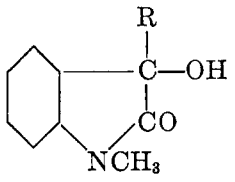
IV. REACTIONS OF ISATIN

A. Reaction with Grignard reagents

The reactions of isatin and its derivatives with Grignard reagents have been studied by Kohn and coworkers (238, 239, 242, 243, 244), by Myers and Lindwall (310), and by other workers (205, 369, 370, 373, 381, 387, 389). With the

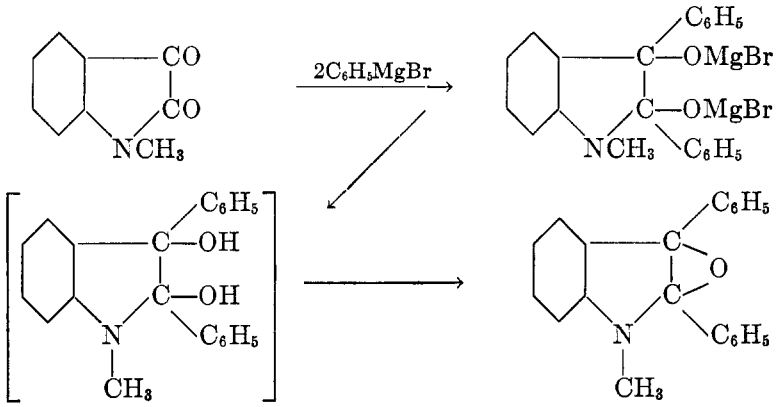


I



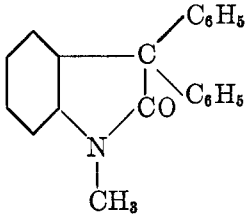
II

Grignard reagents isatin yields the corresponding 3-alkyl(or aryl)-3-hydroxyoxindoles (I). Kohn (243) found that when phenylmagnesium bromide and *N*-methylisatin were allowed to react in equimolecular proportions the analogous 1-methyl-3-phenyl-3-hydroxyoxindole (II) 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. He postulated the following scheme of reactions:



III

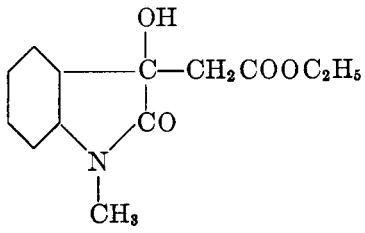
Myers and Lindwall (310) found that Kohn's compound III was not a single substance but a mixture of III with 3,3-diphenyl-1-methyloxindole (IV), formed from III by rearrangement. The reactions of *N*-substituted isatins with



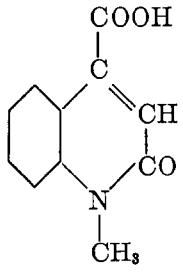
IV

3,3-Diphenyl-1-methyloxindole

Grignard reagents have also been studied by Stollé (381) and by Sumpter (387, 389).



V



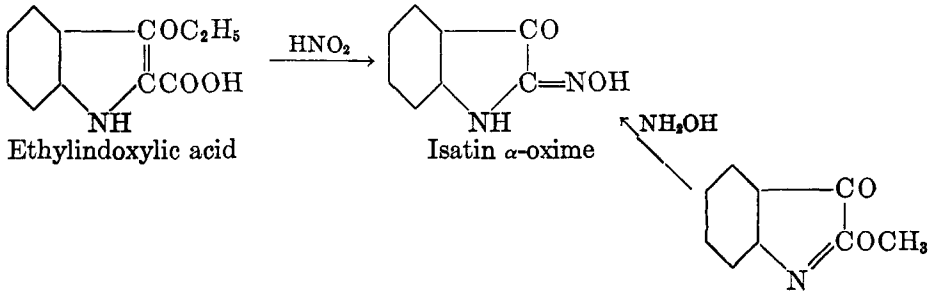
VI

The application of the Reformatsky reaction in the isatin series was made by Myers and Lindwall (309). Isatin does not react in the sense of the Reformatsky reaction, but the *N*-substituted isatins react with zinc and ethyl bromoacetate to give the ethyl ester of (3-hydroxy-1-alkyloxindolyl-3-)acetic acid (V). Hydrolysis of this ester brings about ring opening and subsequent closure to give the quinoline derivative (VI) (compare Aeschlimann (2)).

B. Reaction with hydroxylamine, phenylhydrazine, and aromatic amines

Isatin reacts with hydroxylamine to give isatin β-oxime (23, 45, 59, 129, 130, 159, 243, 249, 280, 414). Isatin β-oxime is identical with nitrosoöxindole and can be prepared by treating oxindole with nitrous acid (24, 46, 129, 148, 149, 243). Direct reaction of isatin and hydroxylamine gives only the β-oxime (249). Isatin dioxime has been prepared from isatin-α-imine and hydroxylamine (335). It is quite readily hydrolyzed and gives isatin β-oxime on heating with aqueous hydrochloric acid. Both carbonyl groups in acetylisatin react directly with hydroxylamine to give the dioxime (249, 359).

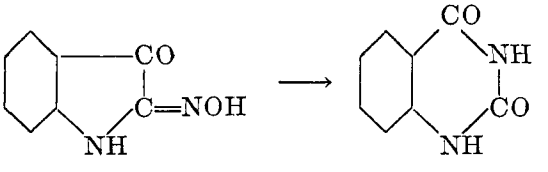
Isatin α-oxime was prepared by Baeyer (21, 22) by the action of nitrous acid on ethylindoxylic acid. Heller (174) obtained the same compound by treating *O*-methylisatin with hydroxylamine.



Ethylindoxylic acid — Isatin α-oxime — *o*-Methylisatin

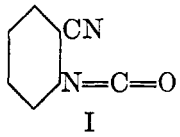
The preparation of the isatin oximes has also been studied by Wieland and coworkers (409, 410). The reduction of both the α- and the β-oximes by zinc dust and acetic acid, followed by treatment with ferrous chloride or nitrous acid, gives isatin.

On standing in alkaline solution both isatin α-oxime and its ethyl ether are converted into benzoyleneurea through a Beckmann rearrangement (174). The



Benzoyleneurea

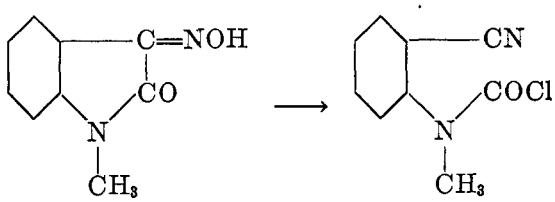
β-oxime does not undergo this rearrangement but with phosphorus pentachloride it gives *o*-cyanophenyl isocyanate (I) (45).



