[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

CONDENSATION REACTIONS OF CYCLIC KETONES. II. THE FORMATION OF QUINOLINE DERIVATIVES FROM CERTAIN INDIGOIDS

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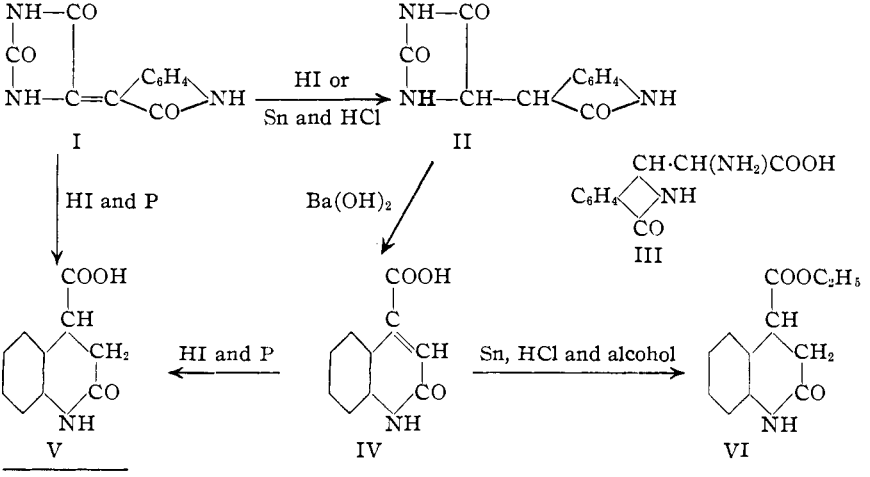
It has been shown by one of us[1] that hydantoin will condense with isatin, giving hydantoin-($\Delta^{5,3'}$)-oxindole, I. Hydrolysis of the reduction product, II, of this compound, should theoretically give oxindole-amino-acetic acid, III, and thus afford a new and convenient method for the synthesis of oxindole acids. This possibility was suggested in the previous paper[1] of this series.

However, we have now found that the hydrolytic reaction proceeds in abnormal fashion, and that the end-product is a quinoline derivative, the nature of which depends upon the type of hydrolytic agent used.[2]

Hydantoin-($\Delta^{5,3'}$)-oxindole reduces smoothly to hydantoin-5,3'-oxindole, II, by the action of tin and hydrochloric acid, or hydriodic acid in acetic acid medium. When the reduced indigoid, II, is hydrolyzed with barium hydroxide, the usual cleavage of the hydantoin ring takes place, but this is followed by profound decomposition, involving opening of the oxindole ring, deaminization and final closure to 2-quinolone-4-carboxylic acid, IV. This substance can be reduced to the saturated acid, V, by hydriodic acid and phosphorus, or by tin and an alcohol solution of hydrogen chloride, the ethyl ester, VI, of the reduced acid being produced by these latter reagents.



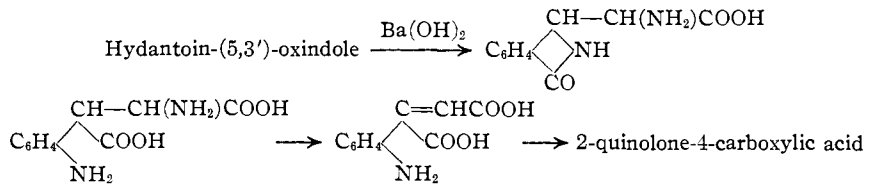
I II III IV V VI

[1] Hill and Henze, THIS JOURNAL, 46, 2806 (1924).

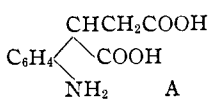
[2] Preliminary paper presented by Hill and Lindwall at the Philadelphia meeting of the American Chemical Society, September, 1926.

Indeed, hydantoin-($\Delta^{5,3'}$)-oxindole itself can be directly transformed into the saturated acid, V, 2-keto-1,2,3,4-tetrahydroquinoline-4-carboxylic acid, by treatment with hydriodic acid and red phosphorus.

