

[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Condensations of Isatin with Acetone by the Knoevenagel Method¹

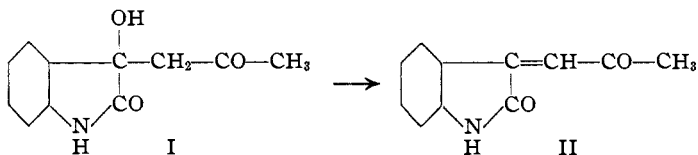
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In a recent article it was shown² that isatin and acetophenone will condense, in the presence of certain bases, to yield 3-hydroxy-3-phenacyloxindole. This reaction suggested the use of other methyl ketones like acetone. Isatin and acetone condense when present with small amounts of diethylamine to yield 3-acetyl-3-hydroxyoxindole (I).

The condensation involves the β -carbonyl of the isatin molecule rather than the nitrogen, for N-methylisatin will also react with acetone to yield a product with chemical properties similar to those of (I).

Compound (I) decomposes upon the application of heat, or upon being warmed with aqueous alcoholic potassium hydroxide solution, into isatin and acetone. This decomposition is evidently another example of a reversed aldol reaction. A longer period of heating with the potassium hydroxide solution results in the formation of 2-methylcinchoninic acid, not, apparently, through rearrangement of the 3-acetyl-3-hydroxyoxindole, but rather through its decomposition into isatin and acetone followed by a Pfitzinger³ type of condensation of the acetone with the *o*-aminobenzoylformic acid, formed by the hydrolysis of the isatin.

Treatment of I with certain acidic reagents effects the loss of one mole of water with the resulting formation of 3-acetylidenoxindole (II), a highly colored red-orange compound.



It might be expected that II, upon ring opening through hydrolysis, would form 2-methylcinchoninic acid as a result of subsequent reaction of the ketone carbonyl with the nuclear NH_2 group. However, II could not be rearranged to the corresponding quinoline derivative by treatment with potassium hydroxide. This is in agreement with the failure of 3-phenacyloxindole and 3-phenacyloxindole to rearrange to cinchophen and 3,4-dihydro-2-phenylcinchoninic acid, as noted in our previous paper. Therefore 3-acetylidenoxindole cannot, apparently, be considered an intermediate in the Pfitzinger synthesis of 2-methylcinchoninic acid from isatin

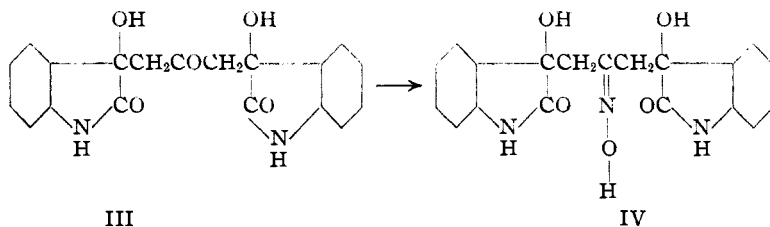
¹ Abstract from a thesis presented by F. Braude in partial fulfillment of the requirements for the degree of Doctor of Philosophy at New York University.

² Lindwall and MacLennan, *THIS JOURNAL*, **54**, 4739 (1932).

³ Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897).

and acetone. It is possible that II is a *trans* isomer and will not form the quinoline derivative for this reason. This point has not yet been completely investigated.

3-Acetyl-3-hydroxyindole will condense with a mole of isatin to yield 1,3-bis-(3-hydroxy-3-oxindyl)-2-propanone (III). This compound also results when 2 moles of isatin condense with one of acetone. N-Methylisatin behaves in an analogous manner with acetone. Compound III yields a monoxime (IV)



Experimental Part

3-Acetyl-3-hydroxyindole (I).—A mixture of 25 g. of isatin, 139 g. of acetone and 13.9 g. of diethylamine was allowed to stand for twenty-four hours at room temperature. Pale yellow crystals separated which became white upon recrystallization from acetone. The product is soluble in ethyl alcohol, *n*-butyl alcohol, acetone and ethyl acetate, but is insoluble in water; m. p. 166–167° with decomposition; yield, 75%.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.62; H, 5.44; N, 6.83. Found: C, 64.48; H, 5.42; N, 6.82.

3-Acetyl-3-hydroxy-1-methyloxindole.—The same proportions and procedure were used as for I (above), replacing the isatin by N-methylisatin. The product was recrystallized from benzene: m. p. 145°; yield, 79%.

Anal. Calcd. for $C_{12}H_{13}O_3N$: N, 6.39. Found: N, 6.28, 6.31.