I

o-Cyanophenyl isocyanate

N-Methyl-β-isatoxime similarly gives the chloride of *N*-methyl-*o*-cyanophenylcarbamic acid. Beckmann and Bark (34) obtained *o*-cyanophenyl isocyanate

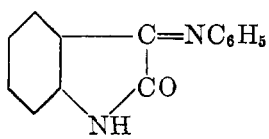


N-Methyl-β-isatoxime

by the action of phosphorus pentachloride and phosphorus oxychloride on *N*-acetylisatin dioxime. Heating isatin β-oxime to 230°C. results in decomposition, yielding *o*-aminobenzonitrile (46). Isatin β-oxime forms insoluble salts with a number of metal ions. Its use as an analytical reagent has been discussed by Hovorka and Sýkora (212, 213).

Isatin reacts with phenylhydrazine to give isatin β-phenylhydrazone (22, 116, 251, 341). The α-phenylhydrazones are prepared by treating the corresponding isatin-*O*-ether or isatin α-chloride with phenylhydrazine (4, 14, 172, 336, 359). Heller has prepared isatin diphenylhydrazone (171) from isatin α-phenylhydrazone and phenylhydrazine. Panaotovic (315) has obtained diphenylhydrazones (osazones) from acetylisatin and its derivatives. Reissert and Hessert (335) have described isatin α-semicarbazone, while the β-semicarbazone was prepared by Marchlewski (281).

Isatin reacts directly with aniline in alcoholic solution to give isatin-β-anilide (II) (36, 106, 236, 304, 313, 325, 327, 349, 380, 396). Isatin-α-anilide (III) was

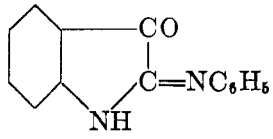


II

Isatin-β-anilide

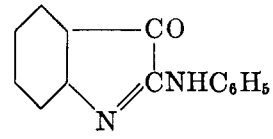
obtained by Sandmeyer in his synthesis of isatin from thiocarbanilide (347). The compound was prepared also by Pummerer and Göttler from nitrosobenzene and indoxylic acid (92, 325, 327). According to Pummerer the compound exists

in two forms (III and IV), the tautomerism having been confirmed by Callow and Hope (68) (compare also references 111 and 343).



III

Isatin-α-anilide

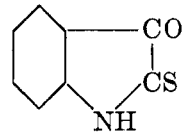


IV

Isatin-α-anilide

Heating isatin-α-anilide with aniline gives isatindianilide (169), which can also be prepared from *O*-methylisatin and aniline. Isatin-α-anilide and phenylhydrazine react to give isatin α-phenylhydrazone (169, 336).

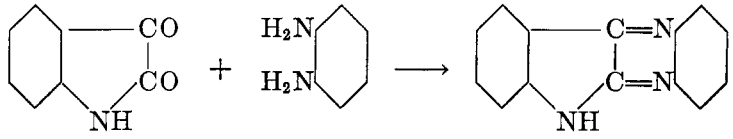
Isatin-α-anilide reacts with hydrogen sulfide in acid solution to give α-thioisatin (V) (347).



V

α-Thioisatin

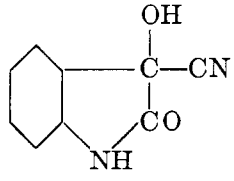
Isatin condenses with *o*-phenylenediamine as shown in the scheme below (61, 247, 281, 283, 360):



Isatin

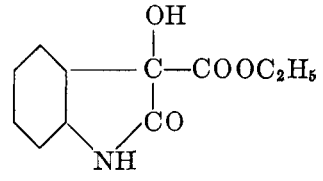
C. Reaction with hydrocyanic acid, ammonia, and aliphatic amines

Heller (198) found that isatin reacts with hydrocyanic acid to give a compound ($C_9H_6O_2N_2$) which he called hydrocyanisatin. Kalb (229) showed that the compound possessed the structure I by converting it into ethyl dioxindole-3-



I

Hydrocyanisatin

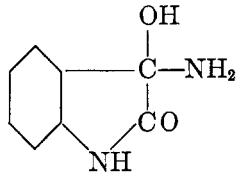


II

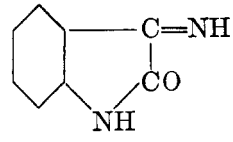
Ethyl dioxindole-3-carboxylate

carboxylate (II) by the action of alcoholic hydrochloric acid. The latter ester was synthesized also from aniline and oxomalonic ester. Martinet (248) found that 1,7-trimethyleneisatin reacted with hydrocyanic acid in the same manner, while the 5,7-diiodo derivative of I was prepared by Kalb and Barrer (230).

Reissert and Hoppmann (336) found that treatment of a cold suspension of isatin in alcohol with dry ammonia results in the separation of colorless crystals of compound III, which decomposes in air to isatin and ammonia. If the treat-



III



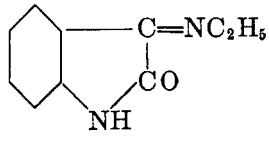
IV

Isatin-β-imide

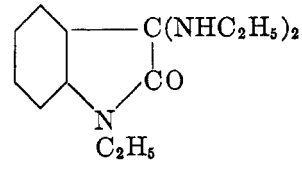
ment with ammonia is interrupted before crystals appear and the mixture is allowed to stand, isatin-β-imide (IV) separates. This reaction has been studied also by Laurent (263), Sommaruga (367, 368), and Jacini (224). Isatin-β-imide gives isatin-β-anilide on treatment with aniline.

Isatin-α-imide has been prepared by Reissert and Hessert (335) from an intermediate product obtained in the reduction of *o*-nitromandelonitrile.

Haslinger (164) found that isatin reacts with alcoholic ethylamine to give isatin-β-ethylimide (V); he also reported the formation of 1-ethyl-3,3-bis-(ethylamino)oxindole (VI) when an excess of diethylamine is used. Just how



V



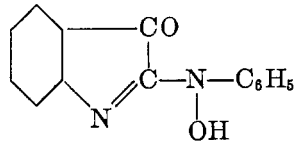
VI

Isatin-β-ethylimide

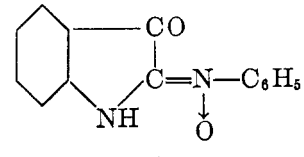
N-alkylation could take place in this reaction remains obscure.

