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

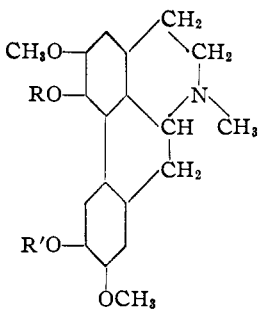
[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO., LTD.]

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.

reagent and recrystallization of the residue from methanol gave a quantitative yield of the *methiodide* melting at 209–210°. Calcd. for $C_{22}H_{27}O_6N_2I$: N, 5.16. Found: N, 5.40. This methiodide (12 g.) in a mixture of concd. hydrochloric acid (250 cc.), acetic acid (50 cc.) and water (250 cc.) was heated and treated with zinc dust (55 g.) in small portions. During the reduction a sparingly soluble salt separated. (When some of this was removed, dissolved in hot water, and the filtered solution treated with strong hydrochloric acid, it separated in fine prisms which darkened at 200° and melted with decomposition at 213–215°. Since it could not be diazotized and since it did not appear to be a quaternary chloride it appears to be the nitrotetrahydroisoquinoline.) In about 3 hours the solid had dissolved and the solution had changed from a deep orange color through green to colorless. The filtered solution was basified with excess sodium hydroxide and exhausted with several successive portions of ether. Evaporation of the extract to a small volume yielded pale yellow needles which when recrystallized twice from ether melted at 110–112°. Calcd. for $C_{22}H_{30}O_4N_2$: N, 7.26. Found: N, 7.40.

2,5,6-Trimethoxy-3-ethoxyaporphine (II).—The above aminobenzylisoquinoline (4.8 g.) in a cooled mixture of methanol (30 cc.) and 2 *N* sulfuric acid (30 cc.) was diazotized with the calculated quantity of sodium nitrite (0.98 g.) in water. After remaining for 30 minutes the solution was heated until nitrogen evolution ceased (0.75 hour). Concentrated hydrochloric acid (7 cc.), acetic acid (0.5 cc.) and zinc dust (3.5 g.) were added and heating continued for one-half hour. The now orange-yellow solution was filtered, extracted twice with ether, rendered strongly alkaline with sodium hydroxide, and exhausted with ether. Removal of the solvent from the dried extract yielded a dark very viscous residue (3.4 g.) which failed to crystallize. It was dissolved in dilute hydrochloric acid and the clarified solution extracted four times with an equal volume of chloroform. The chloroform was removed from the extract and the residue dissolved in water, extracted several times with ether, basified with ammonia, and the liberated base extracted with ether. The residue from the ether extract weighed 1.2 g. and consisted of a pale brown resin. Without further attempts at purification this base (3 g.) was heated with *d*-tartaric acid (1.3 g.) in methanol (10 cc.) until solution was complete. In the course of several days a crop of crystals had formed which were separated by filtration, washed with ethanol, and recrystallized from methanol. The colorless fine prisms of the base II *d*-acid tartrate thus obtained melted at 212° with but slight previous sintering. Further recrystallization did not change the melting point; $[\alpha]^{22}D$ −56.3° (*c* 0.4 in methanol). Calcd. for $C_{26}H_{33}O_{10}N$: C, 60.11; H, 6.36. Found: C, 59.94; H, 6.64.

The bases in the filtrate from the *d*-acid tartrate were recovered and treated in methanol with *l*-tartaric acid (1.0 g.). The *l*-acid tartrate of base II which separated almost immediately was recrystallized from methanol and then melted at 212°; $[\alpha]^{22}D$ +56.6° (*c* 0.4 in methanol).

β-Methoxy-4-ethoxyphenethylamine.—Slotta and Heller[6] have prepared this amine by the action of hypochlorite solutions on β-(3-methoxy-4-ethoxyphenyl)-propionamide. They record that sodium hypobromite gave no amine. The following hypobromite method gave a yield of 51%. To a cooled solution of potassium hypobromite, prepared by adding a cold solution of potassium hydroxide (70 g.) in water (210 cc.) to bromine (30 g.), a slurry of the amide (40 g.) in water (335 cc.) was added. The mixture was then placed on a steam-bath and heated at 60° for 90 minutes during which time most of the amide dissolved. The separated oily amine was isolated by ether extraction and then distilled—m.p. 140–142° (3 mm.). The **picrate** was recrystallized from dilute methanol and obtained in bright orange crystals melting at 187°. Calcd. for $C_{17}H_{20}O_{11}N_4$: C, 48.11; H, 4.72; N, 13.24. Found: C, 48.28, 48.35; H, 4.66, 4.81; N, 13.26, 13.05.

