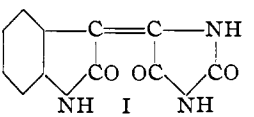
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

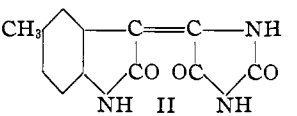
Hydrolysis and Reduction of Hydantoin-Oxindoles[1]

BY HENRY R. HENZE AND CHARLES M. BLAIR

The only recorded instance of the direct hydrolysis of an unsaturated hydantoin-carbonyl compound is that of anisalhydantoin,[2] the action of barium hydroxide producing *p*-methoxyphenylpyruvic acid. The primary purpose of this investigation was to study the direct hydrolysis of hydantoin-$\Delta^{5,3'}$-oxindole (I) and its 5'-methyl homolog (II). Since a supply of (I) was available it was possible to repeat the conflicting researches of



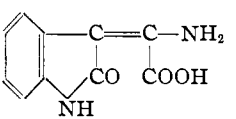
I



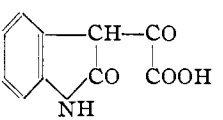
II

Kotake[3] and of Hill and collaborators[4] and thus to establish the structure of the quinolone acid obtained by the reduction and hydrolysis procedures. With the exception of a minor difference in one melting point, the results of the latter investigators have been verified. On the contrary, Kotake's synthesis of 2,3-dihydroxy-3,4-dihydroquinoline-4-carboxylic acid could not be confirmed.

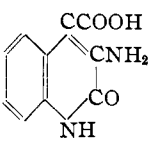
From a knowledge of the behavior of the hydantoin and oxindole groupings, respectively, toward alkali it would seem possible to predict one or more of the following compounds as the reaction product of the interaction of barium hydroxide and hydantoin-$\Delta^{5,3'}$-oxindole (I)



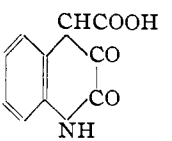
III



IV



V



VI

If normal cleavage of the hydantoin ring, unaccompanied by any change in the oxindole portion of the molecule, should take place the resulting product would be the unsaturated alpha amino acid, $C_{10}H_8N_2O_3$ (III). If, however, in addition to the usual decomposition of the hydantoin nucleus the amino group was eliminated by hydrolysis, the compound thus produced would be a substituted pyruvic acid, $C_{10}H_7NO_4$ (IV). Finally, since it is known that the oxindole nucleus is opened by alkali and that subsequent ring closure, upon acidification, would favor the formation of a six rather than a five-membered ring, it might be expected that hydrolysis

(1) This paper is from a portion of the dissertation submitted by Charles M. Blair to the faculty of the University of Texas, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1933.

(2) Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368 (1911).

(3) Kotake, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **6**, 61 (1927).

(4) Hill, Schultz and Lindwall, THIS JOURNAL, **52**, 769 (1930).

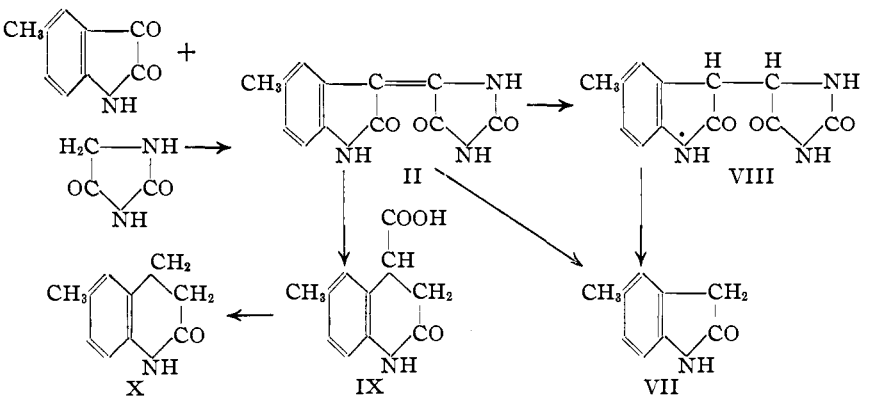
would result in the formation of a quinolone carboxylic acid, either $C_{10}H_8N_2O_3$ (V) or $C_{10}H_7NO_4$ (VI), according to whether or not an amino group was eliminated during the reaction.