Isatin by the Decomposition of 3-Acetyl-3-hydroxyindole (I).—A mixture of 2 g. of (I), 22.5 cc. of ethyl alcohol and 10.5 cc. of 33% potassium hydroxide was heated on a steam-bath for one hour. The resulting solution was acidified with dilute hydrochloric acid. A brown precipitate resulted which proved, upon crystallization, to be isatin; m. p. 198°; m. p. mixed with a known sample of isatin, 198°.

2-Methylcinchoninic Acid from 3-Acetyl-3-hydroxyindole.—The mixture described above was heated for eight hours on a steam-bath. Acidification with hydrochloric acid yielded a light brown precipitate. Crystallization from boiling water gave a white crystalline product which was identified, by melting point and mixed melting point, as 2-methylcinchoninic acid.

3-Acetylideneoxindole (II).—3-Acetyl-3-hydroxyindole (10 g.) was heated with 45 cc. of ethyl alcohol and 11.5 cc. of concd. hydrochloric acid until a clear solution was obtained. The solution was then poured over 80 g. of ice. A bright yellow-red solid formed. Recrystallization from ethyl alcohol yielded red needles, soluble in ether, acetone, ethyl acetate, ethyl alcohol and hot benzene: m. p. 168–171°; yield, 42%.

Anal. Calcd. for $C_{11}H_9O_2N$: N, 7.49. Found: N, 7.43, 7.48.

3-Acetylidene-1-methyloxindole.—3-Acetyl-3-hydroxy-1-methyloxindole was treated as outlined above in the preparation of II. The product is red and soluble in alcohol and ether: m. p. 120–122°; yield, 57%.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.90; H, 5.51; N, 6.97. Found: C, 71.45; H, 5.51; N, 6.84, 7.00.

Attempted Rearrangement of 3-Acetylidenexindole to 2-Methylcinchoninic Acid.—A mixture containing 1.25 g. of 3-acetylidenexindole, 2.9 g. of sodium hydroxide and 22 cc. of water was heated on a steam-bath for eight hours. Acidification with hydrochloric acid caused the precipitation of a brown solid. Attempts to isolate 2-methylcinchoninic acid from this material were not successful.

1,3-Bis-(3-hydroxy-3-oxindyl)-2-propanone (III).—(A) A mixture of 2.9 g. (1 mol), of isatin, 4.1 g. (1 mol) of 3-acetyl-3-hydroxyoxindole, 2.7 g. of diethylamine, and 27 cc. of absolute ethyl alcohol was allowed to stand for forty-eight hours. The solid material which separated was recrystallized from ethyl alcohol and obtained as colorless prisms: m. p. 212–214°, with apparent decomposition; yield, 78%.

(B) A solution of 4.5 g. of isatin, 1.8 g. of acetone, 2.5 g. of diethylamine, and 25 cc. of absolute alcohol was allowed to stand at room temperature for twenty-four hours. A solid formed which, after crystallization from alcohol, was found to be identical with the product from method "A"; yield, 16%.

Anal. Calcd. for $C_{19}H_{16}O_5N_2$: C, 64.76; H, 4.58; N, 7.95. Found: C, 64.54; H, 4.75; N, 7.80, 7.85.

1,3-Bis-(3-hydroxy-3-oxindyl)-2-propanone Oxime (IV).—Compound III (4.3 g.) was dissolved in 50 cc. of hot ethyl alcohol, and a water solution of 2.6 g. of hydroxylamine hydrochloride and 4.8 g. of sodium acetate was added. The solution was boiled gently for a half hour. After cooling and evaporation of solvent a solid resulted which was crystallized from 50% ethyl alcohol, and thus obtained as colorless needles, decomposing at 158–160°.

Anal. Calcd. for $C_{19}H_{17}O_5N_3$: N, 11.45. Found: N, 11.64.

1,3 - Bis - (3 - hydroxy - 1 - methyl - 3 - oxindyl) - 2 - propanone.—3 - Acetyl-3-hydroxy-1-methyloxindole and N-methylisatin were allowed to react using the procedure described in method "A" for the preparation of III. The product was recrystallized from toluene and obtained thus as colorless plates: m. p. 178–181°, with apparent decomposition.

Anal. Calcd. for $C_{21}H_{20}O_5N_2$: N, 7.39. Found: N, 7.24.

Summary

Isatin and acetone condense in the presence of certain organic bases to yield 3-acetyl-3-hydroxyoxindole and 1,3-bis-(3-hydroxy-3-oxindyl)-2-propanone.

3-Acetylidenexindole is apparently not an intermediate in the Pfitzinger synthesis of 2-methylcinchoninic acid, since it does not yield that product upon treatment with alkali.

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