Synthesis and Reactions of Certain 3-Formyl- and 3-Cyanooxindoles[1]

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On reaction with ethylene glycol under acid catalysis, 3-formyl-1-methyloxindole (**2**) gives a separable mixture of the ethylene acetal and its open-chain tautomer (**4**), both of which are readily cleaved by either acid or base. 3-Ethoxymethylene-1-methyloxindole (**5**) with N-bromosuccinimide undergoes bromination in the 5 position followed by addition of succinimide to the exocyclic double bond to give **8** which undergoes stepwise hydrolysis. Compound **2** with N-bromosuccinimide yields 3-bromo-3-formyl-1-methyloxindole (**11**) which undergoes hydrolysis to 1-methyldioxindole or 1,1′-dimethylisoindigo. Compound **11** with ethanedithiol gives the expected thioacetal which, on heating or with base, decomposes to **2** and 1,2,5,6-tetrathiocane. 3-Cyanoethoxycarbonylmethyleneoxindole and its 1-methyl derivative readily add hydrogen cyanide to the exocyclic double bond to give compounds of the type of **18** which undergo hydrolysis, partial decomposition, and rearrangement with concentrated hydrochloric acid to give dihydro-2-quinolone-4-carboxylic acids. Knoevenagel condensation of isatin with *t*-butyl cyanoacetate gave geometrical isomers of **22a**; N-methylisatin gave a single compound. Addition of hydrogen cyanide to **22a** and **22b** and subsequent pyrolysis gave the 3-cyano-3-cyanomethylisatins, the nitrile groups of which could not be reduced to aldehyde with aluminum hydrides.

In connection with work currently under way in these laboratories, 3-formyl-1-methyloxindole-3-acetaldehyde (**1**) was required. Although the desired goal has not been achieved, in the course of exploration of several possible routes to **1**, we have made a number of observations which are not without interest in connection with the chemistry of oxindole derivatives and which are presented in this communication.

When 3-formyl-1-methyloxindole (**2**)[2] was allowed to react with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid; the ethylene acetal **3** was obtained in 3.2% yield and the major product of the reaction (70.2%) was the tautomeric 3-(2′-hydroxyethoxy)methylene-1-methoxindole (**4**). The infrared spectrum of **4** shows hydroxyl and ethylene absorption. Compounds **3** and **4** are interconvertible in the presence of acid. In addition, **3** and **4** are also attacked by base with regeneration of **2**.

When **2** was allowed to react with ethyl orthoformate in the presence of acid, the expected acetal was not formed. Rather, the product was the known 3-ethoxymethylene-1-methyloxindole (**5**)[3] (see Scheme I).

With ethanedithiol 3-bromo-3-formyl-1-methyloxindole (**11**) readily gave the ethylene thioacetal **6**. When **6** was heated in dimethylformamide or on reaction with sodium acetylide in liquid ammonia, decomposition to **2** and 1,2,5,6-tetrathiocane (**7**) ensued.

It thus was apparent that stabilization of the aldehyde tautomer of **2** by acetal formation preparatory to nucleophilic substitution in the 3 position with bromoacetal was not effective.

It has been reported[4] that certain vinyl ethers, *e.g.*, 3-ethyl-5,6-dihydropyran, undergo addition of N-bromosuccinimide (NBS) to the double bond. Therefore, addition of NBS to **5** was investigated. However, bromination occurred in the 5 position of the oxindole ring followed by addition of succinimide to the exocyclic double bond to give **8**. The structure assigned to **8** was shown by degradation of **8** to **10** and by an alternate synthesis based on the formylation procedure of Arnold.[5] (See Scheme II.)

Bromination of acetanilide, which can be considered to be structurally analogous to **5**, with NBS in water[6] or in carbon tetrachloride[7] results in the formation of *p*-bromoacetanilide. It appears, therefore, that the rate of nuclear bromination of **5** must be relatively faster than the rate of addition of NBS to the vinyl ether. On the other hand, 1-methyloxindole is brominated in the **5** position with bromine in aqueous or acetic acid solution, but in carbon tetrachloride the 3,3-dibromo derivative is formed.[8]

In contrast to the behavior of **5** with NBS, **2** undergoes bromination in the 3 position with no nuclear bromination with one equivalent of the reagent to give 3-bromo-3-formyl-1-methyloxindole (**11**). The bromine and formyl group in **11** are labile and can easily be removed. In hot water simple hydrolysis occurs with formation of 1-methyldioxindole (**12**). However, in the presence of base the reaction takes a different course and 1,1′-dimethylisoindigo (**13**) is the product. Although **13** results from the action of aqueous sodium hydroxide solution on **11**, water is not required; compound **13** was also obtained when sodium acetylide in liquid ammonia was the reagent. Confirmation of the structure assigned to **13** was provided by comparison with an authentic sample prepared by application of known reactions for the synthesis of isoindigo to the preparation of its 1,1′-dimethyl derivative *via* **14**.[9] (See Scheme III.)

The mechanisms by which **12** and **13** are formed must be different. Formation of **12** obviously results from a simple displacement of the bromine atom and formyl group in **11**. However, **12** cannot be an intermediate in the formation of **13** since it is oxidized to 1-methylisatin in the presence of base. It is suggested that **13** is formed *via* an intermediate carbene (**15**). The formation of **13** from the tosylhydrazone of 1-methylisatin (**16**) on heating the latter with sodium ethylene glycolate, a procedure which has been demonstrated to generate carbenes,[10] supports this interpretation.

(1) The work here reported was supported by U. S. Public Health Service Research Grant No. HE-04179 from the National Heart Institute to the University of Michigan.

