2-Methyl-1,4-naphthohydroquinone Diallyl Ether (VII).—2-Methyl-1,4-naphthohydroquinone (11 g.) was refluxed for six hours with 22.8 g. of allyl bromide, 22 g. of potassium carbonate, and 50 ml. of acetone in a nitrogen atmosphere and in the presence of sodium hydrosulfite. The solvent was evaporated and the oily product extracted with ether. The ether solution was washed repeatedly with 10% sodium hydroxide solution containing sodium hydrosulfite to remove all traces of unreacted 2-methyl-1,4-naphthohydroquinone. The ether solution was dried over magnesium sulfate and the ether evaporated. The residual oil was distilled under reduced pressure and 14 g. (87% yield based on 2-methyl-1,4-naphthohydroquinone) of amber-colored liquid which boiled at 164–166° (5 mm.) was collected. This liquid gave a positive Craven test[13] for quinones. The product was taken up in ether, the solution again washed with 10% sodium hydroxide solution containing sodium hydrosulfite, dried, and the ether evaporated. The oil was then distilled under reduced pressure in a nitrogen atmosphere and in the presence of a small amount of sodium hydrosulfite. 2-Methyl-1,4-naphthohydroquinone diallyl ether boiled at 155–155.5° (3 mm.); $n^{25}D$ 1.5580; negative Craven test.

(13) Craven, *J. Chem. Soc.*, 1605 (1931).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.27; H, 7.12. Found: C, 79.98; H, 7.28.

Summary

1. 2-Acetoxymethyl-1,4-naphthoquinone does not inhibit the vitamin K activity of 2-methyl-1,4-naphthoquinone, when administered simultaneously in ten times the amount of the methylnaphthoquinone. The synthesis of the former compound has been described in detail, and an improved procedure for the preparation of 2-chloromethylnaphthalene is given.

2. 2-Methyl-1,4-naphthoxydiacetic acid, its dipotassium salt, 1-hydroxy-2-methyl-4-naphthoxy-γ-crotonic acid, dimethyl 2-methyl-1,4-naphthoxydi-γ-crotonate and the diallyl ether of 2-methyl-1,4-naphthohydroquinone have been synthesized, and have been found to have less than 1% of the activity of 2-methyl-1,4-naphthoquinone.

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[CONTRIBUTION FROM NICHOLS LABORATORY, NEW YORK UNIVERSITY]

Synthesis and Properties of 1-Cyanoethylisatin

BY FREDERICK J. DI CARLO AND H. G. LINDWALL

The reaction of acrylonitrile with isatin in the presence of trimethylbenzylammonium hydroxide as a catalyst yielded 1-cyanoethylisatin (I). Ethyl alcohol was found to be a more satisfactory solvent for this reaction than either dioxane or tertiary butyl alcohol. Upon saponification, the cyanoethylation product was converted to isatin-1-propionic acid. Catalytic hydrogenation of the β-oxime of this acid in a solution of alcoholic hydrogen chloride gave ethyl 3-amino-1-oxindolepropionate hydrochloride, which is isomeric with the ethyl ester hydrochloride of oxytryptophan. Under similar conditions, isatin-β-oxime was hydrogenated to β-amino oxindole hydrochloride which Baeyer and Knop[1] synthesized by the reduction of isatin-β-oxime with tin and hydrochloric acid. A Schiff base was prepared from the hydrochloride and *p*-dimethylaminobenzaldehyde in the presence of sodium acetate.

Cyanoethylisatin was condensed with acetone and with acetophenone under Knoevenagel conditions. Perkin conditions were employed to effect condensations with hydantoin and with rhodanine. The interaction of I and malonic acid produced normal ring expansion to yield 1-cyanoethyl-2-quinolone-4-carboxylic acid.

In the presence of iodine, cyanoethylisatin formed an anil with *p*-anisidine and 6-cyanoethylindophenazine with *o*-phenylenediamine.