N-β-(3-Methoxy-4-ethoxyphenethyl)-3,4-dimethoxy-6-nitrophenylacetamide.—The acid chloride of 3,4-dimethoxy-6-nitrophenylacetic acid[7] was prepared in small portions by treating the acid (3 g.) in freshly distilled chloroform (30 cc.) with phosphorus pentachloride at ice-bath temperatures. The acid slowly dissolved as reaction progressed. Six such portions were prepared in rapid succession and added in small amounts to a cooled and stirred mixture of 17 g. of β-3-methoxy-4-ethoxyphenethylamine in chloroform (100 cc.) and *N* sodium hydroxide solution (1 l.). The separated and washed chloroform solution (dil. hydrochloric acid) was evaporated to a small volume and the residue treated with methanol. The product thus obtained consisted of fine matted faintly yellow needles (10 g.) which melted at 165°. Calcd. for $C_{21}H_{26}O_7N_2$: C, 60.43; H, 6.00; N, 6.71. Found: C, 60.32, 60.27; H, 6.19, 6.16; N, 6.81, 6.91.

1-(3,4-Dimethoxy-6-nitrobenzyl)-6-methoxy-7-ethoxy-3,4-dihydroisoquinoline.—The above amide (2 g.) in dry toluene (150 cc.) was heated to boiling and treated during 90 minutes with phosphorus pentoxide (20 g.) added in small portions. After boiling for another 2 hours the mixture was decomposed with ice and hydrochloric acid (5 cc.) and the toluene removed by heating under reduced pressure. The aqueous solutions from eleven such runs were combined, filtered with the aid of charcoal and basified with excess ammonia. The partly crystalline precipitate was separated by filtration and then extracted first with ethanol and then with chloroform. The combined extracts were washed with water and the chloroform layer freed of solvent. The yellow residue crystallized in contact with methanol to yield fine yellow needles melting at 183–184° (14.5 g.). Calcd. for $C_{21}H_{24}O_6N_2$: C, 63.00; H, 6.00; N, 7.00. Found: C, 62.82, 63.29; H, 6.10, 6.17; N, 6.98, 7.23.

The methiodide prepared in almost quantitative yield by heating the amine with an excess of methyl iodide at 100° in a bomb for 20 minutes, crystallized from hot methanol in bright orange needles melting at 241° (dec.). Calcd. for $C_{22}H_{27}O_6N_2I$: C, 48.71; H, 4.98. Found: C, 48.36, 48.48; H, 5.03, 5.01.

1-(3,4-Dimethoxy-6-aminobenzyl)-2-methyl-6-methoxy-7-ethoxytetrahydroisoquinoline.—A suspension of the above described methiodide (4 g.) in water (40 cc.) and hydrochloric acid (80 cc.) was heated on a steam-bath and zinc dust (13 g.) added in portions during 45 minutes. The filtered solution was basified with ammonia and exhausted with ether. The oil (2 g.) from the washed and evaporated extract was treated in ethanol with a hot ethanolic solution (200 cc.) of picrolonic acid (3 g.). The **dipicrolonate** which separated almost at once was recrystallized from absolute ethanol to yield fine yellow needles (3 g.) melting at 212–213°. Calcd. for $C_{22}H_{30}O_4N_2 \cdot 2C_{10}H_8O_5N_4$: C, 55.14; H, 5.03; N, 15.32. Found: C, 55.28, 55.50; H, 5.26, 5.30; N, 15.38, 15.49.