D. Reaction with phenylhydroxylamine

Isatin condenses with β-phenylhydroxylamine to give a product which Rupe formulated as the α-derivative (lactim form) (I). Rupe (342, 343, 344, 345)



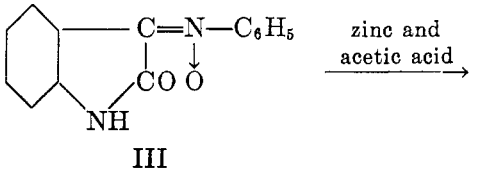
I



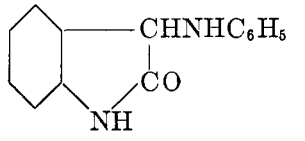
II

concluded that the product was an α-derivative of isatin from the fact that it was formed also from isatin-α-chloride and β-phenylhydroxylamine. It appears that evidence drawn from such a reaction is not always trustworthy, since Naimen and Bogert (311) found that both α- and β-derivatives of isatin can be obtained from isatin-α-chloride, depending on experimental conditions. Heller (184) suggested that Rupe's compound was the β-derivative (III).

Alessandri (5) prepared from *o*-nitrophenylacetylene and nitrobenzene a compound which he formulated as (II) the lactam of I. Alessandri's compound on mild reduction gave isatin-α-anilide and with phenylhydrazine gave isatin-α-phenylhydrazone. On the other hand Rupe's compound gave isatin β-phenylhydrazone (345) with phenylhydrazine and on reduction gave 3-anilinoöxindole (IV), identical with the compound obtained by reducing isatin-3-anilide (68).

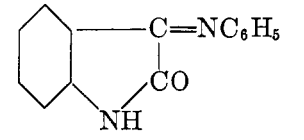


III



IV

3-Anilinoöxindole

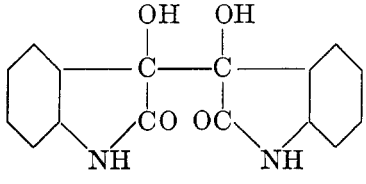


Isatin-3-anilide

The evidence seems conclusive that Rupe's product is the β-derivative (III) and not the α-derivative (I or II), as maintained by Rupe.

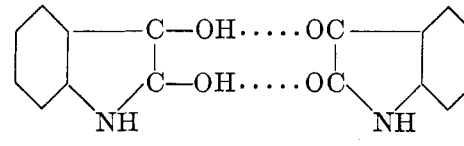
E. Reaction with dioxindole, oxindole, and indoxyl

Isatin condenses readily with dioxindole in the presence of piperidine to give isatide. This same very insoluble substance is very frequently encountered in the reduction of isatin. The most generally accepted structure for isatide is that of isatin pinacol (I) (152, 240, 241, 242, 244, 268, 382, 385, 403). On the other hand Heller has proposed a quinhydrone structure (II) for isatide (174,



I

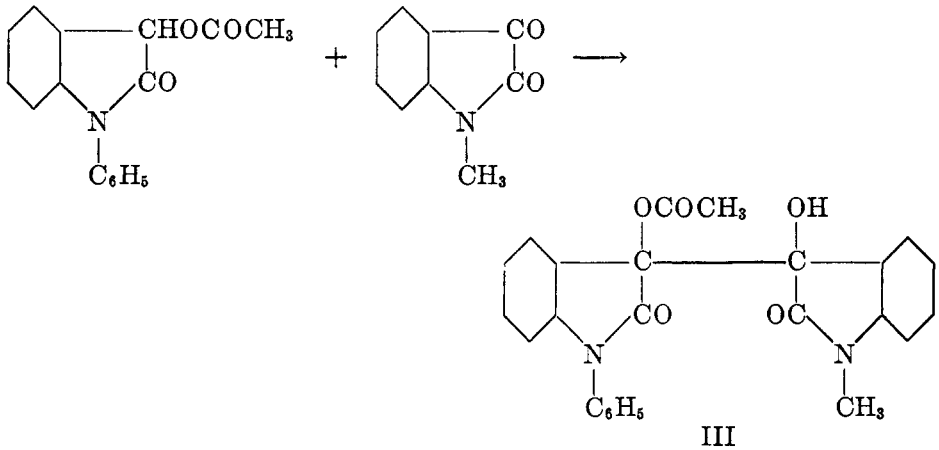
Isatide



II

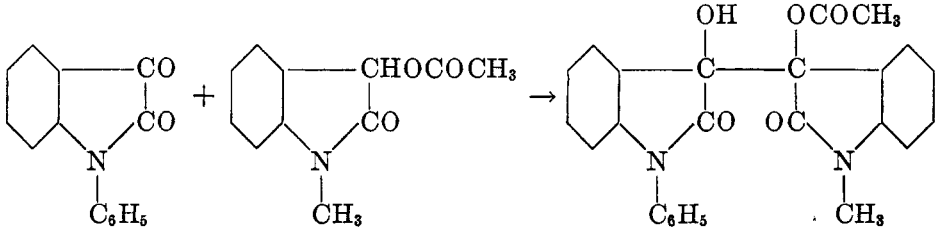
Isatide

186, 197). The problem of the constitution of isatide seems to have been resolved in favor of the isatin pinacol formula by the work of Stollé and Merkle (382). These workers found that 1-alkyl(or aryl)-3-acyldioxindoles were capable of condensing with isatins to give the corresponding acyl isatides. Since the 3-acyldioxindoles condense quite as readily as do the dioxindoles having a free



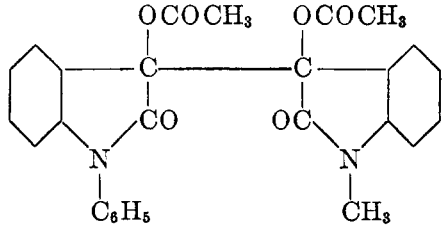
III

hydroxyl group in position 3, the formulation of Heller is untenable. In further support of the pinacol formula Stollé found that compound III and the isomer IV obtained from *N*-phenylisatin and 1-methyl-3-acetyldioxindole gave the same



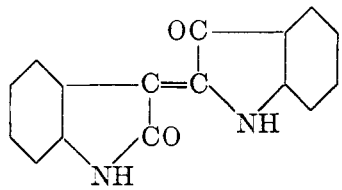
IV

diacetyl derivative (V) when treated with acetic anhydride.



V

Isatin condenses with indoxyl to give indirubin (VI) (51, 111, 123, 312, 398,

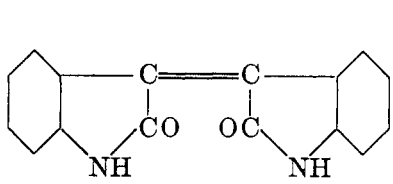


VI

Indirubin

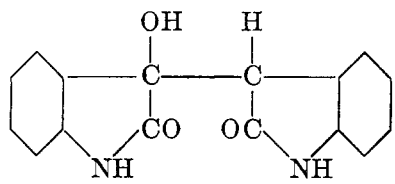
400), which can also be prepared from isatin-α-chloride and oxindole (398).