(2) P. L. Julian, J. Pikl, and D. Boggess, *J. Am. Chem. Soc.*, **56**, 1797 (1934).

(3) E. Wenkert, A. K. Bose, and T. L. Reid, *ibid.*, **75**, 5514 (1953). Compound **5**, first prepared by Julian, Pikl, and Boggess[2] by reaction of the sodium salt of **2** with ethyl iodide, was originally assigned the structure of 2-ethoxy-3-formyl-1-methylindole.

(4) R. Paul and S. Tchelintcheff, *Compt. Rend.*, **236**, 1968 (1953).

(5) Z. Arnold, *Chem. Listy*, **52**, 2013 (1958).

(6) M. F. Abdel-Wahab and M. Z. Barakat, *Monatsh. Chem.*, **88**, 692 (1957).

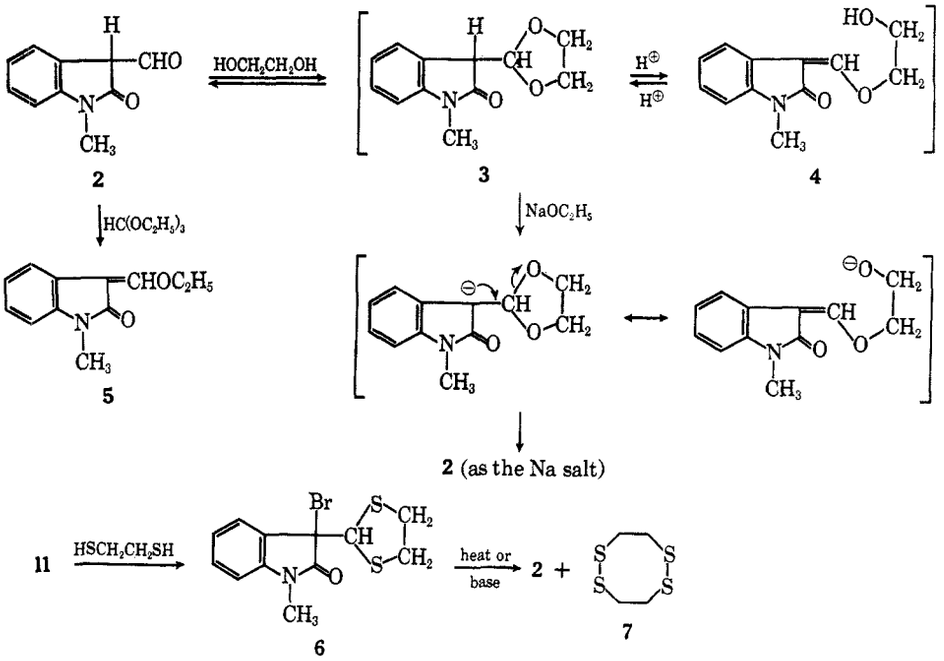
(7) Ng. Ph. Buu-Hoï, *Ann. Chem.*, **556**, 1 (1944).

(8) P. L. Julian, E. W. Meyer, and H. C. Printy, in "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 183.

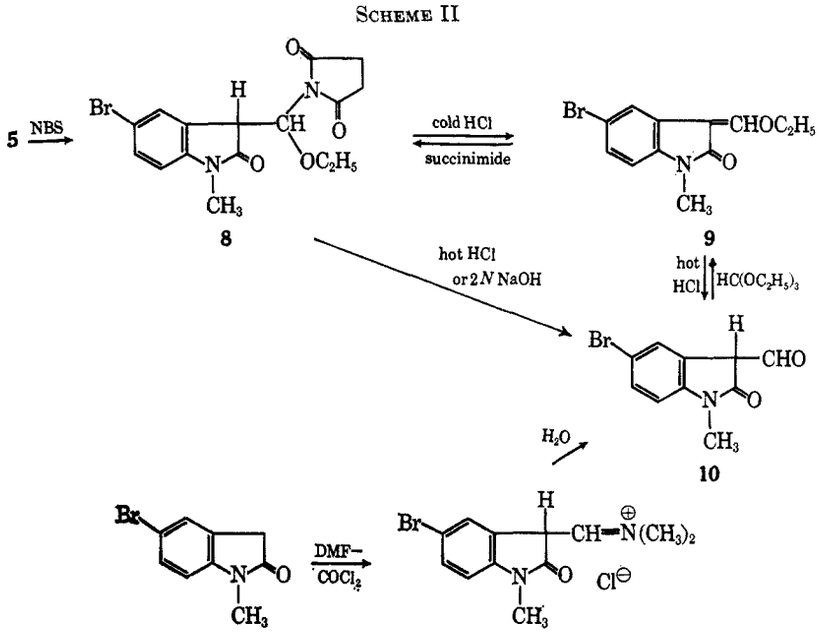
(9) A. Wahl and W. Hansen, *Compt. Rend.*, **178**, 393 (1924); A. Wahl and T. Faivret, *Ann. Chim.* (Paris), [10] **5**, 314 (1926).

(10) L. Friedman and H. Schechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959).

