Anal. Calcd. for $C_{16}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.79; H, 8.76.

The 2,4-dinitrophenylhydrazone, crystallized from acetone, was red and melted at 273–275° (dec.).

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62. Found: C, 64.09; H, 5.81.

This derivative was unaffected when heated in ethanol or in acetic acid for 24 hours; nor was there any change when a solution of the derivative in ethanol was made basic by addition of potassium hydroxide and then heated on the steam-bath for two hours. No pyrazoline was formed under any of these conditions.

Hydrolysis of the 2,4-Dinitrophenylhydrazone of VII.—The derivative (0.2 g.) was refluxed with sulfuric acid (60%, 500 cc.) for a few minutes to complete the rapid hydrolysis. The mixture was steam distilled at once until the distillate contained several drops of oil. This oil decolorized permanganate in acetone, reacted by addition with bromine in carbon tetrachloride, and gave the red 2,4-dinitrophenylhydrazone of VII melting at 270–275°. The residue from the steam distillation was allowed to stand overnight and was steam distilled again; the distillate contained a light yellow solid which melted at 76–85° and was the hydrindone X (mixed m.p., 79–85°; see below).

6-Tetralylcarboxylic Acid.—Powdered potassium permanganate (1.5 g.) was added in small portions and with shaking to a solution of the ketone VII (1.07 g.) in acetone (30 cc.) at room temperature and the acid was recovered after removal of the sludge of manganese dioxide. After crystallization from ethanol, it weighed 0.3 g., and melted at 151–153°, in agreement with the value in the literature.[8]

Cyclization of VII. A.—Aluminum chloride (1.5 g.) was added to a solution of VII (1 g.) in carbon bisulfide (5 cc.) and the mixture was saturated with hydrogen chloride. The flask was stoppered (care) and shaken for 30 minutes, then the solvent was removed and the residue was poured over iced hydrochloric acid. The viscous oil was removed and converted into a mixture of 2,4-dinitrophenylhydrazones, which was separated by crystallization from acetone into a red solid melting at 263–265° (dec.) and a mixture of red and orange crystals melting at 243–250°. The red solid (m.p. 263–265°), when chromatographed from petroleum ether as described above and then recrystallized from acetone, gave red crystals melting at 268–271° (dec.). This was the derivative of hydrindone X, but it was still not pure. The mixture (m.p. 243–250°) of derivatives was hydrolyzed (slow, seven hours), and then steam distilled, as described above. The light yellow solid (m.p. 71–76°) in the distillate was removed and chromatographed from petroleum ether (b.p., 45–70°) onto alumina. The section of the column fluorescing under ultraviolet light was removed and extracted with acetone; the white solid (X), recrystallized from petroleum ether (b.p. 30–60°), melted at 80–84°. When mixed with VIII, it melted at 45–63°; when mixed with IX, it melted at 45–65°.

3,3-Dimethyl-(4,5)-tetrahydrobenzhydrindone (X): *Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.21; H, 8.63. The 2,4-dinitrophenylhydrazone of X, crystallized several times from acetone, formed deep-red feathery crystals melting at 273–274° (dec.). A mixture of this with the corresponding derivative of VII (m.p. 267–268°) melted at 265–269°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62. Found: C, 63.92; H, 5.65.

Hydrindone X (0.05 g.) was dissolved in sulfuric acid (95%, 15 cc.) at room temperature; the solution was allowed to stand overnight, and then poured over ice. The solid was removed and dried; it melted at 84–86° alone or when mixed with X.

B.—The ketone VII (3 cc.) was dissolved in sulfuric acid (95%, 30 cc.) and the deep red solution was allowed to stand at room temperature for 18 days. The solution was poured over ice and extracted with ether; the extract was washed with water, dried (sodium sulfate) and the ether was removed. The residual yellow oil was converted into a mixture of 2,4-dinitrophenylhydrazones which were separated by fractional crystallization from acetone. Two red derivatives were obtained: one identical with the derivative of hydrindone VIII, m.p. and mixed m.p. 253–255°. The second red derivative was identical with the derivative of hydrindone X, m.p. 273–274°. Hydrolysis of the latter (slow, six hours) by refluxing it with aqueous sulfuric acid (60%) gave the hydrindone X which, after crystallization from petroleum ether, melted at 82–84°, alone or when mixed with X as prepared in A above.