Oxidations of N-methylisatin and of isatin-1-propionic acid with 3% hydrogen peroxide proceeded rapidly in alkaline solution to yield N-methylanthranilic acid and N-(2-carboxyphenyl)-β-alanine, respectively. Isatides were readily prepared by the hydrogenations of N-methylisatin and isatin-1-propionic acid in the presence of Adams catalyst. 1,1′-Dimethyl isatide was previously prepared by the condensation of equivalent amounts of 1-methylisatin and 1-methyl dioxindole in the presence of either piperidine or alcoholic hydrogen chloride.[2]

(1) Baeyer and Knop, *Ann.*, **140**, 37 (1866).

Experimental

1-Cyanoethylisatin (I).—Acrylonitrile (40 cc.) was added dropwise to a solution containing 49.0 g. (0.33 mole) of isatin and 7 cc. of "Triton B" in 2.5 liters of alcohol, with stirring. The stirring was continued for a few hours and the solution was then allowed to stand (uncovered) at room temperature for several days. Cyanoethylisatin separated as either large red prisms or large rosets of fine orange needles. After filtration and washing with methyl alcohol, the yield was 33.2 g. (50%); m. p. 130–131°. Recrystallized from acetone, the product melted at 133°.

Concentration of the mother liquor yielded a mixture of cyanoethylisatin and isatin which was difficult to separate but which could be dissolved in alcohol and treated again with acrylonitrile.

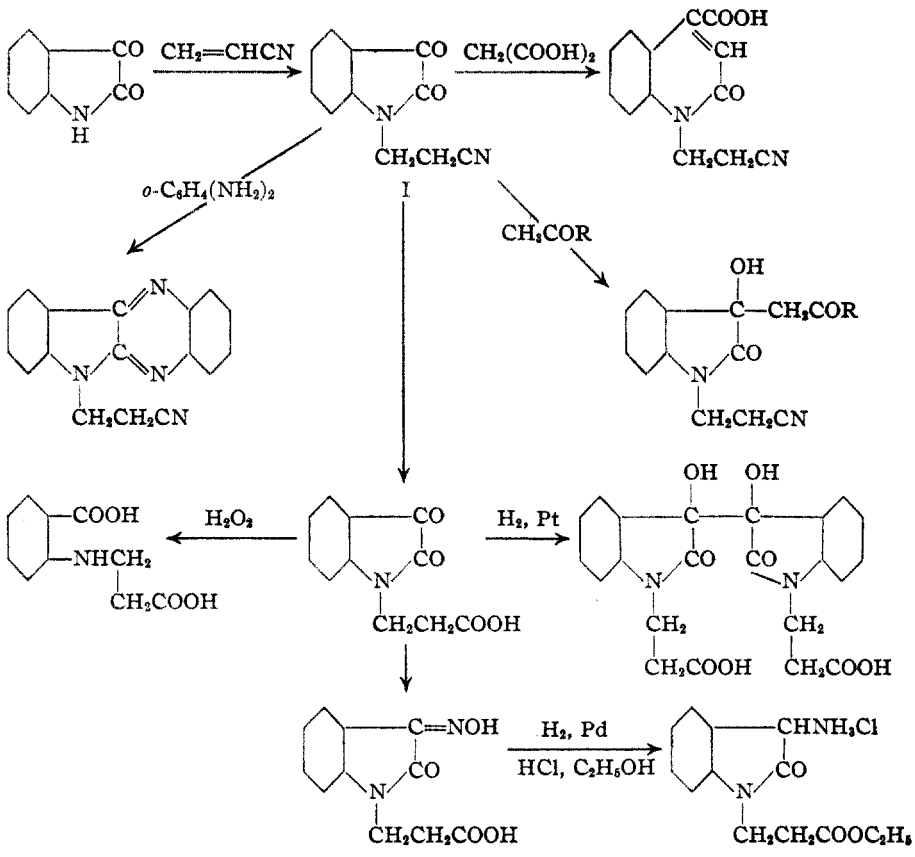
Anal. Calcd. for $C_{11}H_8O_2N_2$: N, 14.00. Found: N, 14.20.