SCHEME I



SCHEME II



We have also investigated a possible route to **1** by selective reduction of 3-cyano-3-cyanomethyloxindole derivatives. Knoevenagel condensation of isatin and 1-methylisatin with ethyl cyanoacetate[11] gave **17a** and **17b**, respectively, which on addition of hydrogen cyanide gave the dinitriles **18a** and **18b** in substantially quantitative yields. Attempts to remove the ethoxycarbonyl group from **18a** and **18b** selectively were unsuccessful. Hydrolysis with concentrated hydrochloric acid in acetic acid resulted in partial decarboxylation and rearrangement to the known dihydro-2-quinolone-4-carboxylic acids (**19a** and **19b**).[13] Analogous rearrangements have been noted previously.[2] Hydrolysis of **18b** with ethanolic hydrochloric acid gave a 5.2% yield of a high melting compound of empirical formula $C_{12}H_{10}N_2O_3$ for which the most probable structure is **20.** Assignment of structure **20** rather than the alternative **21** is supported by the nmr spectrum in dimethyl sulfoxide which showed a singlet at τ 7.18 ($N-CH_3$) and a broadened singlet at 7.05 (CH_2) [$(CH_3)_4Si$ as internal reference] in addition to the aromatic protons. Integration was consistent with this interpretation.

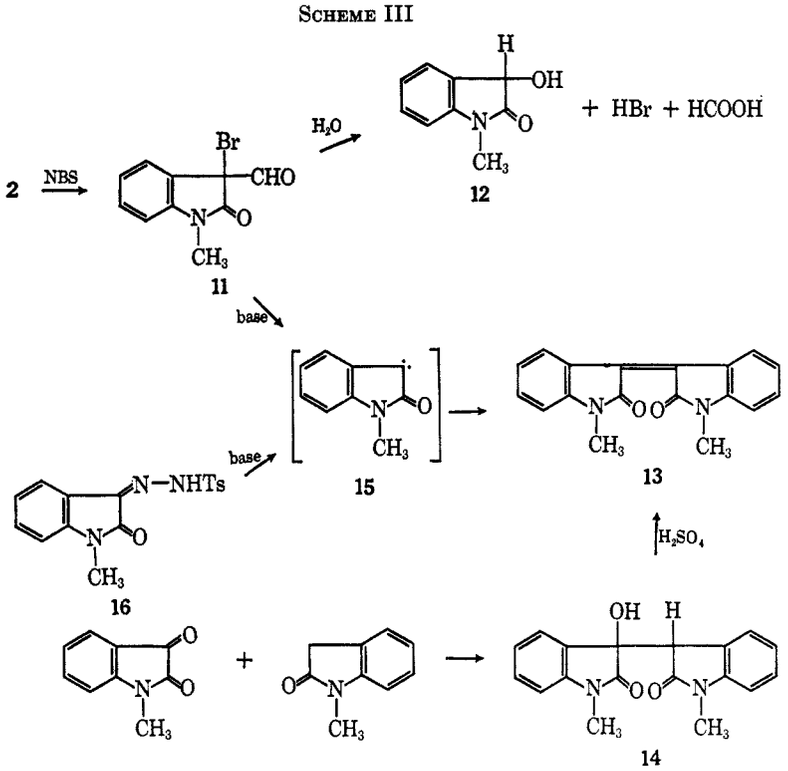
When isatin was allowed to react with 1 equiv of *t*-butyl cyanoacetate with piperidine acetate as catalyst, three products were obtained. Two of them had the expected empirical formula, $C_{15}H_{14}N_2O_3$, corresponding to **22a**. The color and melting points of the two differed considerably. Inasmuch as they are not polymorphic crystal modifications (the infrared spectra in chloroform solution differed), but since they gave the same addition product with hydrogen cyanide (**23a**), they undoubtedly are geometrical isomers. Jones and

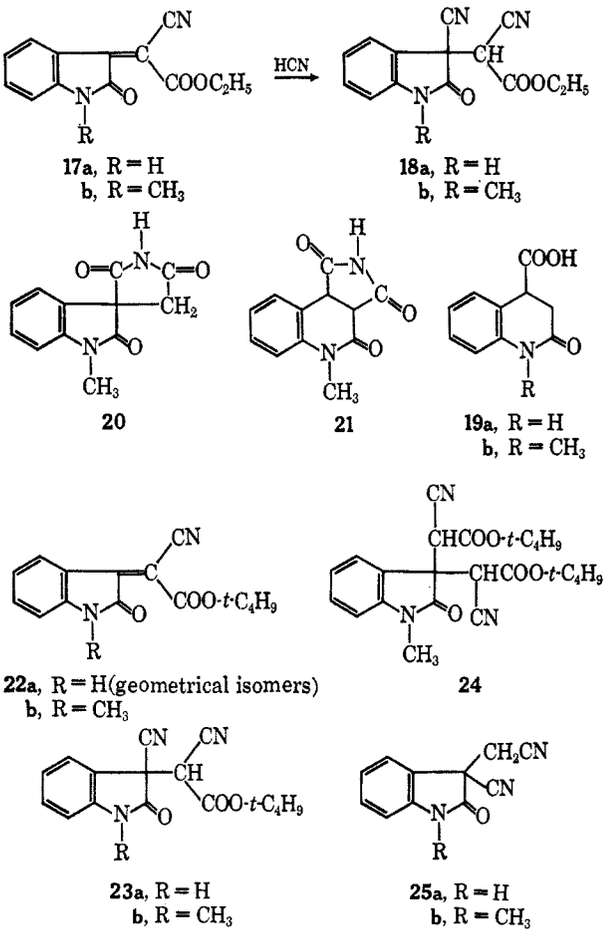
(11) J. Harley-Mason and R. F. J. Inglesby, *J. Chem. Soc.*, 3639 (1958). The earlier confusion concerning these reactions has been resolved since this work was completed by Jones and Rae.[12]

(12) G. Jones and W. J. Rae, *Tetrahedron*, **22**, 3021 (1966).

(13) J. A. Aeschlimann, *J. Chem. Soc.*, 2902 (1926).