The mechanism of the formation of 2-quinolone-4-carboxylic acid from hydantoin-(5,3')-oxindole would appear to be as follows

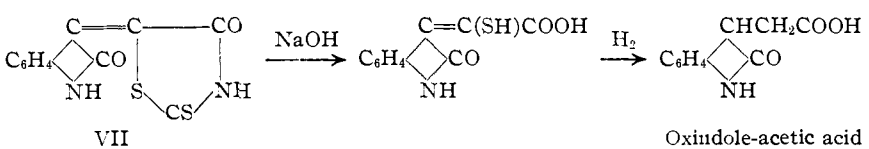


In the last step ring closure may theoretically take place to give either an indolinone or a quinoline ring depending on the carboxyl group which functions in the change. However, conditions favor the formation of the six-membered ring. A somewhat similar interpretation may be given to the reaction with hydriodic acid and red phosphorus. It would differ chiefly in having an additional step representing the formation of the saturated acid (A), which would be derived either from the corresponding unsaturated acid or from the amino acid. It will be observed that oxindole-acetic acid would have been formed had the closure involved the carboxyl group derived from the original isatin carbonyl group, or had the oxindole ring remained unbroken during the reaction. That the five-membered ring does not form will be demonstrated by a number of considerations.



A

Coincident with our discovery of these interesting reactions of hydantoin-($\Delta^{5,3'}$)-oxindole, Granacher[3] published an account of a procedure for making so-called oxindole-acetic acid, the starting material being β-rhodanal-oxindole, VII. His method is outlined as



VII Oxindole-acetic acid

The properties of our reduced acid, V (later shown to be a quinoline derivative), and also its derivatives, were identical with those of Granacher's oxindole-acetic acid and its derivatives. These facts were presented by two of us,[4] but with reservations regarding the correctness of the structural interpretations, having in mind the possibility of the cleavage of the oxindole ring during these reactions.

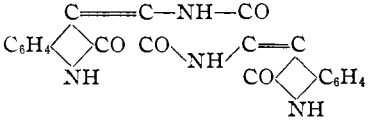
[3] Granacher and Mahal, *Helv. Chim. Acta*, **6**, 467 (1923).

[4] Hill and Schultz, Washington Meeting of the American Chemical Society, April, 1924.

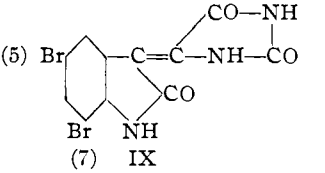
Accordingly we synthesized 2-quinolone-4-carboxylic acid by two well-known methods, first, by treating acetyl-isatin with sodium hydroxide[5] and, second, by condensing isatin with malonic acid.[6] The substance resulting from either of these two procedures was identical with our unreduced acid, IV, and the reduced acid derived from any one of the three sources was identical with Granacher's so-called oxindole-acetic acid. The end-product of our synthesis and also that of Granacher's is, therefore, 2-keto-1,2,3,4-tetrahydroquinoline-4-carboxylic acid, V. The correctness of our conclusions is further substantiated by Aeschlimann's[7] recent work, which also deals with the structure of 2-quinolone-4-carboxylic acid, and with Granacher's "oxindole-acetic acid."

The application of diketopiperazine to the preparation of 2-keto-tetrahydroquinoline-4-carboxylic acid was productive of results wholly similar to those obtained with hydantoin. The condensation of diketopiperazine with two molecules of isatin was readily accomplished in sodium acetate–acetic acid–acetic anhydride medium, the end-product, VIII, being acetylated by reason of the necessity of using a large excess of acetic anhydride in order to effect condensation.

On simultaneous reduction and hydrolysis of this compound with hydriodic acid and phosphorus, 2-keto-tetrahydroquinoline-4-carboxylic acid was formed.