2,3,6-Trimethoxy-5-ethoxyaporphine (III).—The above dipicrolonate (2.29 g., 0.0025 mole) was added to a solution of sulfuric acid (1.2 cc.) in cold methanol (24 cc.). The precipitated picrolonic acid was separated by filtration (recovery, 90%) and the filtrate diazotized at −5 to 0° with sodium nitrite (0.2 g.) in a little water. The bluish-green solution changed to amber after heating on a steam-bath for 30 minutes. A little water and hydrochloric acid (1.4 cc.) was added and then heating continued while zinc dust (0.54 g.) was introduced. After another 20 minutes of heating the filtered mixture was basified with excess ammonia and extracted with chloroform. The yield of crude product from the chloroform extract was about 1.0 g.

When a portion of this was treated with methyl iodide in methanol it deposited a crop of the **methiodide** after about 7 days which when recrystallized from methanol–ether melted at 218°. Calcd. for $C_{23}H_{30}O_4NI$: N, 2.72. Found: N, 2.69, 2.78.

For further purification the crude base was dissolved in a slight excess of dilute hydrochloric acid and the filtered solution extracted four times with an equal volume of chloroform. From the aqueous solution a small amount of dark colored base could be recovered. It yielded a crystalline but impure hydrochloride and was not further investigated. The combined chloroform extract was freed of solvent, redissolved in water, and the free base regenerated from the resinous residue. The yield of this base was about 20% based on the dipicrolonate.

Resolution.—The purified base (2.1 g.) in methanol (15 cc.) was heated with *d*-tartaric acid (0.9 g.) until solution was complete. The sparingly soluble ***d*-acid tartrate** which crystallized readily was recrystallized from hot abs. ethanol and then consisted of fine colorless prisms which melted at 189°, with some sintering at 184°. Calcd. for $C_{26}H_{33}O_{10}N$: C, 60.11; H, 6.36. Found: C, 60.04; H, 6.57; $[\alpha]^{25}D$ −102.4° (*c* 0.25 in water).

The base was regenerated from the filtrate from the *d*-

(6) K. H. Slotta and H. Heller, *Ber.*, **63**, 3039 (1930).

(7) A. Oliverio, *Gazz. chim. ital.*, **65**, 143 (1935).

tartrate and treated with three-sevenths of its weight of *l*-tartaric acid as above. When the sparingly soluble ***l*-acid tartrate** was recrystallized from abs. ethanol it was obtained in fine colorless prisms which melted at 189° beginning to sinter at 184°. When this was admixed with a specimen of the *l*-tartrate of glaucentrine O-ethyl ether it melted at the same temperature. Found: C, 59.94; H, 6.60. A Dumas nitrogen determination on these tartrates gave consistent high values and this tendency was confirmed with an analysis on *d*-glaucine *l*-acid tartrate; $[\alpha]^{25}D$ +100° (*c* 0.25 in water).

Glaucentrine O-Ethyl Ether.—A small specimen of glaucentrine in ethanol was treated with an excess of an ether solution of diazoethane. The non-phenolic base which had been purified by solution in dilute oxalic acid was converted into its *l*-**acid tartrate**. This when recrystallized from abs. ethanol consisted of colorless fine prisms which melted at 189° sintering at 184°. The **methiodide** was prepared in ether solution containing a small amount of methanol. It crystallized in a short time and when recrystallized from methanol–ether melted at 225° either alone or in admixture with a specimen similarly prepared from the synthetic *l*-tartrate. Calcd. for $C_{23}H_{30}O_4NI$: C, 54.01; H, 5.87. Found: C, 54.01; H, 5.82.

GUELPH, ONTARIO, CANADA RECEIVED FEBRUARY 28, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

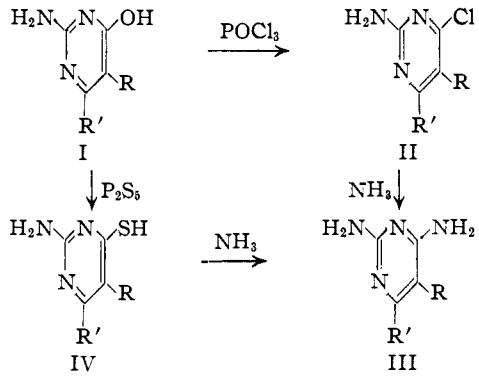
2,4-Diaminopyrimidines as Antimalarials. I.[1] 5-Aryloxyl and 5-Alkoxyl Derivatives