Isatin and oxindole condense in acid media to give isoindigo (VII) (114, 152, 259, 277, 312, 398, 399, 400, 401, 403) and in the presence of pyridine to give isatane (VIII) (152, 261, 268, 277, 399, 403).



VII

Isoindigo

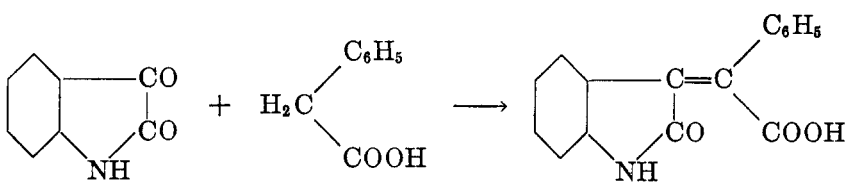


VIII

Isatane

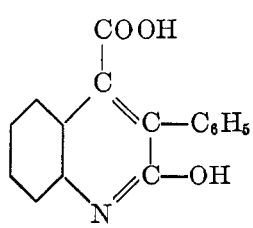
F. Condensation with reactive methylene groups

Isatin was condensed with phenylacetic acid by Gysae (147), who formulated the reaction as shown below. It was found later by Borsche and Jacobs (43)



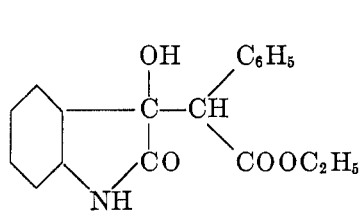
Isatin

that the product was α-hydroxy-β-phenylcinchoninic acid (I), identical with the product obtained by Hübner (214) from isatin and phenylacetic anhydride.

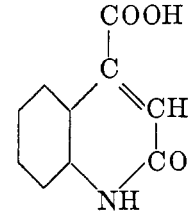


I

Zrike and Lindwall (416) condensed ethyl phenylacetate with isatin, obtaining a product (II) which on hydrolysis gave compound I. Condensation of isatin

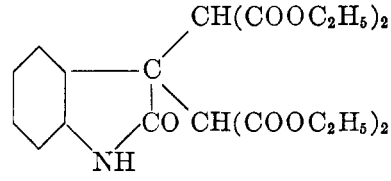


II



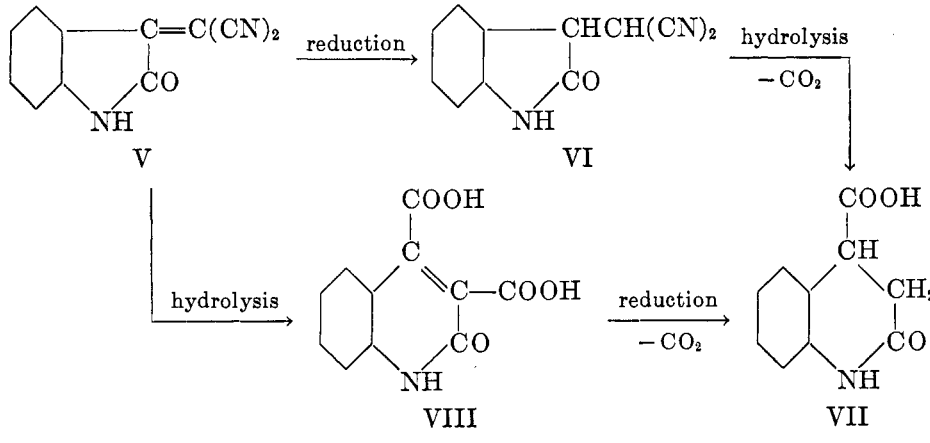
III

with malonic acid gives α-hydroxycinchoninic acid (III, written here as the lactam) (2, 43). The same compound is obtained when 1-acetylisatin is heated with alkali (2, 70, 315). Isatin condenses with diethyl malonate in the presence of diethylamine to give the tetraethyl ester of 3,3-bis(methane-diacid)oxindole (IV) (276).



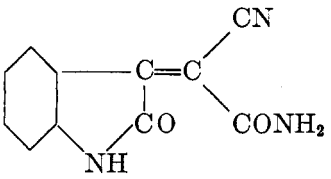
IV

Isatin and malonitrile were condensed by Walter (405), the product being compound V. The latter compound was also prepared by Zrike and Lindwall (416) and reduced to VI, which on hydrolysis gave 1,2,3,4-tetrahydro-2-quinolone-4-acid (VII). Hydrolysis of compound V by concentrated hydrochloric acid gave a dibasic acid, $C_{11}H_7O_5N$, which Zrike and Lindwall regarded as probably having the structure VIII (and which lost carbon dioxide on reduction, giving VII). This dibasic acid did not melt below 340°C., but treatment of its disilver salt with ethyl iodide gave the diethyl ester (IX), m.p. 150–151°C. The same dibasic acid (VIII) was also obtained by the hydrolysis of IV and of the



V VI VIII VII

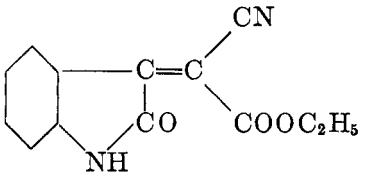
product (X) obtained by condensing isatin with cyanacetamide (416). Isatin also condenses with malonamide and with malonanilide mole for mole to give the



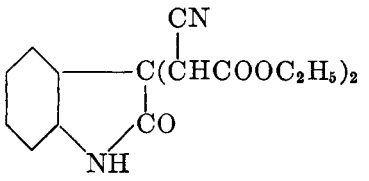
X

corresponding isoindigoid derivatives.

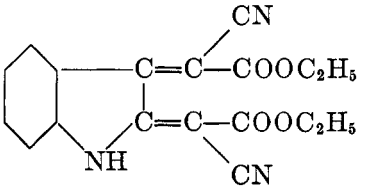
The condensation of isatin with ethyl cyanoacetate has been studied by Hill and Samachson (204), Yokayama (413), and Sumpter (390). The reaction takes place in absolute alcohol in the presence of diethylamine or piperidine to give a product, $C_{18}H_{17}O_5N_3$, which melts at about 116°C. (depending on the rate of heating) with decomposition into ethyl cyanoacetate and compound XI. The condensation product was formulated by Hill and Samachson as XII, while Yokayama thought it to be the hydrate of XIII. There appears to be no analogy in isatin chemistry for the formation of XIII, which should be highly colored. The lack of color and general properties of the compound suggest that formula XII is correct.