VIII



(7) IX

The writers have been successful in condensing 5-bromo- and 5,7-dibromo-isatin with both hydantoin and diketopiperazine. Owing to the fact that these highly colored indigoids are extremely insoluble, the study of their reduction and subsequent hydrolysis has been rendered difficult. However, it is significant that hydantoin-($\Delta^{5,3'}$)-5',7'-dibromoxindole, IX, is converted into 2-keto-tetrahydroquinoline-4-carboxylic acid by heating with phosphorus and hydriodic acid.

Experimental Part

Hydantoin-5,3'-oxindole (II) by the Reduction of Hydantoin-($\Delta^{5,3'}$)-oxindole

A. Reduction with Tin and Hydrochloric Acid.—Ten grams of hydantoin-($\Delta^{5,3'}$)-oxindole was suspended in 200 cc. of ethyl alcohol and after the addition of 13 g. of tin, hydrogen chloride was passed into the hot solution until the metal had dissolved. The indigoid was completely reduced after a second treatment with 13 g. of tin, followed by

[5] Camps, *Arch. Pharm.*, **237**, 687 (1899).

[6] Borsche and Jacobs, *Ber.*, **47**, 354 (1914).

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

saturation of the solution with hydrogen chloride. The excess alcohol and acid was removed by distillation under diminished pressure and hydrochloric acid (10%) was added to the residual material. Acid was used in preference to water in order to prevent precipitation of basic tin compounds. Hydantoin-(5,3′)-oxindole separated from this solution upon standing. It was filtered off and purified by crystallization from water; it separated from this solvent in small needles which melted with decomposition at 276°, though incipient fusion took place somewhat below this temperature. It is soluble in glacial acetic acid, alcohol and alkali, but insoluble in ether, benzene and acetone.

Anal. Calcd. for $C_{11}H_9O_3N_3$: N, 18.18; C, 57.14; H, 3.89. Found: N, 17.87; C, 57.36; H, 4.12.

B. **Reduction with Hydriodic Acid in Glacial Acetic Acid.**—Ten grams of hydantoin-($\Delta^{5,3'}$)-oxindole, 45 cc. of hydriodic acid (sp. gr. 1.7) and 100 cc. of glacial acetic acid were gently boiled in an oil-bath for forty-five minutes, or until complete solution was effected. After removal of the acids by distillation under diminished pressure, the residue was carefully extracted with boiling water and any solid material filtered off. On cooling the filtrate, the reduced hydantoin separated in characteristic needles, which were purified as in the previous method by crystallization from water. This substance melted unchanged (276°) when mixed with the product obtained by the reduction with tin and hydrochloric acid.

Anal. Calcd. for $C_{11}H_9O_3N_3$: N, 18.18. Found: N, 18.00.

2-Quinoline-4-carboxylic Acid. (IV.) A. By the Action of Barium Hydroxide on Hydantoin-(5,3′)-oxindole.—Ten grams of hydantoin-(5,3′)-oxindole, 75 g. of barium hydroxide, and 75 cc. of water were digested in an oil-bath under return condenser for two days, or until the evolution of ammonia had ceased. The reaction mixture was then diluted with 100 cc. of boiling water, the barium carbonate filtered off, thoroughly washed with water and the washings combined with the filtrate. Carbon dioxide was passed into the latter and, after boiling, a further quantity of barium was removed by filtration. By careful addition of dilute sulfuric acid to this hot filtrate, the remaining barium was completely precipitated as sulfate, which was immediately filtered off in order to avoid loss of the quinoline acid, which would have crystallized from the cool solution. The solution was then acidified strongly with acetic acid. Upon standing, it deposited silky needles of 2-quinolone-4-carboxylic acid. It was purified by three crystallizations from water. The yield was 2 g., or 25% of the theoretical.

The acid is soluble in alkali (from which it is precipitated by acid), and in hot water, but practically insoluble in cold water, absolute alcohol or benzene. It does not melt below 300°.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.70; N, 7.41. Found: C, 62.95; H, 3.79; N, 7.45.

B. **By the Action of Sodium Hydroxide on Acetyl-isatin.**—Five grams of acetyl-isatin dissolved in a 10% sodium hydroxide solution was heated for one hour on the steam-bath. On cooling and acidifying, the product separated, contaminated with some isatin. It was purified by crystallization from water after decolorization with Norite; yield, 3 g.