Phenylhydrazone.—Prepared in aqueous solution, it was recrystallized from alcohol as yellow needles; m. p. 177°.

Anal. Calcd. for $C_{17}H_{14}ON_4$: N, 19.31. Found: N, 19.54.

Isatin-1-propionic Acid.—10.0 g. (0.05 mole) of cyanoethylisatin was refluxed with 120 cc. of 10% sodium hydroxide for one-half hour. The solution was acidified with concentrated hydrochloric acid. By allowing the hot solution to cool slowly and then to stand in the refrigerator for a day, 9.8 g. (90%) of long orange needles separated which

(2) Stollé and Merkle, *J. prakt. Chem.*, **139**, 334 (1934).



melted at 153°. Recrystallization from water involved very little loss and did not change the m. p.

Anal. Calcd. for $C_{11}H_9O_4N$: N, 6.39. Found: N, 6.42.

Phenacyl Ester.—Prepared from phenacyl bromide[3]; pale orange crystals from alcohol; m. p. 150°.

Anal. Calcd. for $C_{19}H_{15}O_5N$: N, 4.15. Found: N, 4.17.

β-Aminoöxindole Hydrochloride.—Four grams of dry hydrogen chloride was passed into a solution of 4.1 g. of isatin-β-oxime (synthesized according to the procedure of Borsche and Sander,[4] m. p. 224°) in 150 cc. of absolute alcohol. Palladium catalyst (1.0 g.) prepared according to the method of Hartung[5] was added and the mixture was hydrogenated for two hours; the starting pressure was 50 lb. per sq. in. A considerable amount of the amine hydrochloride separated. The hydrogenation mixture was diluted to 650 cc. with absolute alcohol, boiled and filtered while hot. The catalyst was washed with hot absolute alcohol. Dry hydrogen chloride was passed into the red filtrate until the color was discharged. Then the mixture was concentrated under reduced pressure to *ca.* 40 cc. and an equal volume of ether was added. The precipitate was filtered off, washed with ether and dried *in vacuo;* 3.1 g. of white amine hydrochloride. The m. p. was indefinite.

Anal. Calcd. for $C_8H_9ON_2Cl$: N, 15.18. Found: N, 15.45.

3-(*p*-Dimethylbenzylideneamino)-oxindole.—A mixture of 0.5 g. of β-aminooxindole hydrochloride, 0.5 g. of *p*-dimethylaminobenzaldehyde, 0.3 g. of fused sodium acetate, and 50 cc. of absolute alcohol was refluxed for one hour. After cooling, the solid was filtered off and successively washed with water, alcohol and ether; m. p. 241°.

Anal. Calcd. for $C_{17}H_{17}ON_3$: N, 15.05. Found: N, 15.25.

Cyanoethylisatin-β-oxime.—A mixture of 3.0 g. of cyanoethylisatin, 1.0 g. of hydroxylamine hydrochloride, 3.0 g. of sodium acetate and 50 cc. of water was refluxed for twenty-five minutes. After crystallization of the precipitate from methyl alcohol, 2.0 g. of yellow needles was obtained which melted at 216°.

Anal. Calcd. for $C_{11}H_9O_2N_3$: N, 19.53. Found: N, 19.40.

3-Oximino-oxindole-1-propionic Acid.—A solution of 9.0 g. of isatin-1-propionic acid, 9.0 g. of sodium acetate and 6.0 g. of hydroxylamine hydrochloride in 100 cc. of water was refluxed until the solution became yellow (*ca.* forty minutes). Then 5 cc. of concentrated sulfuric acid was added. The oxime separated after cooling the solution and was crystallized from alcohol; 9.0 g. as yellow needles; m. p. 215°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: N, 11.97. Found: N, 12.07.

