of the colorless compound was 173–173.5°, which agrees with that given by Maxwell and Adams.[9]

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.31; H, 7.09; neut. equiv., 254. Found: C, 80.29; H, 7.39; neut. equiv., 256.

Mesitylphenylacetic acid was also synthesized by boiling a mixture of 1 g. of mesitylphenylglycolic acid, 30 cc. of glacial acetic acid and 6 g. of zinc under reflux for eighteen hours. There was obtained 0.5 g. of product which, on recrystallization, melted at 173°. A mixed melting point with the product obtained in the iodine and phosphorus reduction of mesitylphenylglycolic acid showed no depression.

Summary

Mesityl phenyl diketone reacts as a monoketone toward the Grignard reagent, semicarbazide, 2,4-dinitrophenylhydrazine and hydroxylamine. Toward hydrogen peroxide, as well as in the benzilic acid rearrangement, the diketone behaves normally.

Reducing agents convert the diketone to a mixture of the two isomeric benzoins. Drastic reduction *affects only the hindered carbonyl group* and gives phenyl 2,4,6-trimethylbenzyl ketone.

URBANA, ILLINOIS

RECEIVED APRIL 13, 1936

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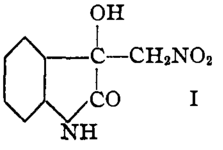
[9] Maxwell and Adams, THIS JOURNAL, **52**, 2959 (1930).

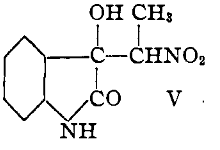
[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Oxindole Amines from Isatin[1]

BY WILLIAM R. CONN[2] AND H. G. LINDWALL

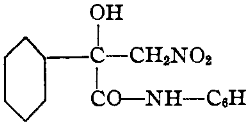
It has been reported previously[3] that nitromethane will condense with beta-naphthisatin to yield 3-hydroxy-3-(nitromethyl)-β-naphthoxindole. It has now been found that a similar reaction with nitromethane occurs in the case of isatin, and of certain substituted isatins in the presence of diethylamine, with the formation of the corresponding aldol-like condensation products. Isatin and nitromethane yield 3-hydroxy-3-(nitromethyl)-oxindole (I); substituted derivatives of I (II, III and IV) result from the condensations employing, respectively, N-ethylisatin, 5-bromo-N-ethylisatin and N-methylisatin. Nitroethane and isatin yield an analogous product (V).


I


V

At room temperature or for short periods of heating, these five nitro compounds exhibit unexpected resistance toward dehydrating agents such as acetic anhydride, acetyl chloride or hydrochloric acid. When heated with neutral solvents gradual decomposition takes place with the formation of the original isatin and the nitro-alkane. The extent of this decomposition can be greatly decreased by the presence of a small amount of glacial acetic acid in the solvent. Heated alone, these nitro compounds again decompose through reversal of the aldol condensation; examination of the melts shows the presence of the isatin and the nitro-alkane. Heating in water containing even small amounts of organic or inorganic base causes speedy reversal of the condensation.

For purposes of generalization, a straight-chain alpha-keto-amide, benzoylformanilide, was condensed with nitromethane. The product, VI, has properties similar to those described above for compounds I–V.


VI

Reduction of 3-hydroxy-3-(nitromethyl)-oxindole (I) catalytically with Adams platinic oxide catalyst[4] or by treatment with concentrated hydrochloric acid and mossy tin, gave the hydrochloride of 3-hydroxy-3-(aminomethyl)-oxindole (VII). Similar treatment of II and III with tin and hydrochloric acid yielded in the same manner the hydrochlorides of the aminomethyloxindoles, respectively, IX and X.

In one of several runs of the reduction of I to form VII by the tin–hydrochloric acid method, VII was obtained contaminated with a compound which was found to be the intermediate reduction

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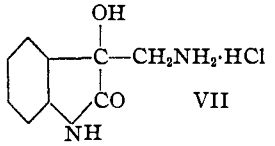
[1] From the dissertation presented by William R. Conn to the Faculty of the Graduate School of New York University in candidacy for the degree of Doctor of Philosophy.

