[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

The Reformatsky Reaction in the Isatin Series[1]

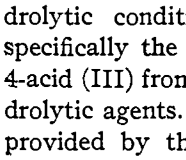
BY FREDERICK J. MYERS AND H. G. LINDWALL

The ketonic characteristics of the beta carbonyl group of the isatin molecule suggested the application of the Reformatsky reagents in the synthesis of beta-substituted derivatives of oxindole, and the reactions of zinc and ethyl bromoacetate with isatin, with O-methylisatin, and with N-alkylisatins have been investigated.

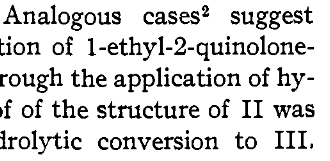
There is no evidence of reaction in the case of isatin, even with wide variations in the physical conditions employed, and with O-methylisatin only tarry material and isatin result. N-Alkylisatins, however, undergo definite changes with the Reformatsky reagents.

When equimolecular amounts of zinc, ethyl bromoacetate, and N-ethylisatin are used, the principal product is N-ethyldioxindole (I). The identity of I was proved by comparing it with a known sample of N-ethyldioxindole; furthermore, repetition of the procedure yielded I again as the only recognizable product.

With two moles of zinc and of ethyl bromoacetate for each mole of N-ethylisatin, another product (II) resulted. The analysis of II was in agreement with that calculated for ethyl (1-ethyl-3-hydroxy-oxindolyl-3)-acetate, which would be the product to be anticipated from the normal Reformatsky reaction.

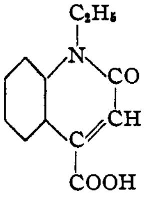


I



II

An oxindole derivative of this type (II) should undergo conversion to a quinolone acid under hydrolytic conditions. Analogous cases[2] suggest specifically the formation of 1-ethyl-2-quinolone-4-acid (III) from II through the application of hydrolytic agents. Proof of the structure of II was provided by this hydrolytic conversion to III. Compound III has not been prepared previously, but the N-methyl analog is known; employing Aeschlimann's[3] method for the preparation of 1-methyl-2-quinolone-4-acid, III was obtained without difficulty. Comparison of samples of III from these two sources showed them to be identical.



III

Compound II, upon treatment with concentrated ammonium hydroxide, yielded the amide, (1-ethyl-3-hydroxy-oxindolyl-3)-acetamide (IV). Compound IV, like II, gave III upon strenuous hydrolytic treatment.

The corresponding N-methyl analogs of II, III, and IV (V, VI and VII, respectively) also were prepared. Their preparation proceeded smoothly using methods like those described above. The ethyl ester of (3-hydroxy-1-methyloxindolyl-3)-acetic acid (V) and its amide (VII) yield 1-methyl-2-quinolone-4-acid (V) upon treatment with concentrated potassium hydroxide solutions.

The oxindole derivatives described are being studied further.

Experimental Part

N-Ethyldioxindole (I).—Equimolecular amounts of N-ethylisatin, ethyl bromoacetate, and zinc turnings (0.02 mole of each) were heated in 25 cc. of absolute benzene on the steam-bath for nine hours. An appreciable amount of tar formed; treatment with cold dilute sulfuric acid yielded I, which was identified by comparison with a sample of N-ethyldioxindole prepared by the reduction of N-ethylisatin with tin and hydrochloric acid.

The Ethyl Ester of (3-Hydroxy-1-ethyloxindolyl-3)-acetic Acid (II).—N-Ethylisatin (3.5 g., 0.02 mole) was added to a mixture of ethyl bromoacetate (6.68 g., 0.04 mole) and zinc turnings (2.64 g., 0.04 mole) in 25 cc. of absolute benzene. The mixture was heated on the steam-bath for one and one-half hours, and then was added to ice and sulfuric acid. The product separated after four hours of standing: yield, 4.0 g. (76%); soluble in glacial acetic acid, methyl alcohol, ethyl alcohol, water; crystallized from water as large colorless plates, m. p. 127–128.5°.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.63, 63.86; H, 6.43, 6.58; N, 5.38, 5.23.

The Ethyl Ester of (3-Hydroxy-1-methyloxindolyl-3)-acetic Acid (V).—Compound V was prepared as above for II: yield, crude, 76%; recrystallized from water as large colorless plates, m. p. 100–101.5°.

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[1] Presented in part at the Rochester meeting of the American Chemical Society, September, 1937.

[2] Zrike and Lindwall, THIS JOURNAL, **58**, 49 (1936).

[3] Aeschlimann, *J. Chem. Soc.*, **128**, 2902 (1926).

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.84; H, 6.15, 5.95; N, 5.57.