SCHEME III





Rae[12] have assigned a structure analogous to **17a** to the product of the reaction of ethyl cyanoacetate with isatin on the basis of nmr data and have demonstrated the formation of geometrical isomers in the Knoevenagel condensation of 1-tetralone with cyanoacetamide. The third compound, **24**, isolated was the result of addition of a second molecule of *t*-butyl cyanoacetate to **22a**.

On the other hand, condensation of 1-methylisatin with *t*-butyl cyanoacetate gave but a single product, **22b**, which on addition of hydrogen cyanide gave **23b**.

Pyrolysis of the dinitriles, **23a** and **b**, gave the desired dinitriles **25a** and **25b**. Reduction of **25b** with sodium diisobutylaluminohydride[14] or with "lithium triethoxyaluminohydride,"[15] reagents by which nitriles have been reduced to aldehydes, failed to yield the desired dialdehyde. In one experiment a crude product which showed nitrile absorption in the infrared was obtained, but no satisfactory means of purification could be found.

Experimental Section[16]

Reaction of 1-Methyl-3-formyloxindole with Ethylene Glycol.—1-Methyl-3-formyloxindole[2] (8.75 g, 0.05 mole) and ethylene glycol (6.2 g, 0.1 mole) were refluxed in 250 ml of benzene containing 0.2 g of *p*-toluenesulfonic acid in a flask equipped with a Dean–Stark trap for separation of entrained water. After 6 hr solution was complete and most of the benzene was removed by distillation. On addition of petroleum ether (60–70°) to the concentrate, an oil separated which crystallized on scratching and refrigeration overnight. The crude mixture of **3** and **4** was collected and washed with dilute sodium bicarbonate solution and water to give 8.1 g (74%).

1-Methyl-3-formyloxindole Ethylene Acetal (3).—The crude mixture obtained above was extracted with 200 ml of hot petroleum ether (90–100°); the extract was treated with decolorizing carbon and concentrated to dryness under reduced pressure leaving 0.35 g (3.2%) of oily residue which crystallized slowly on standing. Recrystallization from petroleum ether gave colorless crystals, mp 110°. The infrared spectrum (amide absorption at

(14) L. I. Zakharkin and V. V. Gavrilenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2245 (1960); *Chem. Abstr.*, **55**, 14352*i* (1961).

(15) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **86**, 1085 (1964).

(16) All melting points are uncorrected and were taken on a Thomas–Hoover Unimelt apparatus. Infrared spectra were taken on a Perkin-Elmer Infracord Model 137 spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrophotometer. Microanalyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich.

1705 and ether absorption at 1130 cm^{-1}), taken as a Nujol mull, and the nmr spectrum in $CDCl_3$ were consistent with the acetal structure.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 5.92; N, 6.41.

3-(2'-Hydroxy)ethoxymethylene-1-methyloxindole (4).—The residue (7.7 g, 70%), insoluble in petroleum ether, from the above extraction on recrystallization from 600 ml of carbon tetrachloride gave colorless shiny crystals of **4**, mp 124–125°. The infrared spectrum showed hydroxyl absorption at 3400, C=C absorption at 1605, ether absorption at 1100, and amide absorption at 1705 cm^{-1} (Nujol mull). The nmr spectrum in $CDCl_3$ was consistent with the assigned structure.

Anal. Found: C, 65.70; H, 5.92; N, 6.49.

Conversion of 3 to 4.—A solution of 360 mg of **3** in 5 ml of dry benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 6 hr. Addition of 30 ml of petroleum ether (60–70°) precipitated **4** which was identified by its infrared spectrum.

Conversion of 4 to 3.—A solution of 4.9 g of **4** in 25 ml of benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 30 min, washed with dilute sodium bicarbonate solution, and taken to dryness under reduced pressure. Extraction of the residue with 100 ml of hot petroleum ether and concentration of the extract to 15 ml gave a small amount of **3** on cooling. Identification was made by infrared spectroscopy.

Reaction of 4 with Base.—A solution of 1.1 g (0.005 mole) of **4** in sodium ethoxide prepared from 0.11 g of sodium and 10 ml of absolute ethanol was heated for 10 min and concentrated to dryness under reduced pressure. On trituration with very little absolute ethanol the dark residue dissolved. On scratching, the sodium salt of **2** crystallized. Recrystallization from 98% ethanol gave the sodium salt as the hemihydrate (hydroxyl absorption in the infrared) from which the water could not be removed in 5 hr at 138° (1 mm). The infrared spectrum was identical with that of an authentic sample.

When **3** was treated similarly with sodium ethoxide, the sodium salt of **2** was also obtained.

Anal. Calcd for $C_{10}H_8NNaO_2 \cdot O \cdot 5H_2O$: C, 58.22; H, 4.40; N, 6.79; Na, 11.14. Found: C, 58.69; H, 4.42; N, 6.70; Na, 11.02.

3-Ethoxymethylene-1-methyloxindole (5).—A mixture of 7 g (0.040 mole) of **2**, 7.2 g (0.048 mole) of ethyl orthoformate, and 4 g of ethanol containing 1 drop of sulfuric acid was refluxed for 1.5 hr. After removal of excess ethyl orthoformate and ethanol under reduced pressure, the residue was dissolved in a few milliliters of ethyl acetate. On addition of 300 ml of petroleum ether (60–70°) and cooling, 5.69 g (70%) of **5** crystallized. The crude product was contaminated by a yellow impurity which was removed by recrystallization from petroleum ether with charcoal. The melting point and mixture melting point with an authentic sample of **5**[2] were identical as were the infrared spectra.