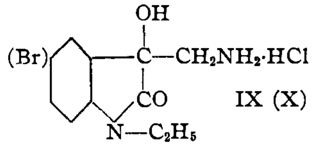
[2] University Fellow in Chemistry.

[3] Zrike and Lindwall, THIS JOURNAL, **57**, 207–8 (1935).

[4] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., 1932, p. 452.



VII

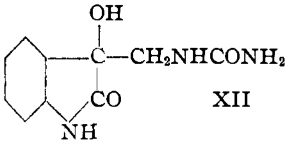


IX (X)

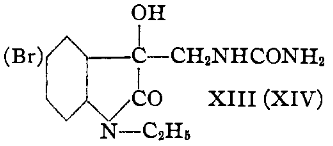
product (VIII) 3-hydroxy-3-(hydroxylaminomethyl)-oxindole hydrochloride. Compound VIII was not encountered in the other runs of this reaction.

Reduction of VI (the product of condensation of nitromethane with benzoylformanilide) with tin and hydrochloric acid did not follow the normal course; the reduction product was not investigated.

Compounds VII, IX and X were found to exhibit several of the properties common to primary amines. With potassium cyanate the corresponding substituted ureas, the uramidomethyloxindoles, XII, XIII and XIV, respectively, are formed.

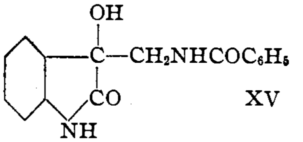


XII

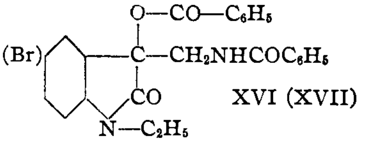


XIII (XIV)

Treatment of VII with benzoyl chloride brings about benzoylation of the amino group and yields 3 - hydroxy - 3 - (benzoylaminomethyl) - oxindole (XV). For compounds IX and X the hydroxy group, as well as the primary amino group, is benzoylated, yielding XVI and XVII, respectively.

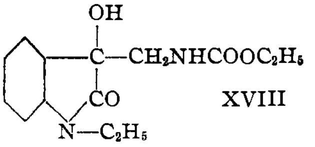


XV

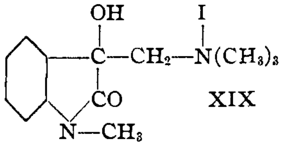


XVI (XVII)

Furthermore, treatment of IX with ethyl chloroformate causes the formation of the urethan (XVIII). Methylation of VII with methyl iodide gives the quaternary ammonium salt (XIX).



XVIII



XIX

It is planned to continue this work on the synthesis of oxindole-amine derivatives. Certain of these products will be studied physiologically.

Experimental Part

3-Hydroxy-3-(nitromethyl)-oxindole (I).—Isatin (44.1 g.) was suspended in a solution of nitromethane (36.6 g.) and 40 cc. of absolute ethyl alcohol. After cooling in ice, 3 cc. of diethylamine was added. In one day at ice-box temperature 71% of crude product separated. Crystallization from glacial acetic acid yielded hexagonal colorless crystals, m. p. 135–140°, dec., soluble in alcohol, acetone, benzene. Compounds II, III and IV were prepared by the same general method, and have solubilities similar to those of I.

Anal. Calcd. for $C_9H_8O_4N_2$: C, 51.90; H, 3.88; N, 13.46. Found: C, 52.24; H, 3.82; N, 13.24.

3 - Hydroxy - 3 - (nitromethyl) - 1 - ethyloxindole (II) from N-ethylisatin and nitromethane; yield, crude, 60% after two days; colorless prisms from carbon tetrachloride; m. p. 84–85°, dec.

Anal. Calcd. for $C_{11}H_{12}O_4N_2$: N, 11.86. Found: N, 11.91.

3 - Hydroxy - 3 - (nitromethyl) - 5 - bromo - 1 - ethyloxindole (III) from 5-bromo-N-ethylisatin and nitromethane; yield, crude, 93% after overnight; small colorless plates from ethyl alcohol containing a trace of glacial acetic acid; m. p. 123–125°, dec.