The hydrolysis of hydantoin-$\Delta^{5,3'}$-oxindole proceeded in a manner totally different from those outlined above in that a compound of the molecular formula C_8H_7NO was formed. Hence, during the hydrolysis not only had the usual decomposition of the hydantoin ring taken place, but, in addition, cleavage had occurred at the double bond thus removing a fragment containing two carbon atoms. This fact was established by identifying oxalate in the reaction residue.

As the hydrolysis product agreed in empirical formula and in melting point with these properties recorded for oxindole, the latter was synthesized by the method of Marschalk[5] and comparison of it with the compound C_8H_7NO indicated that the two substances were identical. Since the formation of oxindole was so unexpected further substantiation of this structure was obtained by converting the hydrolysis product into isatoxime and final proof was secured by synthesizing monobromo oxindole from it.

In complete analogy to the foregoing the condensation product of hydantoin and 5-methylisatin upon treatment with barium hydroxide solution yielded 5-methyloxindole (VII).

Reduction of hydantoin-$\Delta^{5,3'}$-5'-methyloxindole (II), catalytically or by means of hydriodic acid, led smoothly to the formation of the anticipated compound, hydantoin-(5,3')-5'-methyloxindole (VIII). The latter on hydrolysis by means of barium hydroxide and subsequent acidification formed 5-methyloxindole (VII) rather than a quinolone carboxylic acid. However, when the hydantoin-$\Delta^{5,3'}$-5'-methyloxindole was treated with hydriodic acid in the presence of red phosphorus 2-keto-6-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (IX) resulted.



(5) Marschalk, *Ber.*, **45**, 584 (1912).

Experimental

Hydrolysis of Hydantoin-$\Delta^{5,3'}$-oxindole.—Sixty-eight grams of hydantoin-$\Delta^{5,3'}$-oxindole (I), 510 g. of barium hydroxide and 510 cc. of water were digested in an oil-bath at 115–120° under reflux condenser until ammonia was no longer evolved. Five hundred cubic centimeters of boiling water was added and the barium removed with carbon dioxide and the required amount of sulfuric acid. The presence of oxalate in the precipitated barium salts was established. The filtrate was acidified with glacial acetic acid and evaporated to dryness. Recrystallization of the residue from water produced 25 g. of colorless needles melting sharply at 127° (corr.). Analysis of the purified product indicated that its formula was C_8H_7NO.

Anal. Calcd. for C_8H_7NO: C, 72.15; H, 5.30; N, 10.52; mol. wt., 133. Found: C, 72.00, 72.05; H, 5.12, 5.16; N, 10.54, 10.64; mol. wt. (in freezing glacial acetic acid), 134.

When the compound C_8H_7NO was mixed with oxindole[5] of known purity, which melted at 127° (corr.), the resulting mixture melted unchanged at the same temperature.

The action of nitrous acid on the product C_8H_7NO yielded an oxime, $C_8H_6N_2O_2$, which melted at 202° (corr.) and which corresponded in all respects with isatoxime.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.45; H, 3.99; N, 17.42.

A cold aqueous solution of C_8H_7NO was acidified and treated with a volume of Koppeschaar's solution equivalent to one molecular proportion of bromine. The colorless prisms which separated after recrystallization from water and from alcohol melted with decomposition at 220–221° (corr.).[6] The results of the analyses established the molecular formula C_8H_6ONBr corresponding to that of a monobromoxindole.

Anal. Calcd. for C_8H_6ONBr: C, 45.28; H, 2.99; N, 6.61; Br, 37.70. Found: C, 45.24; H, 2.86; N, 6.54; Br, 37.96.

Hydantoin-$\Delta^{5,3'}$-5'-methyloxindole (II).—This compound was obtained by heating 80.5 g. of 5-methylisatin, 50 g. of hydantoin, 100 g. of fused sodium acetate and 500 cc. of glacial acetic acid (containing 20 g. of acetic anhydride) in an oil-bath at 150° for five hours. The usual procedure for hydantoin condensations was followed and yielded 78 g. of a reddish-brown solid of melting point above 310° and insoluble in all the common solvents except alkaline solutions.