BY ELVIRA A. FALCO, PETER B. RUSSELL AND GEORGE H. HITCHINGS

The preparation of six 2,4-diamino-5-alkoxypyrimidines and forty-nine 2,4-diamino-5-aryloxypyrimidines *via* the corresponding 2-amino-4-hydroxy- and 2-amino-4-chloropyrimidines is described. Unsubstituted amino groups in the 2,4-diaminopyrimidine moiety appear essential to high antimalarial activity. This activity reaches a maximum in the phenoxy series with an electron-attractive substituent in the *para* position of the benzene ring and a methyl radical in the pyrimidine-6 position.

During the study of a series of pyrimidines as antagonists of nucleic acid derivatives,[2] 2,4-diaminopyrimidines and condensed systems containing this moiety were found generally to interfere with the utilization of folic acid by *Lactobacillus casei*.[3] A similarity in microbiological properties and a structural resemblance between chlorguanide (N_1-*p*-chlorophenyl-N_5-isopropylbiguanide) and certain 2,4-diamino-5-phenoxypyrimidines was noted.[4] The testing of 5-(4′-chlorophenoxy)-2,4-diaminopyrimidine[4] and its 6-methyl homolog[5] as antimalarials revealed activities of encouraging dimensions. Accordingly the preparation and testing for antimalarial properties of a considerable number of 2,4-diaminopyrimidines were undertaken.[6] The most fundamental structural requirement for antimalarial activity in this series appears to be the nature of the substituent in the 5-position. A considerable variety of 5-substituents may give rise to active antimalarials, for example, alkyl, alkoxyl, aralkyl, aryloxyl and aryl radicals, whereas the bromo and nitropyrimidines, amides of 2,4,5-triaminopyrimidine and 5-unsubstituted pyrimidines, are inactive.[6] The present paper deals primarily with the alkoxyl and aryloxyl derivatives. Succeeding papers will present the 5-aralkyl, 5-aryl and other diaminopyrimidines.

The preparations of the diamino alkoxy and aryloxypyrimidines (III) are readily carried out from the 2-amino-4-hydroxypyrimidine (I) *via* the 2-amino-4-chloropyrimidine (II) although an alternative route *via* the 2-amino-4-mercaptopyrimidine (IV)



may be used.[7,8] In the preparation of 2-amino-4-chloro-5-phenoxypyrimidine (II, R = OC_6H_5, R′ = H) Hull, *et al.*,[9] found that acetylation of the 2-amino-4-hydroxypyrimidine prior to treatment with phosphoryl chloride was necessary to avoid excessive losses. This was confirmed; however, the direct chlorination of the other 2-amino-4-hydroxy-5-aryloxypyrimidines to be reported proceeded smoothly and in most instances in excellent yield.

The 2-amino-4-hydroxypyrimidines were prepared by the condensation of an appropriately substituted α-formylacetic ester or β-ketoester with guanidine. The esters were obtained in the main along conventional lines, alkoxyacetic esters from chloroacetic acid[10,11] and a sodium alkoxide followed by esterification, aryloxyacetic esters from ethyl bromoacetate and a sodium phenoxide,[12] and

(1) Presented in part at the 119th Meeting of the American Chemical Society, April, 1950.

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(3) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *ibid.*, **174**, 765 (1948).

(4) E. A. Falco, G. H. Hitchings, P. B. Russell and H. VanderWerff, *Nature* **164**, 107 (1949).

(5) L. G. Goodwin, *ibid.*, **164**, 1133 (1949).

(6) E. A. Falco, L. Goodwin, G. H. Hitchings, I. M. Rollo and P. B. Russell, *Brit. J. Pharm.*, **6**, 185 (1951).

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(8) P. B. Russell, G. B. Elion, E. A. Falco and G. H. Hitchings, *ibid.*, **71**, 2279 (1949).

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(10) H. G. Rule, W. Hay and J. Paul, *ibid.*, 1347 (1928).

(11) R. C. Fuson and B. H. Wojeck in "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 260.

(12) M. S. Newman, W. Fones and M. Renoll, THIS JOURNAL, **69**, 718 (1947).