MINNEAPOLIS 14, MINN. RECEIVED FEBRUARY 23, 1951

(8) G. Stork, THIS JOURNAL, **69**, 579 (1947).

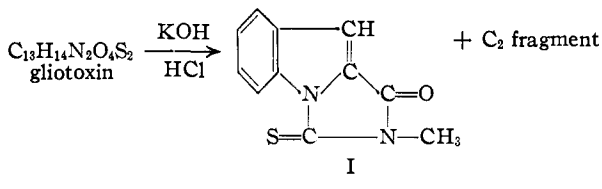
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin. IX. Synthesis of the $C_{11}H_8N_2OS$ Degradation Product[1]

BY JOHN R. JOHNSON AND JAMES B. BUCHANAN[2]

The crystalline sulfur-containing degradation product derived from gliotoxin by the action of alcoholic alkalies, $C_{11}H_8N_2OS$, has been synthesized by cyclization of the condensation product from 2-bromobenzaldehyde and 3-methyl-2-thiohydantoin. This mode of synthesis establishes definitely the position of the sulfur atom in the degradation product. The structure of this compound is consistent with the view that one of the sulfur atoms in gliotoxin is attached at the 4-position of the pyrazinoindole nucleus.

The action of methanolic potassium hydroxide on gliotoxin or its diaroyl derivatives, followed by acidification of the hydrolysate, gives rise to a yellow-orange, crystalline product, m.p. 188°, for which the molecular formula $C_{11}H_8N_2OS$ has been established.[3] On the basis of its chemical and physical properties, this sulfur-containing degradation product was assigned the structure (I) of a thiohydantoin related to 2-indolecarboxylic acid: 2-methyl-3-thioxoimidazo[3,4a]indol-1(2)-one. The nature of the C_2-fragment which is eliminated in the formation of the C_{11}-compound could not be established.



I

The carbon–nitrogen skeleton of the proposed thiohydantoin structure has been established by Dutcher and Kjaer[4] through oxidative desulfurization to the corresponding hydantoin, $C_{11}H_8N_2O_2$, which was shown by degradation and by synthesis to be the oxygen analog of the thiohydantoin I. This evidence does not fix the location of the sulfur atom of the thiohydantoin, since an isomer of structure I having the thioamide group attached at

(1) Previous paper, THIS JOURNAL, **72**, 2862 (1950).

(2) The Wm. S. Merrell Company Fellow in Chemistry, 1948–1949.

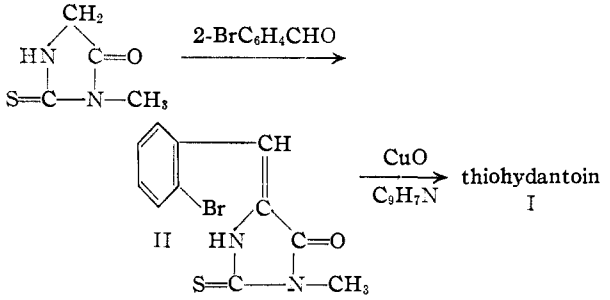
(3) J. D. Dutcher, J. R. Johnson and W. F. Brucc, THIS JOURNAL, **67**, 1736 (1945).

(4) J. D. Dutcher and A. Kjaer, *ibid.*, **73**, in press (1951).

the 2-position of the indole ring would give the same $C_{11}H_8N_2O_2$ compound.

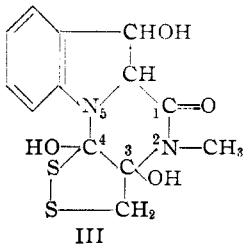
The position of attachment of the sulfur atom has now been established by two independent synthetic methods leading to an authentic thiohydantoin of structure I. Elvidge and Spring[5] obtained a C_{11}-thiohydantoin identical with that from gliotoxin by heating methyl 2-indolecarboxylate with methyl isothiocyanate in a sealed tube at 180°. They established that ring closure had occurred at the 1-position of the indole system by comparison with a model compound in which the 3-position was blocked by a methyl group.