Anal. Calcd. for $C_{12}H_9O_3N_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.42; H, 3.84; N, 17.37.

Hydrolysis of Hydantoin-$\Delta^{5,3'}$-5'-methyloxindole (II).—Twenty-three grams of (II), 173 g. of barium hydroxide and 173 cc. of water were refluxed in an oil-bath at 115–120° for two days, ammonia being evolved. Here, too, the residue of barium salts gave a positive test for oxalate. The purified product, weighing 4 g. and consisting of colorless crystals melting at 175° (corr.),[7] was 5-methyloxindole.

Anal. Calcd. for C_9H_9ON: C, 73.43; H, 6.12; N, 9.52. Found: C, 73.26; H, 6.10; N, 9.65.

2-Quinolone-4-carboxylic Acid. A.—Following the method of Hill, Schultz and Lindwall, hydantoin-$\Delta^{5,3'}$-oxindole was reduced forming hydantoin-($^{5,3'}$)-oxindole (which was found to melt at 281–282° (corr.) (dec.) instead of at 276°) which upon hy-

(6) Since the melting point reported by von Baeyer and Knopp [*Ann.*, **140**, 1 (1866)] for monobromoxindole is 176°, this compound was resynthesized by treating oxindole with bromine water. The melting point of the monobromoxindole thus obtained, as well as a mixture of it with the C_8H_6ONBr, was 220–221° (corr.) with decomposition.

(7) M. p. given as 168° by Reissert and Scherk [*Ber.*, **31**, 393 (1898)], by Wahl and Faivert [*Ann. chim.*, **5**, 314 (1926)] and by Stollé, Bergdoll, Luther, Auerhahn and Wacker, *J. prakt. Chem.*, **128**, 1 (1930).

drolysis with barium hydroxide was converted into 2-quinolone-4-carboxylic acid thus confirming the work of these investigators.

B. Isatin and hydantoin were condensed according to the method of Kotake forming 1-acetyl-hydantoin-$\Delta^{5,3'}$-1'-acetyloxindole, which Kotake described as charring at 245° but which in this investigation was found to sinter at 240–245° and to melt with decomposition at 258° (corr.). Reduction of this diacetyl derivative by means of zinc and acetic acid produced hydantoin-(5,3')-1'-acetyloxindole melting at 248° (corr.) [K.—m. p. about 243°].[8] The melting point of hydantoin-(5,3')-oxindole obtained by solution of the monoacetyl derivative in dilute sodium hydroxide and subsequent acidification was 281–282° (corr.) [K.—m. p. 283–284°]. When the directions recorded by Kotake for the hydrolysis of hydantoin-(5,3')-oxindole were followed explicitly the compound obtained was 2-quinolone-4-carboxylic acid and not 2,3-dihydroxy-3,4-dihydroquinoline-4-carboxylic acid.

Hydantoin-(5,3')-5'-methyloxindole (VIII).—A suspension of 50 g. of hydantoin-$\Delta^{5,3'}$-5'-methyloxindole, 225 cc. of hydriodic acid (sp. gr. 1.7) and 500 cc. of glacial acetic acid was boiled gently in an oil-bath for one hour. When all solids had dissolved, the solution was steam distilled to remove acid, chilled in an ice-bath and the separated product filtered off and washed with water and acetone. The dried residue, weighing 26 g., was recrystallized from water yielding snow white silky needles melting with decomposition at 306–307° (corr.).

Anal. Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.78; H, 4.49; N, 17.14. Found: C, 58.95; H, 4.61; N, 17.32.

For the preparation of small quantities of VIII catalytic reduction using Adams platinum catalyst with alcohol as the solvent was very satisfactory.