3-Bromo-3-formyl-1-methyloxindole Ethylene Thioacetal (6).—To a solution of 2.54 g (0.010 mole) of **11** in 200 ml of warm acetic acid, 2 ml of ethanedithiol was added. A yellow solid separated almost immediately. After addition of 400 ml of ether the mixture was left at 0° for 2 hr and 2.31 g (70%) of **6** was collected and washed thoroughly with ether. No suitable solvent could be found for recrystallization of the thioacetal. It decomposed at 202° and was analytically pure as obtained.

Anal. Calcd for $C_{12}H_{12}BrNOS_2$: C, 43.64; H, 3.66; Br, 24.20; N, 4.24; S, 19.42. Found: C, 43.47; H, 3.78; Br, 24.20; N, 4.24; S, 19.51.

Cleavage of 6.—When 3.3 g (0.010 mole) of **6** was boiled for 5 min with 10 ml of dimethylformamide, the substance dissolved in part and the remainder formed an almost insoluble oil. Ethanedithiol was evolved as judged by odor. After cooling, the oil and solution were worked up together. The oil was extracted twice with hot dimethylformamide. After washing the insoluble oil with chloroform and ether, it crystallized as light yellow material (0.92 g, 50%) which on recrystallization from nitrobenzene melted at 152–154° dec. The infrared spectrum was identical with that of an authentic sample of **7**.[17] Contrary to an earlier report,[17] **7** gave a bright green solution when warmed with concentrated sulfuric acid.

Anal. Calcd for $C_4H_8S_4$: C, 26.06; H, 4.37; S, 69.56. Found: C, 25.89; H, 4.43; S, 69.72.

Dilution of the combined dimethylformamide mother liquor and extracts with water precipitated 1.49 g (85%) of **2** identified by its infrared spectrum.

When **6** was allowed to react with sodium acetylide in liquid ammonia in an attempt to displace the bromine by an acetylene residue, a similar decomposition occurred with formation of **2** and **7**.

Ethoxy-3-(5-bromo-1-methyloxindolyl)-N-succinimidomethane (8). A. From 5.—A mixture of 4.06 g (0.020 mole) of **5**, 3.56 g (0.020 mole) of NBS, and 20 ml of carbon tetrachloride was refluxed for 12 hr when solution was substantially complete. After filtration from a small amount of insoluble material the hot solution deposited 2.93 g (50.6%) of crystals on cooling. Recrystallization from ethanol gave colorless needles of **8**, mp 143–144°.

Anal. Calcd for $C_{16}H_{17}BrN_2O_4$: C, 50.41; H, 4.50; Br, 20.96; N, 7.35. Found: C, 50.50; H, 4.55; Br, 20.92; N, 7.26.

B. From 9.—A mixture of 2.82 g (0.010 mole) of **9** and 0.99 g (0.010 mole) of succinimide in 10 ml of carbon tetrachloride and 5 ml of ethanol was refluxed for 11 hr. After removal of most of the solvent, 3.43 g (90%) of **8** separated. Identification was by mixture melting point and infrared spectroscopy.

5-Bromo-3-ethoxymethylene-1-methyloxindole (9). A. From 8.—Compound **8** (1.91 g) was triturated with 2.5 ml of *cold* concentrated hydrochloric acid for several minutes. After addition of 5 ml of cold water the precipitate was collected and recrystallized from a very small amount of ethanol to give 1.3 g (92.5%) of **9** as shiny leaflets, mp 118–120°.

Anal. Calcd for $C_{12}H_{12}BrNO_2$: C, 51.08; H, 4.29; Br, 28.32; N, 4.97. Found: C, 50.90; H, 4.61; Br, 28.33; N, 4.95.

B. From 5-Bromo-3-formyl-1-methyloxindole.—A mixture of 2.54 g (0.010 mole) of **10**, 3.6 g of ethyl orthoformate, 10 ml of ethanol, and one drop of concentrated sulfuric acid was refluxed for 2.25 hr. On cooling 2.24 g (79.5%) of large crystals separated from the red solution. Recrystallization from ethanol gave material identical with **9** prepared from **8** on the basis of mixture melting points and infrared spectra.

5-Bromo-3-formyl-1-methyloxindole (10). A. From 8.—When 1.91 g of **8** was heated with 10 ml of 18% hydrochloric acid on the steam bath, the suspended solid became oily and then resolidified. After collection of the solid and thorough washing with water, 1.18 g (93%) of **10** was obtained. It melted at 254–256° dec after recrystallization from dioxane or acetic acid. The substance gave a purple color test with ferric chloride in ethanol.

Anal. Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; Br, 31.45; N, 5.51. Found: C, 47.33; H, 3.25; Br, 31.50; N, 5.61.

When **8** was warmed with 2 *N* sodium hydroxide solution, it went into solution. Acidification of the solution with hydrochloric acid precipitated **10**.

B. By Formylation of 5-Bromo-1-methyloxindole.—To a solution of 0.98 g (0.010 mole) of phosgene in 10 ml of 1,2-dichloroethane cooled in ice, 0.8 ml of dimethylformamide was added. The complex of phosgene with DMF separated immediately. A solution of 2.3 g (0.010 mole) of 5-bromo-1-methyloxindole[18] in 4 ml of 1,2-dichloroethane was added gradually to the suspension. Addition of petroleum ether to the resulting yellowish solution precipitated 3.04 g (96%) of almost colorless immonium salt. For purification the material was dissolved in the minumum amount of cold methanol, and an equal amount of 1,2-dichloroethane was added. After stirring the mixture with decolorizing carbon and filtration, the product, mp 196–200° dec, was precipitated as colorless crystals by addition of petroleum ether.

