[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Quinolone Acids from Oxindole Derivatives

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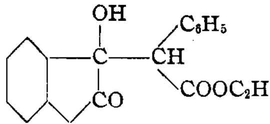
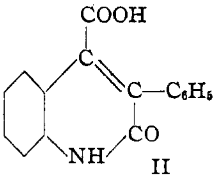
Ethyl phenylacetate condenses with isatin in the presence of diethylamine to yield 3-hydroxy-3-(phenyl, carbethoxy)-methyloxindole (I). This compound shows the aldol characteristic of decomposition into the original reactants upon treatment with alkali; it is quite stable toward cold mineral acid, but warming in this medium causes the formation of the known 3-phenyl-2-quinolone-4-acid (II).[1]

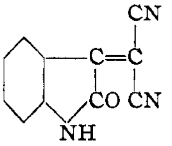


I

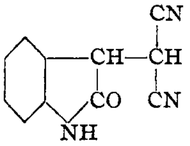


II

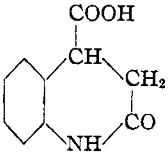
Malonitrile condenses with isatin forming 3-(dicyano)-methyleneoxindole (III), the "isatomalonitril" of Walter.[2] Reduction of III yields 3-(dicyano)-methyloxindole (IV), which is unstable in hot solvents forming a red material which was not investigated. Hydrolytic agents, acid or alkali, cause the formation of 1,2,3,4-tetrahydro-2-quinolone-4-acid (V) which was identified by comparison with a known[3] sample.



III



IV



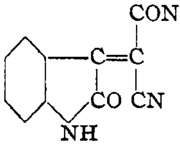
V

Since compound IV produced V upon hydrolysis, it was expected that III would also yield a monobasic acid, specifically 2-quinolone-4-acid, but that product was not obtained. Instead, hydrolytic agents caused the formation of a compound (VI) having the formula $C_{11}H_7O_5N$. This compound (VI) is evidently a dibasic acid, forming a di-silver salt from which the diethyl ester (VII) can be prepared. The properties and analysis of VI suggest that its structure is 2-quinolone-3,4-diacid, but a definite statement concerning structure must await synthesis by other methods.

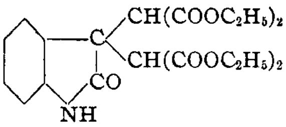
Compound VI yields 1,2,3,4-tetrahydro-2-quinolone-4-acid (V) upon reduction with zinc and acetic acid at steam-bath temperature; reduction of VI at lower temperatures with sodium amalgam also gives V and carbon dioxide. Both reduction methods thus involve the loss of carbon dioxide equivalent to one carboxyl group.

Condensation of cyanoacetamide with isatin yields 3 - (cyano, formamido) - methyleneoxindole (IX), which also forms the dibasic acid (VI) upon treatment with acidic hydrolytic agents.

The tetraethyl ester of 3,3-bis-(methane diacid)-oxindole (X)[4] is exceedingly stable in the presence of mineral acids, but when heated with an excess of alkali, hydrolysis and the loss of one mole of malonic acid takes place, with the formation again of compound VI. When smaller amounts of alkali, or a shorter time of heating, are used, a red intermediate compound forms which is converted to VI by further treatment with alkali; this red substance was not investigated.



IX



X

The samples of VI from the various sources were shown to be identical through formation of the diethyl ester (VII) from the di-silver salt.

Experimental Part

3 - Hydroxy - 3 - (phenyl, carbethoxy) - methyloxindole (I).—A mixture of isatin (10 g.), ethyl phenylacetate (12 g.) and 3 cc. of diethylamine in 5 cc. of absolute ethyl alcohol was allowed to stand at room temperature for five days. The solid product was crystallized from a benzene–ligroin medium; yield 71%; needles, m. p. 154–156°. Warming in 1% sodium hydroxide produces isatin.

Anal. Calcd. for $C_{18}H_{17}O_4N$: C, 69.42; H, 5.51; N, 4.50. Found: C, 69.74; H, 5.28; N, 4.37.

3-Phenyl-2-quinolone-4-acid (II) from I.—A mixture of 2 g. of I in 20 cc. of concentrated hydrochloric acid containing 2 cc. of alcohol was refluxed for six hours; yield 90%; recrystallized from glacial acetic acid; m. p. 295°, with no depression when mixed with a known sample.

Anal. Calcd. for $C_{16}H_{11}O_3N$: N, 5.28. Found: N, 5.23.

3 - (Dicyano) - methyloxindole (IV) from III.—"Isatomalonitril" (III) (5 g.), prepared by Walter's method,[2]

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[1] Gysae, *Ber.*, **26**, 2484 (1893); Hübner, *ibid.*, **41**, 483 (1908); Borsche and Jacobs, *ibid.*, **47**, 354 (1914).