Hydrolysis of Hydantoin-(5,3')-5'-methyloxindole.—Twenty-three grams of VIII, 173 g. of barium hydroxide and 173 cc. of water were heated for two days in an oil-bath at 115–120°. Barium compounds were removed in the usual manner and gave a positive test for the presence of oxalate. The filtrate was evaporated to dryness, the residue upon recrystallization from water yielding 4 g. of small, nearly colorless needles melting at 175°. A mixture of this product with 5-methyloxindole melted at the same temperature.

Anal. Calcd. for C_9H_9ON: C, 73.43; H, 6.12; N, 9.52. Found: C, 73.36; H, 6.18; N, 9.39.

2-Keto-6-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic Acid (IX).—Eight grams of hydantoin-$\Delta^{5,3'}$-5'-methyloxindole, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) was heated for seven hours in an oil-bath at 150°. The mixture was steam distilled, filtered from phosphorus, decolorized and cooled. The product was recrystallized from water yielding 2 g. of colorless needles melting at 219–220° (corr.). This melting point is not changed by mixing the compound with a sample of 2-keto-6-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid of known purity.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.37; H, 5.41; N, 6.86. Found: C, 64.22; H, 5.33; N, 6.73.

This acid was decarboxylated by dry distillation with barium hydroxide forming 2-keto-6-methyl-1,2,3,4-tetrahydroquinoline (X) which melted at 114–115° (corr.).[9]

Summary

1. The action of barium hydroxide solution on the condensation products of hydantoin with isatin and 5-methylisatin completely destroyed the

(8) Concerning this reduction product Kotake's statement is extremely confusing in that, while the analyses reported agreed quite well with $C_{14}H_{13}O_4N_3$, he concluded that "the analytical results indicated $C_{11}H_{13}O_3N_4$ representing no conceivable formula."

(9) M. p. given as 106° by Mayer, van Zütphen and Phillips, *Ber.*, **60B**, 858 (1927).

hydantoin nucleus and reduced the isatin portion to the corresponding oxindole.

2. Toward barium hydroxide solution hydantoin-5,3′-oxindole and its 5′-methyl homolog differ in their behavior in that the former is converted into 2-quinolone-4-carboxylic acid and the latter into 5-methyloxindole.

3. The synthesis of 2-quinolone-4-carboxylic acid by Hill, Schultz and Lindwall has been confirmed, whereas the conflicting research of Kotake has, in part, been shown to be in error.

AUSTIN, TEXAS

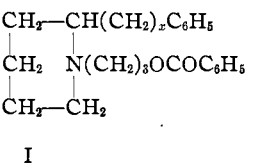
RECEIVED JULY 13, 1933
PUBLISHED NOVEMBER 7, 1933

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

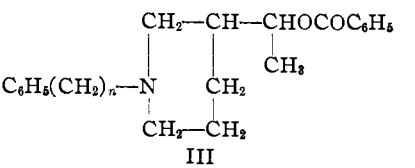
Piperidine Derivatives. XIII.[1] Phenyl and Phenylalkyl Substituted Piperidinopropyl Benzoates

BY L. A. WALTERS AND S. M. MCELVAIN

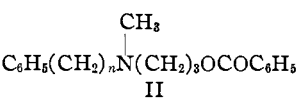
In a previous paper[1] the unusual local anesthetic action of compounds of type I on mucous surfaces was reported. Since the substances in which x is 1 and 2 were many times more effective as anesthetics than the compound in which a phenylethyl group substitutes the 4 position of the piperidine nucleus, it appeared that there might be an optimum position of the phenyl group relative to the nitrogen atom for maximum anesthetic action. In subsequent work an effort was made to test this possibility by the preparation of series of anesthetics of types II[2] and III[3] in which the number of carbon atoms separating the nitrogen atom from the phenyl group was varied from 1 to 5. However, compounds of type II and III proved to be so irritating to the mucous surfaces (rabbit's cornea) that no definite conclusion could be drawn in this connection.



I



III



II

It therefore seemed desirable to extend the study to structures of type I. The present paper reports the preparation and properties of the 2-phenyl-

(1) Bailey and McElvain, THIS JOURNAL, **52**, 1633 (1930).
(2) Cope and McElvain, *ibid.*, **53**, 1587 (1931).
(3) Strong and McElvain, *ibid.*, **55**, 816 (1933).