XI



XII

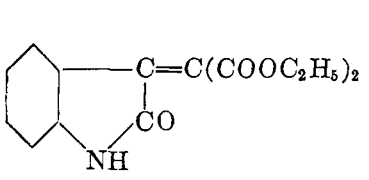


XIII

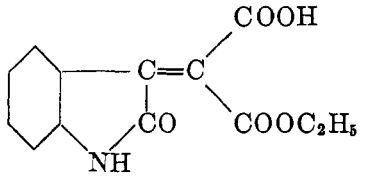
Hill and Samachson found that hydrolysis of XI by concentrated hydrochloric acid gave a product (not analytically pure) melting above 300°C., which on reduction gave VII. More recent work (390) has shown that this hydrolytic product is identical with compound VIII of Zrike and Lindwall, since it is readily converted into the diethyl ester (IX).

Yokayama reported that treatment of XI with concentrated sulfuric acid and absolute alcohol gave XIV (m.p. 149°C.) and XV (m.p. 219°C.). Treatment of XV with sodium hydroxide gave VIII (Yokayama incorrectly reported the melt-

ing point 304–305°C.). Yokayama's compound XIV (m.p. 149°C.) has been found to be identical with compound IX (390).



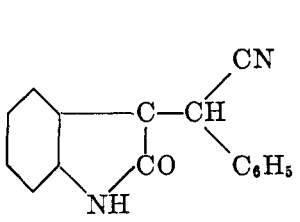
XIV



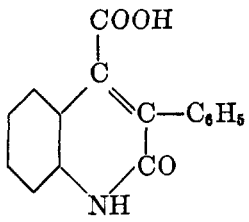
XV.

Compounds having structures XIV and XV should be highly colored, while the actual products are colorless and are better formulated as the diethyl ester (IX) and the monoethyl ester of VIII, respectively.

Analogous results were obtained by Hill and Samachson in condensing 5-iodoisatin and 5,7-dibromoisatin with ethyl cyanoacetate. These same investigators also found that isatin and phenylacetonitrile condense to give 3-(phenylcyanomethyl)-3-hydroxyöxindole (XVI), which on hydrolysis gives 2-quinolone-3-phenyl-4-carboxylic acid (XVII).

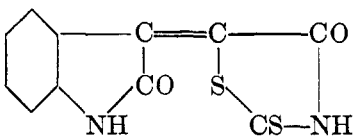


XVI

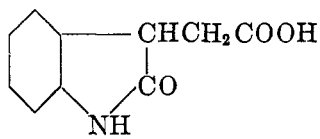


XVII

Gränacher and Mahal (133) obtained β-rhodanal oxindole (XVIII) by condensing isatin and rhodanine. β-Rhodanal oxindole on reduction and hydrolysis



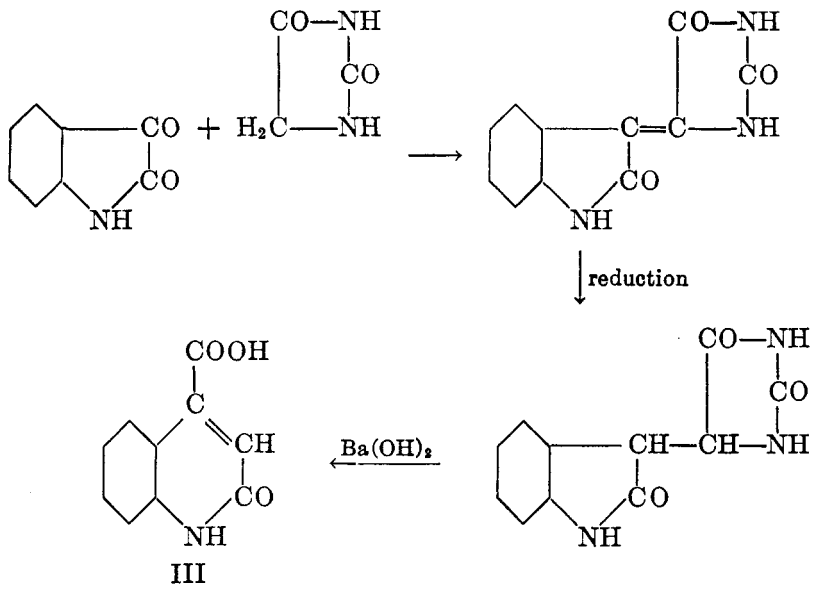
XVIII



XIX

gave a compound which Gränacher described as oxindoleacetic acid (XIX), but which was shown by Hill, Schultz, and Lindwall (206) to be 2-keto-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (VII). The synthesis of rhodanine oxindoles has been studied also by Andreasch (6) and by R. V. Jones and Henze (227), while the condensation of rhodanic acids with isatin and with nitroisatin has been studied by Hann (151) and by H. A. Jones and Hann (226).

The condensation of isatin with hydantoin has been studied by Hill and coworkers (203, 206). The results obtained by these investigators may be summarized in the following scheme:

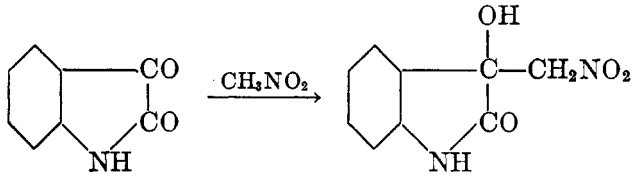


III

Reduction of compound III gave compound VII, which was identical with Gränacher's "oxindole acetic acid". Furthermore, compound III was found to be identical with the product obtained by Camps (70) from acetylisatin and sodium hydroxide and by Borsche and Jacobs (43) from malonic acid and isatin.

The reaction of isatin and hydantoin was also studied by Kotake (248), whose results were not in complete accord with those of Hill, Schultz, and Lindwall (206). The researches were repeated by Henze and Blair (202), who found the work of Hill, Schultz, and Lindwall correct.

Isatin and substituted isatins condense with nitromethane and nitroethane to give aldol-like condensation products (79, 81, 416).

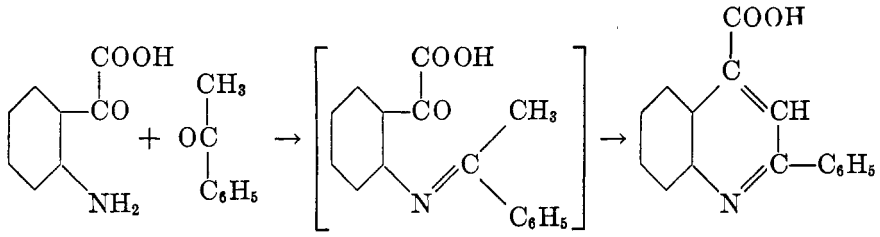


G. Condensation with ketones

Pfitzinger (317, 318, 319, 320) obtained substituted cinchoninic acids when isatin was condensed with methyl ketones in the presence of concentrated potassium hydroxide, the reaction mechanism perhaps being that indicated. Compound I (p. 418) is the drug cinchophen (atophen).