C. **By the Action of Malonic Acid on Isatin.**—Eight grams of malonic acid, 10 g. of isatin and 15 g. of glacial acetic acid were heated on the steam-bath for ten hours. The reaction mixture was poured into water; the impure acid was filtered off, triturated with alcohol to remove isatin and finally crystallized from water in which some Norite was used for decolorization purposes; yield, 8 g.

Methods B and C except for some changes in methods of procedure were based on

those of Camps[5] and of Borsche and Jacobs,[6] respectively. The acid produced by either method was identical with that resulting from method A, and the ethyl ester (m. p. 205°) in either case was identical with that prepared from A.

2-Keto-1,2,3,4-tetrahydroquinoline-4-carboxylic Acid. (V.) A. By the Action of Hydriodic Acid on Hydantoin-($\Delta^{5,3'}$)-oxindole.—Ten grams of hydantoin-oxindole, 6 g. of red phosphorus and 60 cc. of hydriodic acid (sp. gr. 1.7) were heated for seven hours at 150°. The excess hydriodic acid was then removed by distillation under diminished pressure, the residue digested with hot water and the phosphorus filtered off. The tetrahydro acid crystallized from the filtrate upon cooling. It was purified by crystallization from hot water. It separates from this solution in characteristic colorless needles which melt at 217–218°. The yield was 4.5 g., or 54% of the theoretical. It is soluble in hot water and alcohol and slightly soluble in benzene. It dissolves in sodium hydroxide solutions, from which it is reprecipitated unchanged on acidification with strong acids.

Anal. Calcd. for $C_{10}H_9O_3N$:. N, 7.33; C, 62.83; H, 4.71. Found: N, 7.20; C, 62.11; H, 4.54.

B. By the Action of Hydriodic Acid on 2,5-Diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(oxindole).—Two and five-tenths grams of 2,5-diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(oxindole), 1.8 g. of red phosphorus, and 17 cc. of hydriodic acid (sp. gr. 1.7) were heated for seven hours at 150°. It was then isolated from the reaction mixture by the same procedure that was employed in the preceding experiment. The yield was 35% of the theoretical.

Anal. Calcd. for $C_{10}H_9O_3N$: N, 7.33. Found: N, 7.55, 7.45.

C. By the Action of Hydriodic Acid on Hydantoin-($\Delta^{5,3'}$)-5,7-dibromo-oxindole.—The tetrahydro acid was prepared from this condensation product in a manner similar to A; yield, 40% of the theoretical. The isatin nuclei were completely debrominated in this experiment.

D. By the Action of Hydriodic Acid on 2-Quinolone-4-carboxylic Acid.—One and one-half g. of 2-quinolone-4-carboxylic acid, 10 cc. of hydriodic acid and one gram of red phosphorus were heated in an oil-bath at 140° for five hours. After removal of the hydriodic acid by distillation under diminished pressure, the quinolone-carboxylic acid was extracted from the residue with hot water and purified as above; yield, 1 g.

The acid resulting from this method was identical with that produced by Methods A, B and C, respectively, and with Granacher's[3] so-called oxindole-acetic acid, which was prepared by us precisely in accordance with his directions. The ethyl esters prepared by the esterification of the acids derived from any of these sources were identical; m. p. 155°.

The Ethyl Ester of 2-Keto-1,2,3,4-tetrahydroquinoline-4-carboxylic Acid. (VI.) The Action of Tin and Alcoholic Hydrogen Chloride on 2-Quinoline-4-carboxylic Acid.—Five grams of the unsaturated acid and 20 g. of mossy tin in 200 cc. of absolute alcohol were heated on the steam-bath for eight to ten hours, while hydrogen chloride was intermittently passed through the mixture. The unchanged tin was then filtered off and the greater part of the alcohol removed by distillation under diminished pressure. The residue was then poured into water slightly acidified with hydrochloric acid, and the ester separated as a white solid which was purified by crystallization from 50% alcohol. It crystallized in characteristic colorless needles which melted at 155°. It is soluble in water and alcohol, but insoluble in dilute alkali. The same ester was prepared by the direct esterification of the acid derived from each of the various methods given above for the synthesis of 2-keto-tetrahydroquinoline-4-carboxylic acid.