Anal. Calcd. for $C_{11}H_{11}O_4N_2Br$: N, 8.89. Found: N, 8.65.

3 - Hydroxy - 3 - (nitromethyl) - 1 - methyloxindole (IV) from N-methylisatin and nitromethane; yield, crude, 70% after two days; large needles from hot benzene containing a trace of glacial acetic acid; m. p. 98–99°, dec.

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.03; H, 4.54; N, 12.61. Found: C, 54.42; H, 4.70; N, 12.55, 12.42.

3-Hydroxy-3-(α-nitroethyl)oxindole (V) from isatin and nitroethane; yield, crude, 80% after two days; hexagonal crystals from glacial acetic acid; m. p. 145–150° with reddening at 140°.

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: N, 12.61. Found: N, 12.20, 12.40.

Properties of I, II, III, IV, V. (A) Dehydrating Agents. —Compound I, boiled in acetic anhydride for one minute, was unchanged; prolonged refluxing caused decomposition with evolution of red fumes. Short boiling of I with acetyl chloride, or long standing at room temperature with that reagent, had no effect. Four hours in acetic anhydride at 100° caused no change in IV. Three minutes of boiling in concentrated hydrochloric acid had no effect upon II and IV. Compound IV was unchanged after standing for one week at room temperature in absolute alcohol saturated with dry hydrogen chloride.

(**B**) **Alkali.**—All five of these nitro compounds were decomposed, through reversal of the condensation reaction, to form the original reactants when heated in water or organic solvents containing traces of organic or inorganic bases. Isatin, or the respective isatin derivative, was identified in each case. Compound IV, dissolved in potassium hydroxide solution, imparted a yellow color to the solution; acidification with hydrochloric, acetic or carbonic acids yielded a red gum which became colorless and crystalline upon standing for a few minutes; the product was the original IV.

(**C**) **Heat.**—All five nitro compounds decomposed into the original reactants when melted; this was shown by examination of the melts. Slow decomposition, quantitative in a few hours, takes place when these compounds are heated in neutral organic solvents or in water; this decomposition is effectively avoided when a small amount of acetic acid is present in the solvent.

2-Phenyl-2-hydroxy-3-nitropropaneanilide (VI).—Diethylamine (10 drops) was added to the cooled mixture of benzoylformanilide (13.5 g.), nitromethane (4.1 g.), and 10 cc. of absolute alcohol. Crystals began to form after five minutes; after overnight a 96% yield of crude product resulted; colorless needles after crystallization from glacial acetic acid; m. p. 143–144°, dec.; soluble in alcohol, acetone. Boiling in concentrated hydrochloric acid, or in acetic anhydride, for two hours produced no change; two minutes of boiling in water containing a small amount of diethylamine caused decomposition as shown by the identification of benzoylformanilide.

Anal. Calcd. for $C_{15}H_{14}O_4N_2$: N, 9.79. Found: N, 9.67.

3-Hydroxy-3-(aminomethyl)-oxindole Hydrochloride (VII). (A) Catalytic Reduction of I.—Compound I (20.8 g.) was dissolved in 240 cc. of absolute alcohol containing 11 cc. of glacial acetic acid. To the clear solution was added 0.2 g. of Adams platinic oxide catalyst[4] and the mixture was subjected to the action of hydrogen under 3 atm. pressure at room temperature with mechanical agitation. In two hours the pressure dropped the calculated amount for absorption of three moles of hydrogen; the time varied somewhat with different runs. The catalyst was removed, 12 cc. of concentrated hydrochloric acid was added, and the solution was evaporated to half its original volume at room temperature under diminished pressure. Crystals separated as needles, the yield being augmented to 62% upon further concentration. Acetic acid was necessary in the reduction; without it a non-crystalline substance, not identified, separated before the calculated amount of hydrogen had been used. Compound VII is soluble in alcohol, glacial acetic acid; crystallized from the latter, it is obtained as colorless leaflets, m. p. 195–197°, dec.