Ethyl 3-Amino-1-oxindolepropionate Hydrochloride.—A solution of 4.68 g. (0.02 mole) of the oxime of isatin propionic acid and 3.6 g. (0.1 mole) of dry hydrogen chloride in 200 cc. of absolute alcohol was hydrogenated in the presence of 1.0 g. of palladium catalyst at an initial pressure of 50 lb. per sq. in. The reaction was complete after eighty minutes. The catalyst was filtered off and washed with a small quantity of absolute alcohol. After the filtrate was concentrated to *ca.* 20 cc., it was diluted with approximately ten volumes of ether. The oil which separated became a white solid after standing in the refrigerator overnight. The product was filtered, washed with ether and dried *in vacuo;* 4.9 g., m. p. *ca.* 150°.

Anal. Calcd. for $C_{13}H_{17}O_3N_2Cl$: N, 9.83. Found: N, 9.85.

1-Cyanoethyl-3-acetonyl-3-hydroxyoxindole.—A solution of 4.0 g. of cyanoethylisatin, 2 cc. of diethylamine and 65 cc. of acetone was allowed to stand at room temperature for thirty-six hours. Then the solvent was distilled under reduced pressure. The residue was washed with water and crystallized from acetone; 2.6 g. of white needles, m. p. 154–155°.

Anal. Calcd. for $C_{14}H_{14}O_3N_2$: N, 10.85. Found: N, 10.96.

1-Cyanoethyl-3-hydroxy-3-phenacyloxindole.—Cyanoethylisatin (3.5 g.) and acetophenone (3.0 g.) were dissolved in 500 cc. of absolute alcohol to which was added 2 cc. of diethylamine. The solution was allowed to stand at room temperature for twenty-four hours and then it was concentrated to *ca.* 65 cc. After two days in the refrigerator, the yellow needles which formed were separated by filtration, washed with ether and recrystallized from alcohol; 4.5 g. of pale yellow needles, m. p. 160°

(3) Shriner and Fuson, "Identification of Organic Compounds," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 132.

(4) Borsche and Sander, *Ber.*, **47**, 2819 (1914).

(5) Hartung, THIS JOURNAL, **50**, 3370 (1928).

Anal. Calcd. for $C_{19}H_{16}O_3N_2$: N, 8.75. Found: N, 8.84.

Hydantoin-($\Delta^{5,3'}$)-1'-cyanoethyloxindole.—A mixture of 5.0 g. of cyanoethylisatin, 2.5 g. of hydantoin, 5.0 g. of fused sodium acetate, 25 cc. of glacial acetic acid and 1 cc. of acetic anhydride was digested in an oil-bath at 150° for two hours. The solids dissolved when the boiling point was reached and in a short time the condensation product separated. The mixture was triturated with 250 cc. of water, filtered and the residue washed successively with copious quantities of water and alcohol. After the yellow needles were dried at 100°, the yield was 4.8 g. The product was practically insoluble in ordinary organic solvents and neither melted nor decomposed below 300°.

Anal. Calcd. for $C_{14}H_{10}O_3N_4$: N, 19.86. Found: N, 20.05.

Rhodanine-($\Delta^{5,3'}$)-1'-cyanoethyloxindole.—A mixture of 2.0 g. of cyanoethylisatin, 1.33 g. of rhodanine, 1.64 g. of fused sodium acetate, 22 cc. of glacial acetic acid and 0.3 cc. of acetic anhydride was heated for four and one-half hours at 130°. The reaction mixture was triturated with water, filtered and the residue washed successively with water and alcohol; 3.4 g. of red condensation product, m. p. 284°.

Anal. Calcd. for $C_{14}H_9O_2N_3S_2$: N, 13.33. Found: N, 13.29.

1-Cyanoethyl-2-quinolone-4-carboxylic Acid.—A mixture of 4 g. of cyanoethylisatin, 2.7 g. of malonic acid and 5 cc. of glacial acetic acid was heated in an oil-bath at 100–105° for eleven hours. The viscous solution was poured into water. The crude acid was filtered off and recrystallized from water to which decolorizing charcoal was added; 2.7 g. of white needles, m. p. 232°.

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: N, 11.57. Found: N, 11.39.