[2] Walter, *ibid.*, **35**, 1321 (1902).

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

[4] Lindwall and Hill, THIS JOURNAL, **57**, 735 (1935).

was shaken with 4 g. of sodium hyposulfite ($Na_2S_2O_4$) in 20 cc. of water for fifteen minutes. After the color had disappeared, the solid was crystallized by dissolving in the minimum amount of acetone and diluting with water; long white needles after several hours; m. p. 183–185°, with darkening at 160° approx.; yield, 80%.

Anal. Calcd. for $C_{11}H_7ON_3$: N, 21.32. Found: N, 21.19.

1,2,3,4-Tetrahydro-2-quinolone-4-acid (V) from IV.—To five grams of IV was added 35 cc. of 10% sodium hydroxide and the mixture was refluxed until no more ammonia was given off. Cooling and acidification were followed by evaporation to dryness. Crystallized from alcohol as white needles; m. p. 217–218°, with no depression when mixed with a known sample. Further identification was by conversion to the ethyl ester.

Anal. Calcd. for $C_{10}H_9O_3N$: N, 7.33. Found: N, 7.20.

3-(Cyano, formamido)-methyleneoxindole (IX).—Isatin (5 g.) and cyanoacetamide (3 g.) were condensed by heating on the steam-bath for ten hours in 50 cc. of absolute alcohol containing five drops of piperidine. The product was obtained as red crystals from alcohol; m. p. 248–250°.

Anal. Calcd. for $C_{11}H_7O_2N_3$: N, 19.72. Found: N, 19.51.

Compound VI from III, IX or X. (A) From III or IX.—Three grams of III (or of IX) was heated in 20 cc. of concentrated hydrochloric acid at the boiling point of the mixture until the color was nearly lost, and the material was in solution. The solid matter resulting after evaporation to dryness was crystallized from water.

(B) **From X.**—Compound X proved to be very stable in the presence of mineral acid; alkaline hydrolysis was used. A mixture of 20 g. of X and 100 cc. of 10% sodium hydroxide was refluxed for ten hours. The color became red, then pink. Cooling and acidification yielded a solid as short white needles upon crystallization from water; m. p. above 340°; soluble in water and hot alcohol.

Anal. Calcd. for $C_{11}H_7O_5N$: C, 56.65; H, 3.00; N, 6.01; neut. equiv., calcd. for a dibasic acid, 116.5. Found: C, 57.01, 56.96; H, 3.37, 3.20; N, 5.93, 5.91; neut. equiv., 117.

Di-silver Salt of VI.—Compound VI was dissolved in ammonium hydroxide, and excess ammonia was removed by heating, before addition of silver nitrate; the presence of excess ammonia causes the formation of a tri-silver salt.

Anal. Calcd. for $C_{11}H_5O_5NAg_2$: Ag, 48.30. Found: 48.26.

Diethyl Ester of VI. (VII.)—Ethyl iodide and the di-silver salt of VI produced VII as pale yellow flat needles upon crystallization from water; m. p. 150–151°; soluble in alcohol, benzene and ethyl acetate.

Anal. Calcd. for $C_{15}H_{15}O_5N$: C, 62.30; H, 5.19; N, 4.85. Found: C, 62.41; H, 5.44; N, 4.93.

1,2,3,4-Tetrahydro-2-quinolone-4-acid (V) by Reduction of VI. (A) Zinc and Acetic Acid.—Compound VI (2 g.) was heated on the steam-bath in 10 cc. of glacial acetic acid with twice the calculated amount of zinc. When solution was complete excess zinc was removed and water was added; V separated slowly upon cooling. Crystallization from water yielded white needles; m. p. 218°; identified by comparison with a known sample.

(B) Sodium Amalgam.—Compound VI was treated at room temperature with sodium amalgam and cold water; subsequently the mixture was acidified with concentrated hydrochloric acid and the temperature was allowed to rise to 75°. A brisk evolution of carbon dioxide and a heavy precipitation of V resulted.

Summary

The aldol-type condensation product of isatin and ethyl phenylacetate yields 3-phenyl-2-quinolone-4-acid upon treatment with mineral acid; 3-(dicyano)-methyloxindole similarly gives tetrahydro-2-quinolone-4-acid.

The oxindole derivatives prepared by condensation of cyanoacetamide, malonitrile and diethylmalonate with isatin form a dibasic acid upon hydrolysis; this product yields tetrahydro-2-quinolone-4-acid and carbon dioxide upon reduction.

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