Ethyl methyl ketone condenses with isatin in the Pfitzinger reaction to give both 2,3-dimethylcinchoninic acid (319) and 2-ethylcinchoninic acid (50). The Pfitzinger reaction has been studied by Lindwall and coworkers (48, 102, 103, 274, 275, 416), Henze and coworkers (67, 83, 269), Crippa and Scevola (82), v.

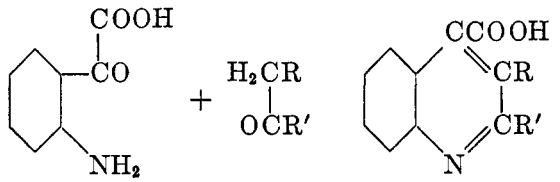
Braun and coworkers (49, 50, 51), and Steinkopf (371), and its applications have been extended to the synthesis of a large number of cinchoninic acids.



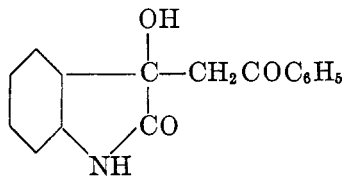
I

Cinchophen

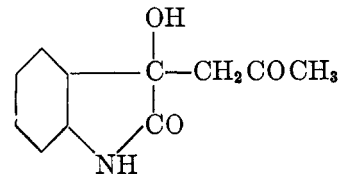
Isatic acid was condensed by v. Walther (406) with iminonitriles, NH=$CRCH_2CN$, to give 2-alkyl-3-cyanocinchoninic acids (406). The reaction was further utilized by Pfitzinger (320) for the synthesis of 2,3-dialkylcinchoninic acids.



Lindwall and coworkers (48, 102, 103, 275, 416) found that acetophenone condenses with isatin under the influence of mildly basic condensing agents to give 3-hydroxy-3-phenacyloxindole (II).



II

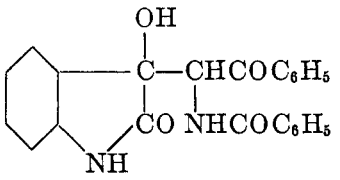


III

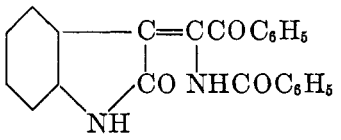
Similarly, acetone condenses with isatin in the presence of diethylamine to give 3-acetonyl-3-hydroxyoxindole (III), and in the presence of concentrated alcoholic potassium hydroxide to give 2-methylcinchoninic acid. 6,8-Dibromo-2-methylcinchoninic acid was prepared similarly from 5,7-dibromoisatin by Lawson, Perkin, and Robinson (267). The aldol-like products, II and III, are readily dehydrated to yield 3-phenacylideneoxindole and 3-acetonylideneoxindole, respectively. Refluxing 3-phenacylideneoxindole with mineral acids causes rearrangement to cinchophen (I) (102, 416). John found that the condensation of benzalacetone with isatin gave 2-styrylquinoline-4-carboxylic acid. Benzylacetone condensed with isatin under the conditions of the Pfitzinger reaction gives 2-phenylethylquinoline-4-carboxylic acid (82).

At room temperature isatin condenses with benzoylphenacylamine (103) in

the presence of piperidine to give 3-hydroxy-3-(α-benzoylamino)phenacyloxindole (IV), while at higher temperature the product is 3-(α-benzoylamino)phenacylideneoxindole (V). Reduction of V and subsequent hydrolysis of the reduction



IV

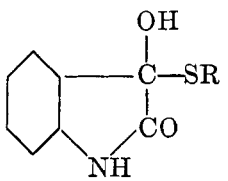


V

product gave cinchophen (I).

H. Reaction with mercaptans

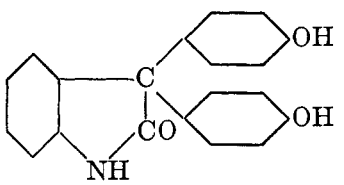
Baumann (33) and Schönberg, Schütz, Arend, and Peter (354) found that isatin and acetylisatin react with mercaptans to give 1:1 addition products probably having the structure shown below (I):



I

I. Condensation with phenol, toluene, and tertiary amines

Baeyer and Lazarus (25, 26) and subsequently Liebermann and Danaila (272) found that isatin condenses with toluene, phenol, resorcinol, anisole, α-naphthol, and aromatic secondary and tertiary amines to give oxindole derivatives of the type of phenolisatin (3,3-bis(4′-hydroxyphenyl)oxindole) (I). In general it was



I

Phenolisatin

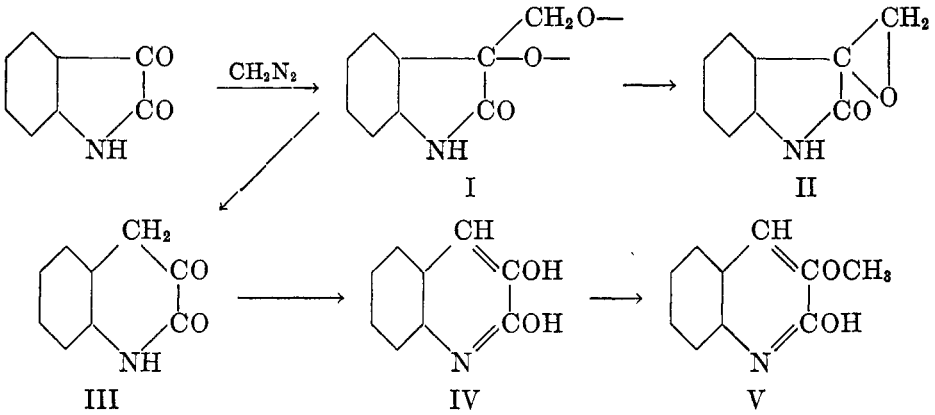
assumed, in agreement with Baeyer, that these condensation products were 3,3-derivatives of oxindole (on the contrary compare Sen (362)), but it remained for Inagaki to establish definitely their structure (216, 217, 218, 219, 220, 221). The condensation of α-naphthol with isatin has been studied by Candea (71), Steopoe (375), and Gabel and Zubarovskiĭ (127).

Phenolisatin (I) and its diacetyl derivative, isacene, have found use pharmacologically as mild purgatives (35, 56, 73, 98, 365, 407).

A number of condensation products of *N*-benzylisatinsulfonic acid with various phenols are said to be of value as mothproofing agents (56).