In the present work an unambiguous synthesis of the thiohydantoin of structure I was accomplished in the following way. 2-Bromobenzaldehyde was condensed with 3-methyl-2-thiohydantoin to form 5-(2-bromobenzylidene)-3-methyl-2-

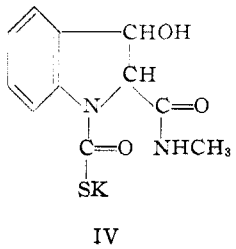


thiohydantoin (II), which was cyclized through elimination of hydrogen bromide by heating for a short period with copper oxide in quinoline at 230°. The ring closure is accompanied by side reactions and decomposition, but from the reaction mixture a crystalline product was isolated in low yields (5–6%). After careful purification the material formed yellow crystals, m.p. 187–188°, which corresponded in composition to the molecular formula $C_{11}H_8N_2OS$. Use of the 2-chloro analog of compound II in cyclization experiments gave even less satisfactory results than the bromo compound, and the 2-iodo analog furnished none of the desired product.

The melting point of the synthetic thiohydantoin was not depressed by admixture with a sample of the compound obtained from gliotoxin, and the ultraviolet absorption spectra of the two substances were identical. Oxidative desulfurization of the synthetic compound gave the corresponding hydantoin, m.p. 179–180°, which showed no depression of the melting point when mixed with the desulfurized hydantoin from gliotoxin.



III



IV

The new structural evidence confirms the structure previously assigned to the $C_{11}H_8N_2OS$ degradation product. Although the sequence of transformations leading from gliotoxin to this compound has not been established, the evidence lends support to our "preferred" formulation of gliotoxin (III),[3] in which one of the sulfur atoms is attached at the 4-position of the pyrazinoindole system. Earlier studies have indicated that the disulfide linkage of gliotoxin is cleaved rapidly by cold alkali with the consumption of two equivalents of alkali per mole, corresponding to the reaction: R–S–S–R → R–SK + R–S–OK. The subsequent steps may be envisaged in several different ways.[5] It is likely that the slow further reaction with alkali, which consumes an additional 0.7–0.8 equivalent of base, leads eventually to an indole derivative such as IV. Subsequent acidification would bring about cyclization to the thiohydantoin. It has been observed that the crystalline product is formed slowly *after* the alkaline mixture has been acidified. At some intermediate stage the elements of water are eliminated from the hydroxyindoline system.

Experimental

3-Methyl-2-thiohydantoin.—This compound was prepared by a modification of the procedure of Marckwald[6] which obviated the formation of a persistent colored impurity. Thirty grams (0.4 mole) of glycine was dissolved in 50 g. of cold 50% potassium hydroxide solution and 60 ml. of ethanol was added. Twenty-eight grams (0.44 mole) of methyl isothiocyanate in 50 ml. of ethanol was dropped into this solution with stirring over a period of 40 minutes. After the addition was complete 50 ml. of water and 60 ml. of concentrated hydrochloric acid were cautiously mixed in, and the solution gently refluxed for one hour. The hot solution was filtered to remove potassium chloride and set aside to cool. After several hours the product had formed a solid crystalline mass, which was collected on a filter, washed repeatedly with 50% aqueous ethanol, and dried. The yield was 43 g. (83% of theoretical), m.p. 158–160°. This product was used in the succeeding step without further purification.

5-(2-Bromobenzylidene)-3-methyl-2-thiohydantoin (II).—A mixture of 19.6 g. (0.15 mole) of 3-methyl-2-thiohydantoin, 28 g. (0.15 mole) of 2-bromobenzaldehyde, 50 g. of fused sodium acetate, 175 ml. of glacial acetic acid and 5 ml. of acetic anhydride was heated in an oil-bath at 145–150° for three hours. The reaction mixture was poured into water and the crystalline precipitate collected and washed repeatedly with water. Crystallization of the product from 350 ml. of ethanol gave 27 g. (60% yield) of pale yellow needles, m.p. 169–170°.[7]

Anal. Calcd. for $C_{11}H_9N_2OSBr$: N, 9.42 Found: N, 9.49, 9.32.