3-(*p*-Methoxyphenylimino)-1-oxindolepropionitrile.—Cyanoethylisatin (7.0 g.) and *p*-anisidine (12.0 g.) were dissolved in boiling alcohol and 0.2 g. of iodine was added. The mixture was refluxed for one-half hour. After cooling, the precipitate was filtered off and washed thoroughly with ether. Crystallization from benzene–petroleum ether yielded 9.0 g. of orange product of m. p. 143°.

Anal. Calcd. for $C_{18}H_{15}O_2N_3$: N, 13.77. Found: N, 13.61.

6-Cyanoethyl Indophenazine.—To a solution of 1.0 g. of cyanoethylisatin and 0.01 g. of iodine in 20 cc. of boiling alcohol, 0.54 g. of *o*-phenylenediamine was added. After refluxing for twenty minutes, the dark solution was poured into 50 cc. of water. The precipitate was filtered off and crystallized from methyl alcohol; pale yellow needles, m. p. 208–209°.

Anal. Calcd. for $C_{17}H_{12}N_4$: N, 20.59. Found: N, 20.78.

N-Methylanthranilic Acid.—To a solution of 7.7 g. of N-methylisatin in 150 cc. of 10% sodium hydroxide was added 150 cc. of 3% hydrogen peroxide over a period of fifteen minutes. After the solution was allowed to stand for one-half hour, it was cooled and made just acidic with hydrochloric acid. The acid which separated was filtered off and recrystallized from alcohol to which boneblack was added. The product melted at 177° and a mixed m. p. with an authentic sample of N-methylanthranilic acid showed no depression.

N-(2-Carboxyphenyl)-β-alanine.—Cyanoethylisatin (4.8 g.) was refluxed for one-half hour with 60 cc. of 10% sodium hydroxide. The resulting solution was cooled and 75 cc. of 3% hydrogen peroxide was added dropwise with stirring over a period of about fifteen minutes. After one-half hour at room temperature, the solution was acidified with concentrated hydrochloric acid and the precipitate which formed was filtered off and washed with water. Recrystallization from water containing decolorizing charcoal yielded 3.0 g. of small white crystals; m. p. 170°. The molecular weight of the acid was found to be 206 as determined from its neutral equivalent; actual, 209. In solution, this compound produced violet fluorescence.

Anal. Calcd. for $C_{10}H_{11}O_7N$: N, 6.69. Found: N, 6.88.

1,1'-Dimethyl Isatide.—A mixture of 4.83 g. (0.03 mole) of 1-methylisatin and 130 cc. of absolute alcohol was hydrogenated in the presence of 0.1 g. of platinic oxide at an initial pressure of 50 lb. per sq. in. The theoretical amount of hydrogen was taken up in twenty minutes. The catalyst was removed by filtration and the pale yellow filtrate was concentrated to a small volume. Upon the addition of several volumes of water, 4.6 g. of the white isatide was precipitated. After crystallization from dilute alcohol, the product melted to a red liquid at 172–174°.

Anal. Calcd. for $C_{18}H_{16}O_4N_2$: N, 8.64. Found: N, 8.75.

Isatide-1,1'-dipropionic Acid.—Hydrogenation of isatin-1-propionic acid (5.48 g.) in 100 cc. of absolute alcohol over 0.1 g. of platinic oxide was complete in ten minutes. After filtration of the catalyst and evaporation of the alcohol under reduced pressure, the crude product was obtained in a practically quantitative yield. Recrystallization from water gave the white isatide which melted to a red liquid at 183–184°.

Anal. Calcd. for $C_{22}H_{20}O_8N_2$: N, 6.36. Found: N 6.44.

Summary

1. Cyanoethylisatin has been prepared and found to undergo condensation reactions with acetone, acetophenone, hydantoin, rhodanine, malonic acid and several amino compounds.

2. N-Methylisatin and isatin-1-propionic acid were oxidized to derivatives of anthranilic acid and were hydrogenated to isatides.

3. β-Aminoöxindole hydrochloride was synthesized by the catalytic hydrogenation of isatin-β-oxime.

4. Isatin-1-propionic acid was converted to ethyl 3-amino-1-oxindolepropionate hydrochloride.

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