Anal. Calcd. for $C_{12}H_{13}O_3N$: N, 6.39. Found: N, 6.57, 6.61.

Condensation Products of Hydantoin with 5-Bromo-isatin and 5,7-Dibromo-isatin. General Procedure.—Five grams of hydantoin, 11.3 g. of monobromo-isatin (or 15.2 g.

of dibromo-isatin), 10 g. of fused sodium acetate, 50 cc. of glacial acetic acid and five drops of acetic anhydride were heated for four hours in an oil-bath at 150°. The solids dissolved upon application of heat and the condensation products separated soon after. In each case the reaction mixture was poured into water and the precipitate triturated several times with hot water, filtered off and dried at 100°. Because of the insolubility of these indigoids in all common solvents, their soluble impurities were removed by successive digestions with acetic acid, water and alcohol. The monobromo condensation product is red in color and the dibromo derivative is orange. The yield in the case of the former was 30%; in the case of the latter, 88%. Neither indigoid melted below 300°.

Anal. (Hydantoin-($\Delta^{5,3'}$)-5'-bromo-oxindole). Calcd. for $C_{11}H_6O_3N_3Br$: N, 13.63; Br, 25.97. Found: N, 13.85; Br, 26.43.

Anal. (Hydantoin-($\Delta^{5,3'}$)-5',7'-dibromo-oxindole). Calcd. for $C_{11}H_5O_3N_3Br_2$: N, 10.85; Br, 41.34. Found: N, 10.77; Br, 41.60.

Condensation Products of Diketopiperazine with Isatin, 5-Bromo-isatin and 5,7-Dibromo-isatin 2,5-Diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(oxindole). (VIII.)—Thirteen grams of isatin, 5 g. of diketopiperazine, 25 g. of anhydrous sodium acetate and 50 cc. of acetic anhydride were heated at 120–130° for five hours. Complete solution occurred immediately on heating this mixture, but this was followed shortly by voluminous precipitation of the condensation product. The mixture was finally poured into water and 16 g. of the impure indigoid obtained by filtration. It was purified by digesting it successively with glacial acetic acid, water and alcohol. The yield was 4.7 g., or 28% of the theoretical. This red condensation product is insoluble in all the common solvents. It dissolves, however, in concd. sulfuric acid, to which it imparts a deep permanganate color. It does not melt below 300°. As would be expected, both isatin nuclei were acetylated in this condensation.

Anal. Calcd. for $C_{20}H_{12}O_4N_4$: N, 12.28; C, 63.15; H, 3.51. Found: N, 12.23; C, 62.79; H, 3.87.

Except for the addition of an amount of fused sodium acetate roughly equivalent to the weight of the isatin derivative used, 5-bromo-isatin and 5,7-dibromo-isatin were condensed with diketopiperazine in similar fashion to the above. The condensation products were even less soluble than the indigoid derived from isatin. They could be superficially purified only by successive treatments with glacial acetic acid, water and alcohol, with a view to removing soluble impurities. The yields were not good. Both compounds are reddish-brown in color, and do not melt below 300°.

Anal. (2,5-Diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(5'-bromo-oxindole)). Calcd. for $C_{20}H_{14}O_6N_4Br_2$: N, 9.12; Br, 26.00. Found: N, 8.4; Br, 25.23.

Anal. (2,5-Diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(5',7'-dibromo-oxindole)). Calcd. for $C_{24}H_{12}O_6N_4Br_4$: N, 7.25; Br, 41.44. Found: N, 7.65; Br, 42.63.

Summary

1. The indigoid hydantoin-($\Delta^{5,3'}$)-oxindole can be converted into hydantoin-(5,3')-oxindole by the action of tin and alcoholic hydrogen chloride, or by hydriodic acid.