The product is insoluble in water but dissolves in cold dilute aqueous alkali. The ultraviolet absorption spectrum in ethanol is almost identical with that previously reported for 5-benzylidene-3-methyl-2-thiohydantoin.[3]

5-(2-Chlorobenzylidene)-3-methyl-2-thiohydantoin.—This compound was prepared from 2-chlorobenzaldehyde using the procedure described above for the bromo analog. The product was obtained in 50% yield and melted at 168–169°.

Anal. Calcd. for $C_{11}H_9N_2OSCl$: N, 11.09. Found: N, 11.00, 11.25.

5-(2-Iodobenzylidene)-3-methyl-2-thiohydantoin.—From 2-iodobenzaldehyde, using the procedure described above, the iodobenzylidene compound was obtained in 15% yield; bright yellow crystals, from ethanol, m.p. 186–187°. The product was soluble in dilute aqueous alkali and its ultraviolet absorption spectrum was similar to that of the chloro and bromo analogs.

Synthesis of the $C_{11}H_8N_2OS$ Compound (I): 2-Methyl-3-thioxoimidazo[3,4a]indol-1(2)-one.—Experiments on the

(5) J. A. Elvidge and F. S. Spring, *J. Chem. Soc.*, S 135 (1949).

(6) W. Marckwald, M. Neumarck and R. Stelzner, *Ber.*, **24**, 3285 (1891).

(7) All melting points are corrected.

cyclization of the 2-chloro- and 2-bromobenzylidenethiohydantoin (II) were carried out under a variety of conditions and with several types of catalysts (copper powder, cupric sulfide, cupric oxide, cuprous iodide and potassium carbonate, etc.) and solvents (pyridine, quinoline, ethanol, nitrobenzene). Although the desired compound was formed in many of these experiments, the following procedure was the most satisfactory.

Five grams of 5-(2-bromobenzylidene)-3-methyl-2-thiohydantoin, dissolved in 50 ml. of redistilled quinoline, was treated with 0.5 g. of cupric oxide (General Chemical Co., C.P., code 1638) and stirred vigorously for one hour at 230–235° in an atmosphere of nitrogen. The reaction mixture was poured into 250 ml. of 6 *N* hydrochloric acid and the acidic solution extracted repeatedly with ether. The ether extract was washed three times with 10% sodium hydroxide solution, twice with 3 *N* hydrochloric acid, and finally with water. After drying the ethereal solution with anhydrous magnesium sulfate and distilling off the solvent, there remained 1.1 g. of a gummy residue. When this material was heated at 125° and 1 mm. in a sublimation apparatus, there was obtained 0.33 g. of a yellow crystalline product, m.p. 172–179°. This crude product consisted almost entirely of the desired cyclization product but contained small amounts of impurities that were very difficult to remove.

When the sublimate was dissolved in 20 ml. of carbon tetrachloride and the solution poured onto an alumina (Brockmann) column, 1.7 cm. in diameter and 9 cm. long, three colored bands developed. The lowest band was readily washed out with carbon tetrachloride and was discarded. The middle band, pale yellow in color, was eluted by passing a mixture of 20% benzene and 80% carbon tetrachloride (by volume) through the column. From this elution there was obtained 0.165 g. of yellow crystals, m.p. 179–184°, which after repeated crystallization from ethanol melted at 187–188°.

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.11; H, 3.70; N, 12.97. Found: C, 61.54, 61.02; H, 3.68, 3.47; N, 13.09, 13.19.

The synthetic hydantoin showed no depression of the melting point when mixed with a sample of the $C_{11}H_8N_2OS$ compound from gliotoxin. The ultraviolet absorption spectra of the two compounds were superposable. Redetermination of the ultraviolet absorption spectrum of the C_{11}-thiohydantoin in the course of the present work has shown that the single peak indicated previously[3] at 266 mμ can be resolved into two distinct peaks at 263 and 269 mμ.