Anal. Calcd for $C_{12}H_{14}BrClN_2O$: C, 45.38; H, 4.44; N, 8.82. Found: C, 45.58; H, 4.41; N, 8.92.

The immonium salt was hydrolyzed by heating 3.2 g (0.010 mole) with 60 ml of water on the steam bath for 2 hr. A yellowish oil which soon solidified separated. After washing with ether 1.83 g (72%) of **10** separated. Identification was by infrared spectroscopy.

3-Bromo-3-formyl-1-methyloxindole (11).—A solution of 3.5 g (0.020 mole) of **2** and 3.56 g (0.020 mole) of NBS in 30 ml of carbon tetrachloride was refluxed for 15 min. After filtering the succinimide from the hot solution, crystallization of **11** began on cooling and was completed by addition of 300 ml of petroleum ether (45–50°) yielding 4.67 g (92%) of crude material. It was recrystallized from petroleum ether (90–100°) to give yellow

(17) H. Fasbender, *Ber.*, **20**, 460 (1887).

(18) R. Stolle, R. Bergdoll, M. Luther, A. Auerhahn, and W. Wacker, *J. Prakt. Chem.*, [2] **128**, 1 (1930).

crystals. The heating period during the recrystallization must be short to avoid decomposition. **11** melted slowly at 117–121°, resolidified at 127–128° with evolution of some gas, and finally melted at 170–180° dec. It decomposed on standing at room temperature for a few days.

Anal. Calcd for $C_{10}H_8BrNO_2$: C, 47.38; H, 3.27; Br, 31.58; N, 5.47. Found: C, 47.27; H, 3.17; Br, 31.45; N, 5.51.

From methanol, **11** crystallized as colorless crystals of a solvate, mp 123–124°, containing 0.5 mole of methanol.

Anal. Calcd for $C_{10}H_8BrNO_2 \cdot 0.5CH_3OH$: C, 46.52; H, 4.09; Br, 29.48; N, 5.17. Found: C, 46.30; H, 4.21; Br, 30.18; N, 5.15.

Hydrolysis of 11. 1-Methyldioxindole (12).—A mixture of **11** (7.62 g, 0.030 mole) with 300 ml of water was heated on the steam bath for 1 hr. After cooling, the strongly acidic solution was filtered and extracted with 400 ml of chloroform. Removal of the solvent from the dried extract left a rapidly crystallizing oil. The yield was 2.78 g (57%). Recrystallization from the minimum amount of chloroform gave colorless crystals, mp 157–158° (lit. mp 147°[19] and 151°[20]).

Anal. Calcd for $C_9H_9NO_2$: C, 66.26; H, 5.55; N, 8.59. Found: C, 66.35; H, 5.53; N, 8.62.

Quantitative hydrolysis of 0.2007 g of **11** in 5 ml of water required 15.43 ml of 0.1 *N* sodium hydroxide on back titration; the calculated value was 15.80 ml.

1,1′-Dimethylisoindigo (13). A. From 11.—When 2.54 g (0.010 mole) of **11** was warmed with 10 ml of 2 *N* sodium hydroxide on the steam bath for 10 min, a reddish brown solid separated which was collected and washed thoroughly with water. The yield was quantitative. Recrystallization from ethyl acetate gave beautiful dark red crystals, mp 270° dec. The infrared spectrum was identical with that of an authentic sample prepared by the procedure previously reported for the synthesis of isoindigo.[9]

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.44; H, 4.94; N, 9.71.

The methanolate of **11** underwent the same reaction.

B. From 1-Methylisatin Tosylhydrazone.—The tosylhydrazone was prepared by refluxing 8.1 g (0.050 mole) of 1-methylisatin and 9.3 g (0.050 mole) of tosylhydrazine in 50 ml of absolute ethanol for 15 min. The yellow hydrazone **16** (15.8 g, 96%) which separated was recrystallized from a large volume of ethanol or ethyl acetate. It decomposed at 202°.

Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; S, 9.74. Found: C, 58.27; H, 4.47; N, 12.88; S, 9.76.

The above hydrazone (1.61 g, 0.050 mole) was heated on the steam bath with a solution of 0.3 g of sodium in 15 ml of ethylene glycol. The mixture turned dark red, nitrogen was evolved and formation of **13** was complete in 3 to 5 min. After addition of water the product (0.63 g, 86%) was collected and recrystallized from ethyl acetate. The infrared spectrum was identical with that of **13** prepared as above from **11**.

1,1′-Dimethylisatin (14).—A mixture of 0.81 g (0.050 mole) of 1-methylisatin, 0.75 g (0.050 mole) of 1-methyloxindole and 5 ml of ethanol containing 1 drop of piperidine was refluxed for 5 min. On cooling and scratching a yellow solid (1.33 g, 86% after washing with ether) separated. It formed colorless crystals from chloroform which decomposed at 185–190°, depending on the rate of heating.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.10. Found: C, 69.94; H, 5.40; N, 8.94.

Ethyl 2-(3-Cyanooxindolyl)cyanoacetate (18a).—To a warm suspension of 3-cyanoethoxycarbonylmethyleneoxindole (**17a**)[11] (9.68 g, 0.040 mole) in 20 ml of ethanol, a solution of 5.28 g (0.080 mole) of potassium cyanide in 10 ml of water was added. After stirring for several minutes, the brown solution was diluted with water. On acidification with 2 *N* hydrochloric acid, a rapidly crystallizing brown oil (10.64 g, 99%) separated. On recrystallization from ethanol, **18a**, mp 161–162°, was obtained.

Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.60. Found: C, 62.48; H, 4.04; N, 15.58.