2. The hydrolysis of hydantoin-(5,3')-oxindole with barium hydroxide yields 2-quinolone-4-carboxylic acid, while hydrolysis with hydriodic acid, in the presence of phosphorus, yields 2-keto-1,2,3,4-tetrahydroquinoline-4-carboxylic acid.

3. 2-Keto-tetrahydroquinoline-4-carboxylic acid may also be prepared

by the direct action of hydriodic acid and phosphorus upon the following: 2-quinolone-4-carboxylic acid; hydantoin-($\Delta^{5,3'}$)-oxindole; hydantoin-($\Delta^{5,3'}$)-5',7'-dibromoxindole and 2,5-diketopiperazine-($\Delta^{3,6,3',3'}$)-di-(oxindole). The ethyl ester of the acid is formed by the action of tin and alcoholic hydrogen chloride on 2-quinolone-4-carboxylic acid.

4. 5-Bromo-isatin, and 5,7-dibromo-isatin will condense with hydantoin and also with diketopiperazine.

NEW HAVEN, CONNECTICUT

[A CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, UNIVERSITY OF WISCONSIN, AND THE OFFICE OF CEREAL CROPS AND DISEASES, BUREAU OF PLANT INDUSTRY]

A METHOD FOR THE DETERMINATION OF URONIC ACIDS[1]

BY ALLAN D. DICKSON, HENRY OTTERSON AND KARL PAUL LINK

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Introduction

During the course of numerous investigations on the composition of the cell wall of various plants we have had occasion to devote considerable time to the chemistry of the acid polysaccharide constituents. These acidic polysaccharide substances are uronic acids or polymerized anhydride derivatives of such acids. In the past twenty years these substances have attracted considerable attention from numerous investigators, not only because of their almost universal occurrence in the plant world but also because these substances without question play an important role in the carbohydrate metabolism of the cell and also serve as structural components of the cell wall.[2]

An aldobionic acid, glucoso-glucuronic, has been shown by Heidelberger and Goebel to be the fundamental building stone of the polysaccharide derived from Type III pneumococcus and to be an important constituent

[1] Published with the permission of the Director of the Wisconsin Agricultural Experiment Station.

[2] Tollens, *Ber.*, **41**, 1788 (1908); Ehrlich, *Chem.-Ztg.*, **41**, 197 (1917); *Z. angew. Chem.*, **40**, 1305 (1927); *Biochem. Z.*, **168**, 263 (1926); *ibid.*, **169**, 13 (1926); *ibid.*, **203**, 343 (1928); Nanji, Paton and Ling, *J. Soc. Chem. Ind.*, **44**, 253T (1925); Schmidt and co-workers, *Ber.*, **58**, 1394 (1925); *ibid.*, **59**, 1585 (1926); *ibid.*, **60**, 503 (1927); also *Zeitschrift "Der Papier Fabrikant"*, 26 Jahrgang, Heft 28, 1–7 (1928); Schwalbe, *Ber.*, **58**, 1534 (1925); Marcusson, *Z. angew. Chem.*, **39**, 898 (1926); Schryver and Norris, *Biochem. J.*, **19**, 676 (1925); O'Dwyer, *ibid.*, **20**, 657 (1926); *ibid.*, **22**, 381 (1928); Hägglund and co-workers, *Z. physiol. Chem.*, **177**, 248 (1928); Cretcher and Nelson, *Science*, **67**, 537 (1928); Cretcher and Butler, *ibid.*, **68**, 116 (1928); Candlin and Schryver, *Proc. Roy. Soc., London*, **103B**, 365 (1928); Henderson, *J. Chem. Soc.*, 2117 (1928); Szent-Györgyi, *Biochem. J.*, **22**, 1387 (1928); Rehorst, *Ber.*, **62**, 519 (1929); Ehrlich and Rehorst, *ibid.*, **62**, 628 (1929); Weinmann, *ibid.*, **62**, 1637 (1929); Norris, *Biochem. J.*, **23**, 195 (1929); Butler and Cretcher, THIS JOURNAL, **51**, 1519 (1929); Norman, *Biochem. J.*, **23**, 524 (1929).