The Amide of (3-Hydroxy-1-ethyloxindolyl-3)-acetic Acid (IV).—Compound II (1.0 g.) in 20 cc. of concentrated ammonoum hydroxide was allowed to stand at room temperature for sixteen days. During this time II dissolved slowly. The product was isolated by slow evaporation of the solution at room temperature. Compound IV is readily soluble in most common solvents, including benzene, ethyl alcohol, acetone, and water. It was purified by crystallization through slow evaporation of the aqueous solution; no attempt was made to isolate more than a small percentage of the theoretical yield; hexagonal colorless prisms, m. p. 186.5–188.5°.

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: N, 11.97. Found: N, 11.53, 11.71.

The Amide of (3-Hydroxy-1-methyloxindolyl-3)-acetic Acid (VII).—Compound VII was prepared by the same method as that used for the preparation of IV: crystallized from water, by slow evaporation of the solution, as colorless stubby prisms; m. p. 191.5–193.5°.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: N, 12.73. Found: N, 12.41, 12.58.

1-Ethyl-2-quinolone-4-acid (III). A. From Malonic Acid and N-Ethylisatin.—N-Ethylisatin (3.4 g.) and malonic acid (2.1 g.) in 10 cc. of glacial acetic acid were refluxed for twenty hours. The product, which separated when the solution was cooled, was recrystallized from dilute ethyl alcohol and was obtained as long white needles, m. p. 205–206°.

B. By Hydrolytic Treatment of II.—A mixture of Compound II (0.5 g.) and 10 cc. of 50% potassium hydroxide solution was refluxed for two hours. At the end of this time the solution was diluted with an equal volume of water, decolorized with charcoal, and filtered. Acidification of the filtrate with dilute sulfuric acid caused the precipitation of III.

C. By Hydrolytic Treatment of IV.—Compound IV was substituted for II in the procedure outlined above in **B.** Compound III again resulted.

The crude samples of III from B and C were purified by crystallization from dilute ethyl alcohol. Each melted at 205–206°, and no depression of the melting point was observed when either was mixed with a sample of III from A.

Ethyl Ester of III.—Individual samples of III from procedures A, B and C above were esterified with ethyl alcohol. The products of these esterifications were found, by melting point methods, to be identical. The ester crystallizes from dilute ethyl alcohol as long white needles; m. p. 88.5–89°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: N, 5.71. Found: N, 5.58.

1-Methyl-2-quinolone-4-acid (VI). (A) From Malonic Acid and N-Methylisatin.—These compounds were heated together in glacial acetic acid according to the method described by Aeschlimann,[3] and yielded VI.

(B) By Hydrolytic Treatment of V or VII.—Compound V (or VII) was heated for two hours in a 50% solution of potassium hydroxide. The product was precipitated by acidification with dilute sulfuric acid, and was obtained as short white needles by crystallization from ethyl alcohol; m. p. 248–250°. Melting point methods and comparison of the ethyl esters proved the samples of VI from A and B to be identical.

Summary

N-Methyl- and N-ethylisatins have been shown to undergo the normal Reformatsky reaction with zinc and ethyl bromoacetate to yield the respective ethyl esters of (3-hydroxy-1-alkyloxindolyl-3)-acetic acid. These esters, and the amides derived from them, yield the corresponding 1-alkyl-2-quinolone-4-acids under hydrolytic treatment.

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Alkylation of Benzene by Esters by the Friedel–Crafts Reaction

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This paper describes the alkylation of benzene by certain esters using anhydrous aluminum chloride as the condensing agent.

Alkylation by the Friedel–Crafts reaction usually has employed alkyl halides. By analogy the same results might be expected using esters. For the most part this was found to be the case, although the structural analogy between esters and acid anhydrides led the author to anticipate the formation, in part at least, of ketones since benzene and acetic anhydride will consistently give more than one mole of acetophenone for each mole of the anhydride. Such formation of ketones from esters has in fact been observed by Kaschtanow,[1a] by Guyot,[2] and by Cryer.[3] Friedel and Crafts,[4] however, showed that ethyl chlorocarbonate alkylated benzene instead of acylating it, as might be expected. Every effort was made in our work to discover ketones in the by-products of the reactions we carried out, but at no time was sufficient material of proper boiling point obtained to permit such identification. The quantity of

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[1] (a) L. I. Kaschtanow, *Chem. Zentr.*, **104**, 600 (1933); (b) **104**, 2512 (1933).

[2] Guyot, *Compt. rend.*, **144**, 1120 (1908).

[3] J. Cryer, *Trans. Roy. Soc. Can.*, [3] **19**, 29 (1925); *C. A.*, **20**, 408 (1926).

[4] Friedel and Crafts, *Compt. rend.*, **84**, 1450 (1877).