Ethyl 2-(3-Cyano-1-methyloxindolyl)cyanoacetate (18b).—This was prepared in 85% yield by a similar procedure from **17b**.[11] The compound, mp 79–80°, was recrystallized from ethanol.

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.52; H, 4.63; N, 14.90.

2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic Acid (19a).—A mixture of 2.7 g (0.010 mole) of **18a**, 20 ml of 18% hydrochloric acid, and 10 ml of acetic acid was refluxed for 6 hr. After removal of the solvent under reduced pressure, 50 ml of water was added to the residue which crystallized rapidly. The yield was 1.54 g (81%) Recrystallization from water gave colorless crystals, mp 222° (lit. mp 220°). The infrared spectrum was identical with that of an authentic sample.[13]

1-Methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic Acid (19b).—This was prepared in 85% yield by the above procedure. For purification the crude material was dissolved in sodium bicarbonate solution, decolorized with carbon and reprecipitated with hydrochloric acid. The acid formed large colorless crystals from water, mp 175–176° (lit.[13] mp 171°).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.44; H, 5.57; N, 6.61.

Action of Ethanolic Hydrochloric Acid on 18b (20).—A mixture of 2.83 g of **18b**, 20 ml of 18% hydrochloric acid, and 10 ml of ethanol was refluxed for 10 hr. After removal of the solvent under reduced pressure, the oily residue was extracted successively with sodium bicarbonate solution, chloroform, and ethanol leaving 0.12 g (5.2%) of insoluble residue which formed colorless crystals, mp 250°, from water. Presumably the acid **19b** which was formed concurrently was removed by the bicarbonate.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.66; H, 4.38; N, 12.17. Found: C, 62.51; H, 4.44; N, 12.41.

Reaction of Isatin with *t*-Butyl Cyanoacetate.—A mixture of 14.7 g (0.1 mole) of isatin, 16 g (0.113 mole) of *t*-butyl cyanoacetate,[21] 2 g of piperidine acetate, and 50 ml of ethanol was refluxed for 4 hr. On cooling, brownish crystals (22.5 g) separated. The crude product was extracted in portions with 1000 ml of petroleum ether (90–100°) and the insoluble residue was then extracted with 700 ml of ether leaving a colorless insoluble residue (3.9 g).

3-(*t*-Butoxycarbonylcyanomethyleneoxindole (22a).—Removal of the solvent from the above ether extract left 13.0 g (48%) of a dark red product which on recrystallization from benzene gave shiny dark red crystals containing 0.5 mole of benzene of crystallization. The substance sintered at 180° and decomposed at 201°.

Anal. Calcd for $C_{15}H_{14}N_2O_3 \cdot O \cdot 5C_6H_6$: C, 69.89; H, 5.54; N, 9.06. Found: C, 69.96; H, 5.53; N, 9.11.

The benzene of crystallization was lost on drying the solvate at 118° (2 mm) for 6 hr. The calculated weight loss was 12.62, and the actual weight loss found was 12.52.

After removal of the solvent from the above petroleum ether extract, the residue was recrystallized from chloroform to give 1.74 g (6.5%) of orange crystals, mp 136°.

Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 66.65; N, 5.22; N, 10.37. Found: C, 66.69; H, 5.26; N, 10.39.

These two compounds are probably geometrical isomers. Their infrared spectra ($CHCl_3$), although differing slightly are consistent with the structure assigned. In ethanolic sodium hydroxide both form bright blue solutions, the color of which fades after several minutes. From the solutions, isatin and **24** can be isolated and identified by melting point and by infrared spectra. Furthermore, both isomers give the same adduct, **23a**, with hydrogen cyanide (see below).

The ether-insoluble residue from the above extraction formed colorless crystals, mp *ca.* 170° dec depending on the rate of heating, from acetic acid. It is assigned the structure **24** on the basis of analyses and analogy with the reaction of isatin with ethyl cyanoacetate.[12]

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.11; H, 6.09; N, 10.18.

3-(*t*-Butoxycarbonylcyanomethylene)-1-methyloxindole (22b).—This was prepared from 1-methylisatin and *t*-butyl cyanoacetate by the above procedure. Only one product was isolated in 67% yield. It formed shiny red needles, mp 175° dec, from petroleum ether (bp 90–100°).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.65; H, 5.66; N, 9.92.

***t*-Butyl 2-(3-Cyanooxindolyl)cyanoacetate (23a).**—A suspension of 3.09 g (0.010 mole) of the benzene solvate of **22a** in 5 ml of ethanol and 2 ml of water was stirred with 1.32 g (0.020 mole) of potassium cyanide. The starting material dissolved after 10 min and was replaced by a colorless solid. After addition of 50 ml of water the product, 2.93 g (99%), was precipitated by

(19) H. G. Colman, *Ann. Chem.*, **248**, 121 (1888).

(20) J. Martinet, *Ann. Chim.* (Paris), [9] **11**, 1 (1919).

(21) R. E. Ireland and M. Chaykovsky, *Org. Syn.*, **41**, 5 (1961).

2 *N* hydrochloric acid. On recrystallization from ethanol it formed colorless crystals, mp 149° dec.

Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.68; H, 5.14; N, 14.07.

When the lower melting isomer of **22a** was subjected to similar treatment, **23a** was obtained in quantitative yield.

***t*-Butyl 2-(3-Cyano-1-methyloxindolyl)cyanoacetate (23b).**—This was obtained in quantitative yield by the procedure used for the preparation of **23a**. It formed colorless crystals, mp 111°, from methanol.

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.28; H, 5.52; N, 13.31.