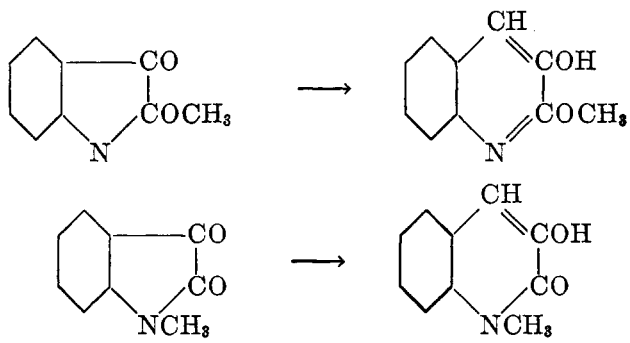
J. Reaction with diazomethane and hydrazoic acid

The reaction of isatin with diazomethane was first studied by Heller (180, 191), who found the principal product to be 2,3-dihydroxyquinoline (III or IV). In his second paper on this subject Heller reported obtaining a second product, possibly the isoquinoline derivative. The reaction was later studied by Arndt and coworkers (9, 10). Arndt assumed that the diazomethane reacts with the β-carbonyl group of isatin to give an addition product (I), which then rearranges to give either the ethylene oxide (II) or 2,3-dihydroxyquinoline (III or IV). Arndt reports increasing yields of V as the reaction period is increased. The



reactions of a number of substituted isatins with diazomethane have been studied by Heller (191). The reaction of 1-hydroxyisatin with diazomethane was also investigated by Arndt (9).

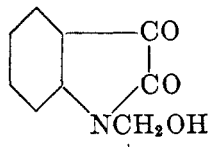
This reaction has likewise been investigated by Ault, Hirst, and Morton (13), who prepared quinoline derivatives from isatin, *O*-methylisatin, and *N*-methylisatin.



Caronna (72) found that isatin and *N*-acetylisatin react with hydrazoic acid to give anthranilamide, while *N*-ethylisatin reacts similarly to give *o*-ethylaminobenzamide.

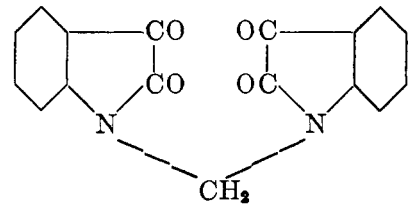
K. Reaction with formaldehyde and phenyl isocyanate

Reissert and Händeler (334) found that isatin and formaldehyde react to give *N*-hydroxymethylisatin (I) and *N*,*N*′-methylenediisatin (II).



I

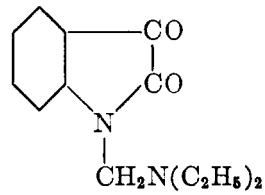
N-Hydroxymethylisatin



II

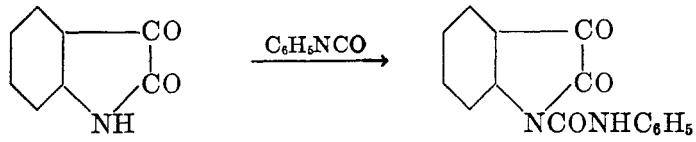
N,*N*′-Methylenediisatin

Einhorn and Göttler (105) treated isatin with formaldehyde and secondary amines, obtaining thereby derivatives of the type of *N*-diethylaminomethyl isatin (III).



III

Gumpert (145) and Goldschmidt and Meissler (132) found that the imino hydrogen atom of isatin reacts with phenyl isocyanate in the usual manner.



L. Table of condensation reactions

A complete listing of the formation of all of the indigoid dyes and other condensation products which have been prepared from isatin and isatin derivatives would require many pages. A comprehensive listing of such reactions has been given by Heller in his review (165). In view of this fact no attempt is made to repeat that listing here. In table 1 will be found a listing of the references to those condensation reactions of isatin and derivatives which have been studied since the publication of Heller's review and which are not discussed elsewhere in this article.

TABLE 1

Condensation reactions of isatin and isatin derivatives

SUBSTANCE REACTING WITH ISATIN OR AN ISATIN DERIVATIVE	REFERENCE
Acetophenone	(415)
Aniline	(54)
o-Anisidine	(54)
Amylcresol	(99, 100)
Amylphenol	(99)
2-Benzylbenzimidazole	(395)
o-Benzylphenol	(98)
o,o'-Biphenol	(98)
Bromoacetophenone	(274)
3-Chloro-2-hydroxybiphenyl	(394)
Cryptopyrrole	(322)
Cryptopyrrolidine	(138)
2,3-Diaminoquinoxaline	(104)
Dihydroisoindole	(138)
Diketopiperazine	(206)
Dimethylaniline	(381)
Dimethylalkoxythionaphtheneones	(120)
2,4-Dinitrophenylhydrazine	(340)
Dithienyl	(370)
1-Ethyloxindole	(380)
Guaiacol	(65)
Hemopyrrolidine	(138)
Hydrazine	(363)
m-Hydroxybiphenyl	(394)
o-Hydroxybiphenyl	(394)
8-Hydroxyquinoline	(128)
Hydroxyproline	(137)
Hydroxythionaphthene	(55)
1,3-Indandione	(117)
p-Iodoacetophenone	(308)
α-Mercaptoacetanilide	(358)
p-Methoxyacetophenone	(274)
5-Methoxy-1-hydroxynaphthalene	(121)
2-Methylbenzimidazole	(395)
2-Methylbenzothiazole	(311)
2-Methyl-6-bromobenzothiazole	(311)
3-Methylcyclohexylacetophenone	(49)
5-Methyl-3-hydroxythionaphthene	(142)
7-Methyl-3-hydroxythionaphthene	(141)
4-Methyl-3-hydroxythionaphthene	(140)
Methylisopropylphenol	(64)
α-Methylpyrrolidine	(138)
α-Naphthol	(127)
2,1-Naphthothioindoxyl	(57)
α-Naphthyl ethyl ether	(286)
p-Nitrophenylhydrazine	(321)
Opsopyrrolidine	(138)
Phenyl esters of fatty acids	(223)

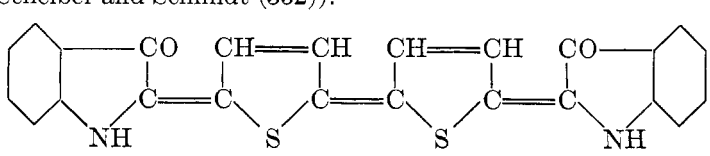
TABLE 1—*Continued*

SUBSTANCE REACTING WITH ISATIN OR AN ISATIN DERIVATIVE	REFERENCE
1-Phenyloxindole	(381)
o-Phenylphenol	(98)
Phyllopyrrole	(322)
Phyllopyrrolidine	(322)
Proline	(138)
5-Propyl-2-hydroxybiphenyl	(394)
Pyridine	(40, 139)
Pyrrole	(322, 324)
Quinoline	(412)
Quinolyl-4-acetonitrile	(41)
Quinoxalyl-2-acetonitrile	(42)
Resacetophenone	(60)
Resorcinol	(63)
Thioindoxyl	(161)
α-Thiol-*N*-phenylacetamide	(358)
Thionaphthene	(208)
Thymol	(99)
o-Toluidine	(58)
1-*o*-Tolylcarbohydrazide	(143)
5,6,7-Trichloro-3-hydroxythionaphthene	(55)
Urea	(62)
Xanthydrol	(215)