Oxidative desulfurization of 60 mg. of the synthetic thiohydantoin, in pyridine with hydrogen peroxide,[4] gave 47 mg. of a white crystalline product. Repeated crystallization from methanol furnished white needles, m.p. 179–180°. This compound was shown to be identical with the $C_{11}H_8N_2O_2$ hydantoin obtained from the gliotoxin degradation product.

ITHACA, N. Y. RECEIVED MARCH 5, 1951

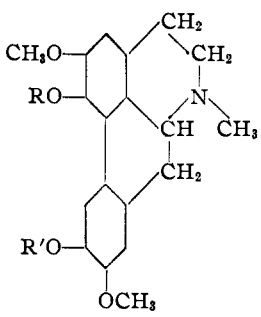
[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO., LTD.]

The Alkaloids of Fumariaceous Plants. XLVI. The Structure of Glaucentrine

BY RICHARD H. F. MANSKE, E. HAROLD CHARLESWORTH AND WALTER R. ASHFORD

Since glaucentrine is monophenolic and on O-methylation yields glaucine it can have only one of four possible structures. Two different trimethoxyethoxyaporphines have been synthesized and one of these, the 2,3,6-trimethoxy-5-ethoxy derivative, after resolution, was identical with glaucentrine O-ethyl ether. Glaucentrine therefore is 2,3,6-trimethoxy-5-hydroxyaporphine.

Glaucentrine has been isolated from *Dicentra eximia* (Ker) Torr.,[1] *D. formosa* Walp.,[2] and from *D. oregana* Eastwood[3] in only very small amounts. It yields *d*-glaucine (I) on O-methylation, and since it has three methoxyls it can have only one of four possible formulas. There was insufficient alkaloid available to carry out degradation experiments to locate the position of the free hydroxyl. A synthesis of some trimethoxyethoxyaporphines was therefore undertaken. The reactions leading to the syntheses of aporphines are now so well known that the routes need not be indicated here. It is sufficient to note that the two aporphines (II and III) were prepared by now standardized and unambiguous reactions.



I, R = R′ = CH_3
II, R = CH_3, R′ = C_2H_5
III, R = C_2H_5, R′ = CH_3
IV, R = H, R′ = CH_3

Since the synthetic compounds are racemic neither could be directly compared with glaucentrine O-ethyl ether. It was found however that resolution of both isomers could be achieved almost quantitatively by the successive use of *d*- and *l*-tartaric acids.

The *d*-base *l*-acid and *l*-base *d*-acid salts are only very sparingly soluble in methanol or ethanol. Unaccountably the *dl*-tartrate of the *dl*-base (III) proved to be moderately soluble and did not crystallize in well formed crystals. The *l*-tartrate of the base of structure III proved to be identical with the *l*-tartrate of glaucentrine O-ethyl ether. The *l*-tartrate of base II was quite different. Glaucentrine therefore is IV.

It may be of interest to point out that the crude mixture of synthetic aporphines contains other basic products which are easily eliminated by extracting the solution of the bases in dilute hydrochloric acid with chloroform. The aporphine hydrochlorides rapidly concentrate in the chloroform layer whereas most of the other bases, such as the benzylisoquinolines, remain in the aqueous phase.

Experimental

1-(3-Methoxy-4-ethoxy-6-aminobenzyl)-2-methyl-6,7-dimethoxytetrahydroisoquinoline.—1-(3-Methoxy-4-ethoxy-6-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[4] (m.p. 142–143°)[5] was heated at 100° in a sealed tube with excess methyl iodide for one hour. Removal of the excess

(1) R. H. F. Manske, *Can. J. Research*, **8**, 592 (1933).
(2) R. H. F. Manske, *ibid.*, **10**, 521 (1934).
(3) R. H. F. Manske, *ibid.*, **10**, 765 (1934).
(4) G. Barger, J. Eisenbrand, L. Eisenbrand and E. Schlittler, *Ber.*, **66**, 450 (1933).
(5) All melting points are corrected.