3-Cyano-3-cyanomethyloxindole (25a).—When **23a** (8.91 g, 0.030 mole) was slowly heated to 149° (1–2 mm), pyrolysis commenced with foaming. After the initial reaction had subsided, the temperature was raised to 160° and held until foaming had substantially ceased. On cooling the residual oil crystallized on trituration with 50 ml of ether. Recrystallization from ethyl acetate gave 5.7 g (96%) of colorless crystals, mp 176°.

Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.16; H, 3.67; N, 21.42.

3-Cyano-3-cyanomethyl-1-methyloxindole (25b).—Similar pyrolysis of **23b** at 130–140° gave a 95% yield of **25b**, mp 127–128°, from methanol.

Anal. Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.46; H, 4.39; N, 19.78.

1-Methylisatin and 1-Methylisatin Dimethyl Ketal.—In employing the procedure of Harley-Mason and Inglesby[11] for the preparation of 1-methylisatin, we have found that, after a single methylation of isatin with dimethyl sulfate, a considerable amount of unreacted isatin remains in the product. Their procedure has therefore been modified.

To a suspension of 14.7 g (0.1 mole) of isatin in 200 ml of anhydrous methanol, 100 ml of 10% methanolic potassium hydroxide solution was added in portions with shaking. To the purple solution 15 ml of freshly distilled dimethyl sulfate was added and, after 30 min, the solution was filtered from potassium methyl sulfate which separated. After removal of about 270 ml of solvent under reduced pressure, the residue was poured into 45 ml of warm water. On cooling 14.8 g of crude product, mp 115°, crystallized. This was extracted twice with 100 ml of petroleum ether. The insoluble part (13 g, 82%) on recrystallization from ethanol gave pure 1-methylisatin, mp 134° (lit. mp 134–136°).

Removal of the solvent from the petroleum ether extracts left 0.93 g (4.5%) of crude 1-methylisatin dimethyl ketal, which after recrystallization from *n*-hexane (charcoal), gave the pure ketal, mp 81–82°.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.92; H, 6.31; N, 6.76.

On hydrolysis with hydrochloric acid, pure 1-methylisatin was obtained from the ketal in quantitative yield.

Registry No.—Sodium salt of **2**, 14179-69-2; **3**, 14179-70-5; **4**, 14179-71-6; **6**, 14179-72-7; **7**, 1940-01-8; **8**, 14179-74-9; **9**, 14179-75-0; **10**, 14179-76-1; immonium salt ($C_{12}H_{14}BrClN_2O$), 14179-77-2; **11**, 14179-78-3; **12**, 3335-86-2; **13**, 3265-16-5; **14**, 14179-81-8; **16**, 3265-25-6; **18a**, 14271-44-4; **18b**, 14179-83-0; **19a**, 14179-84-1; **19b**, 14271-45-5; **20**, 14264-75-6; **22a**, 14179-85-2; **22b**, 14179-86-3; **23a**, 14179-87-4; **23b**, 14179-88-5; **24**, 14179-89-6; **25a**, 14179-90-8; **25b**, 14179-91-0; 1-methylisatin, 2058-74-4; 1-methylisatin dimethyl ketal, 14271-46-6.

The Borohydride Reduction of Thioxanthone Sulfoxide. A Base-Induced Dehydration of Thioxanthenol Sulfoxide

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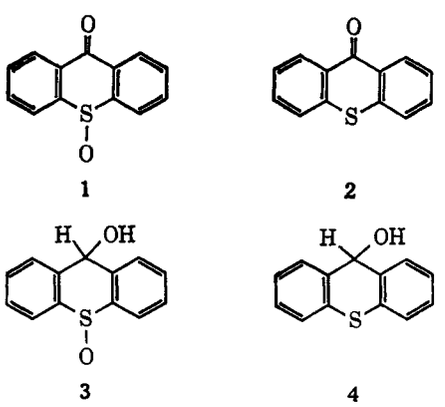
Reduction of thioxanthone sulfoxide with excess sodium borohydride affords mainly *cis*-thioxanthenol sulfoxide. Reduction in an alkaline medium affords thioxanthenol. This latter process is shown to proceed *via* the base-induced dehydration of thioxanthenol sulfoxide to thioxanthone. A comparison of the ultraviolet spectra of the isomeric thianthrene disulfoxides and the isomeric thioxanthenol sulfoxides indicates that the intense short-wavelength transitions present in these spectra are probably best considered to be perturbed aromatic transitions.

Thioxanthone sulfoxide (**1**) may be prepared by the dinitrogen tetroxide oxidation of thioxanthone[2] (**2**). As part of our investigation of this heterocyclic system we attempted to prepare the corresponding alcohols, *cis*- and *trans*-thioxanthenol sulfoxide (**3**α and **3**β), by the sodium borohydride reduction of **1**.[3] The reduction of **1** (in 95% ethanol) afforded *cis*-thioxanthenol sulfoxide (**3**α) as the major product even in the presence of a large excess of borohydride. However, if the same reduction is performed in the presence of trace quantities of base, the product that is obtained is thioxanthenol (**4**). Thus, the *net* reaction in an alkaline medium involves reduction of the sulfoxide group as well as of the carbonyl group.

Results and Discussion

There are two conceptually different pathways that could account for the conversion of thioxanthone sulfoxide (**1**) to thioxanthenol (**4**). The essential difference between these pathways resides in the actual sequence of reductions. In one of these the sulfoxide



(1) To whom inquiries should be directed. This investigation was supported by Public Health Service Research Grant No. CA-10139 from the National Cancer Institute. Presented, in part, at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, p O 105.

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