V. INDOPHENIN AND PYRROLE BLUE

In 1879 Baeyer (19) obtained a blue dye, indophenin, by treating isatin with concentrated sulfuric acid and crude benzene. V. Meyer (301) found that pure benzene did not give the indophenin reaction and that the formation of the dye was due to the presence of a new substance, thiophene, C_4H_4S. Meyer also found that other diketones containing the group —CO—CO— gave the reaction. The indophenin reaction was also studied by Bauer (29) and by Liebermann and coworkers (270, 271, 273) without any definite formulation of structure or mechanism of reaction being established. Liebermann and Krauss regarded indophenin as an α-derivative of isatin (see also Ciamician and Silber (74)).

Schlenk and Blum (350), from studies of the formation of indophenin and mesoxphenin (from mesoxalic ester and thiophene) concluded that indophenin should be represented by formula I. They were able to show that the α-carbon atom of thiophene is involved in the union, since β-methyl derivatives of thiophene still give the indophenin reaction, while α-methyl derivatives do not (see also Scheiber and Schmidt (352)).

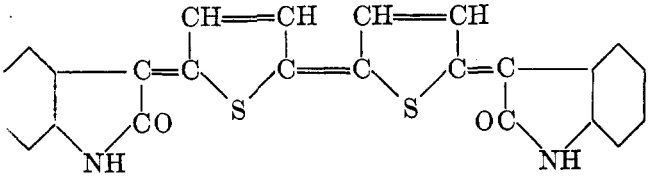


I

Indophenin

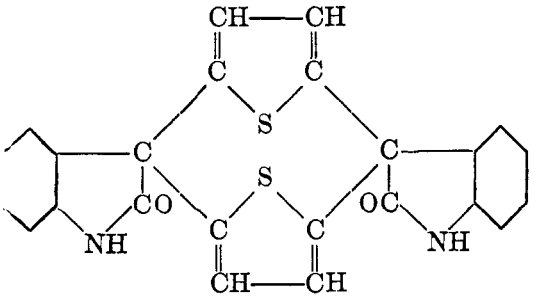
Both Heller (184) and Steinkopf (372) objected to this formulation on the grounds that isatin normally reacts through the β-carbonyl group and that the α-derivatives are obtained by indirect means only. Further, it has been shown (175) that β-derivatives of isatin do not give the indophenin reaction. On the other hand, isatin α-oxime and its ethyl ether (175) and certain other α-derivatives having the β-carbonyl group free do give the reaction (173, 335).

Both Heller (165, page 164; 184, 185) and Steinkopf (369, 370, 372) regard indophenin as a β-derivative of isatin. Heller assigned formula II to the compound, while Steinkopf first suggested formula III but later accepted the Heller formula as correct (369).



II

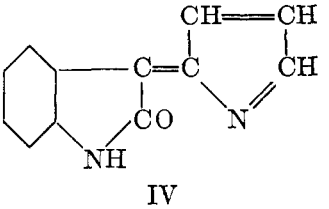
Indophenin



III

Indophenin

Similarly Steinkopf (373) regards the blue dye obtained from pyrrole and isatin by Liebermann (270, 271), Ciamician and Silber (74), and Meyer and Stadler (302) as analogous to indophenin (II) in structure. On the other hand, Pratesi (322, 324) regards pyrrole blue as having the structure IV. Molecular weight determinations by Steinkopf (373) indicate a formula having twice the molecular

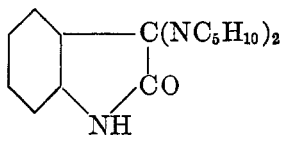


IV

Pyrrole blue

weight of IV for pyrrole blue. However, Pratesi has declined to accept the conclusions of Steinkopf, regards the double molecular weight to be due to association in solution, and holds to formula IV. In a later paper Steinkopf (374) has given further evidence in support of his formulation, and it must be stated that the weight of the evidence seems to be in his favor.

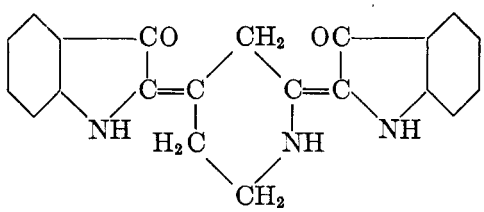
Isatin condenses with piperidine (270, 271, 356) to give two products, isatin-monopiperidide (thought to be an α-derivative by Liebermann (270)) and isatin-dipiperidide (V). The latter compound is changed on heating to isatin blue,



V

Isatindipiperidide

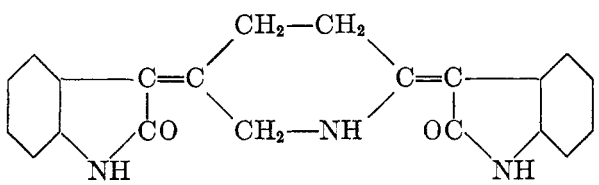
to which Liebermann assigned the formula VI. The formula (VII) suggested



VI

Isatin blue

by Heller (165, page 153), which represents the dye as a β-derivative of isatin, is more acceptable than the Liebermann formula (VI).



VII

Isatin blue

VI. CATALYTIC RÔLE IN CERTAIN ORGANIC REACTIONS

Traube (393) reported that α-aminophenylacetic acid is converted into benzaldehyde in good yield when the acid is heated with isatin in aqueous solution. Benzylamine also gave benzaldehyde in good yield on similar treatment. Abderhalden (1) has reported similarly that isatin reacts at room temperature and above with amino acids to give aldehydes with one less carbon atom. In a series of papers on organic catalysts, Langenbeck (252, 253, 254, 255, 256, 257,

258) has reported that isatin and certain isatin and oxindole derivatives possess enzyme-like activity, particularly in the dehydrogenation of amino acids.

Menke (296) has reported that isatin can be used as a microchemical reagent. The suggested utilization of isatin β-oxime as an organic precipitant (212, 213) has been mentioned.

Knecht and Hibbert (234) have reported that isatin can be determined quantitatively by titration with titanous chloride.

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