Anal. Calcd. for $C_9H_{11}O_2N_2Cl$: N, 13.05; Cl, 16.52; active hydrogen atoms, 5. Found: N, 12.92, 12.86; Cl, 16.41, 16.34; active hydrogen atoms,[5] 5.

Picrate of VII.—Soluble in alcohol, acetic acid, acetone, benzene; long needles from 50% alcohol, which become powdered upon desiccation; m. p. 165–166°, dec.

Anal. Calcd. for $C_{15}H_{13}O_9N_5$: N, 17.20. Found: N, 16.40.

(**B**) **Reduction of I by Tin and Hydrochloric Acid. (VII).**—A sample of I was warmed at 45° with twice the theoretical amount of mossy tin and concentrated hydrochloric acid until most of the tin had been used. The mixture was then diluted and tin removed as the sulfide. Concentration of the solution at room temperature yielded VII. (In one run of several, VIII, described below, was obtained.) The yield of VII after repeated crystallizations from glacial acetic acid was 10%.

3-Hydroxy-3-(hydroxylaminomethyl)**-oxindole (VIII)** was obtained in one run of Method B (VII, above); insoluble in the more common organic solvents; crystallized from dilute hydrochloric acid as colorless needles, m. p. 194°.

Anal. Calcd. for $C_9H_{11}O_3N_2Cl$: Cl, 15.39. Found: Cl, 15.40.

Picrate of VIII.—Fine needles from acetic acid; m. p. 174°.

3-Hydroxy-3-(aminomethyl)-1-ethyloxindole Hydrochloride (IX) from II.—Compound II (23.6 g.) was suspended in 87 cc. of concentrated hydrochloric acid and heated on a steam-bath while 47.6 g. of mossy tin was added gradually. The mixture was then held at its boiling point for three hours with the gradual addition of more tin (23.8 g.) and more hydrochloric acid (45 cc.). The tin was finally removed as the sulfide, and the solution was evaporated to dryness at room temperature; leaflets from isoamyl alcohol; m. p. 180–182°, dec.; yield, 50%; soluble in alcohol, glacial acetic acid.

Anal. Calcd. for $C_{11}H_{15}O_2N_2Cl$: C, 54.41; H, 6.23; N, 11.54; Cl, 14.63; active hydrogen atoms, 4. Found: C, 54.17; H, 6.55; N, 11.54; Cl, 14.46, 14.57; active hydrogen atoms, 4.

Picrate of IX. Yellow flakes from ethyl alcohol; m. p. 168–169°.

Anal. Calcd. for $C_{17}H_{17}O_9N_5$: N, 16.10. Found: N, 16.42.

3-Hydroxy-3-(aminomethyl)-5-bromo-1-ethyloxindole Hydrochloride (X) from III.—This was prepared by the same method as that used above for the preparation of IX; small needles from isoamyl alcohol; m. p. 192–194°, dec.; yield 27%.

Anal. Calcd. for $C_{11}H_{14}O_2N_2ClBr$: Cl, 11.03. Found: Cl, 11.02, 11.16.

Picrate of X.—Small yellow leaflets from ethyl alcohol; m. p. 182–183°.

Anal. Calcd. for $C_{17}H_{16}O_9N_5Br$: N, 13.62. Found: N, 13.39.

Compound XI by the Reduction of VI.—Reduction of VI, by means of tin and concentrated hydrochloric acid, yielded XI which crystallizes as colorless prisms from glacial acetic

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(5) Zerewitinoff, *Ber.*, **40**, 2028 (1907); **41**, 2239 (1908).

acid; yield 8 g. from 14 g. of VI; m. p. 208–210°. Analyses for C, H, N did not agree with the formula for the simple primary amine; the compound has not been investigated further.

3 - Hydroxy - 3 - (uramidomethyl) - oxindole (XII) from VII; 3-Hydroxy-3-(uramidomethyl) - 1 - ethyloxindole (XIII) from IX; 3-Hydroxy-3-(uramidomethyl)-5-bromo-1-ethyloxindole (XIV) from X.—Compounds XII, XIII and XIV were prepared by treatment of the respective amine hydrochlorides in water solution with potassium cyanate. In each case the product was recrystallized from hot water; yields, 90% approx.

Compound XII.—M. p. 208–209°, dec.

Anal. Calcd. for $C_{10}H_{11}O_3N_3$: N, 19.00. Found: N, 18.65.

Compound XIII.—M. p. 216–217°, dec.

Anal. Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.81; H, 6.07; N, 16.86. Found: C, 57.81; H, 6.35, 6.13; N, 16.21.

Compound XIV.—M. p. 218–220°, dec.

Anal. Calcd. for $C_{12}H_{14}O_3N_3Br$: N, 12.82. Found: N, 12.84.

3-Hydroxy-3-(benzoylaminomethyl)-oxindole (XV) from VII.—One gram of VII was dissolved in 10 cc. of water containing 3 g. of sodium carbonate; benzoyl chloride (slightly more than two moles) was added with shaking. The product separated over a period of several hours. It was washed with sodium carbonate solution; flat colorless rods from acetone; m. p. 177°; soluble in alcohol, acetic acid; yield 75%.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.01; N, 10.08. Found: C, 68.45; H, 5.65; N, 10.07.

3 - (Benzoylhydroxy - 3 - (benzoylaminomethyl) - 1 - ethyloxindole (XVI) from IX; 3 - (Benzoylhydroxy) - 3 - (benzoylaminomethyl) - 5 - bromo - 1 - ethyloxindole (XVII) from X.—Compound IX, or X, was dissolved in 10% sodium hydroxide solution, or in sodium carbonate solution, and an excess of benzoyl chloride was added with shaking. Compounds XVI and XVII, respectively, resulted; each was recrystallized from ethyl alcohol. Yields, 90% approx.

Compound XVI.—Hexagonal crystals; m. p. 191°, with dec.

Anal. Calcd. for $C_{25}H_{22}O_4N_2$: C, 72.43; H, 5.35; N, 6.76. Found: C, 72.02; H, 5.31; N, 6.80.

Compound XVII.—Prisms; m. p. 204°.

Anal. Calcd. for $C_{25}H_{21}O_4N_2Br$: C, 60.85; H, 4.30; N, 5.68. Found: C, 60.68; H, 4.70; N, 5.71.

3 - Hydroxy - 3 - (ethylcarbamidomethyl) - 1 - ethyloxindole (XVIII) from IX.—Compound IX (1.2 g.) was dissolved in 6 cc. of water containing 2.1 g. of potassium carbonate. The solution was cooled, and an excess of ethyl chloroformate was added. A quantitative yield of product separated; colorless prisms from ethyl alcohol; m. p. 166°.

Anal. Calcd. for $C_{14}H_{18}O_4N_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 60.12; H, 6.59; N, 10.32.

(3 - Hydroxy - 1 - methyloxindolyl - 3) - methyltrimethylammonium Iodide (XIX) from VII.—Compound VII (1.1 g.) dissolved in 28 cc. of absolute alcohol was treated with 2.5 g. of barium hydroxide hydrate and 2.6 g. of methyl iodide. After standing at room temperature for two days, the mixture was heated at 40° for two days, and finally was heated on the steam-bath for three hours, with addition of 0.5 g. more of methyl iodide. After cooling, 1 cc. of concentrated hydrochloric acid was added, and the solution was dried. To isolate the product, ether was added dropwise; yield 43%; feather-like clusters from ethyl alcohol; m. p. 227°, dec.

Anal. Calcd. for $C_{13}H_{19}O_2N_2I$: C, 43.08; H, 5.29; N, 7.73. Found: C, 42.64; H, 5.41; N, 7.50.

Summary

Isatin, N-ethylisatin, 5-bromo-N-ethylisatin and N-methylisatin react with nitromethane to yield aldol-like nitro condensation products. Isatin and nitroethane react similarly, as does benzoylformanilide with nitromethane.

The products derived thus from isatin, N-ethylisatin, and 5-bromo-N-ethylisatin were reduced to the corresponding primary amine hydrochlorides. These amines yield urea derivatives and benzoylated products. Certain urethan and quaternary ammonium salt formations are described.

NEW YORK, N. Y. RECEIVED APRIL 6, 1936