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Synthesis of 3-Hydroxy-4,5,6-trimethoxyaporphine (Pseudocorydine)

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The synthesis of 3-hydroxy-4,5,6-trimethoxyaporphine (IV) is described.

Only a few phenolic aporphines have been synthetized. In 1954 Hey and Lobo[1] reviewed the different attempts to prepare them. At that time only the phenolic, 6-hydroxy-3,4-dimethoxynoraporphine, had been prepared by total synthesis.[2] In their paper, Hey and Lobo described the synthesis of two nonnatural phenolic aporphines: 3-hydroxy-4-methoxy-5,6-methylendioxyaporphine (isobulbocapnine) and of 3-hydroxy-2-methoxy-5,6-methylendioxyaporphine.

Tomita and Kikkawa[3] were the first to describe the synthetic preparation of a natural diphenolic aporphine, 2,5-dihydroxy-3,6-dimethoxy-*N*-methylaporphine [(±)-laurifoline]. Soon thereafter the synthesis of 5-hydroxy-3,4,6-trimethoxyaporphine [(±) corydine] was reported by Hey and Palluel[4] and by Arumugam, Govindachari, Nagarajan, and Rao.[5]

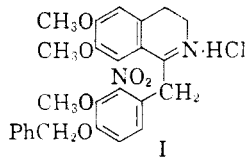
In this paper we describe the preparation of 3-hydroxy-4,5,6-trimethoxyaporphine (IV), a base isomeric with corydine and isocorydine, which we propose to name pseudocorydine.

In one of a series of papers on the synthesis of phenolic aporphines, Gulland and co-workers,[6] had already planned the synthesis of pseudocorydine, at a time when it was thought to be identical with corydine or isocorydine. They reported the preparation of some intermediates up to the stage of the dipicrolonate of base (III).

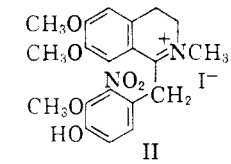
We have studied in detail the different steps of the synthesis. The hydrochloride of the dihydroisoquinoline (I) was prepared by the Bischler-Napieralski reaction from the corresponding amide; its methiodide (II) was reduced to the aminotetrahydroisoquinoline (III) which was isolated as the dipicrolonate. Application of the Pschorr reaction, using copper powder as catalyst, produced not only pseudocorydine (IV) but also, by substitution of the amino group by hydrogen, some pseudocodamine (V).[7]

Separation of the pseudocorydine from the pseudocodamine was done by column chromatography on alumina. The identification of the pseudocorydine is based on the ultraviolet spectrum which contains the two typical maxima of the aporphine alkaloids.

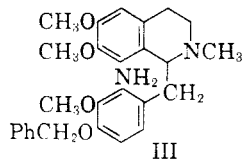
The formation of an aprophine and/or a benzylisoquinoline alkaloid when the Pschorr reaction is applied to the bases of type III, has already been



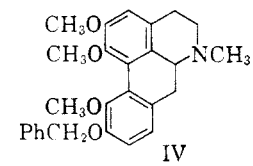
I



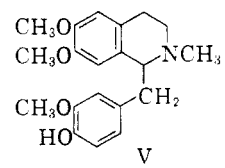
II



III



IV



V

described, but the conditions that favor one or the other product have not been worked out. While we obtained both types of bases using copper powder, a result similar to that described by Arumugam *et al.*[5] in the synthesis of corydine, Tomita and Kikkawa[3] found that this catalyst favored the exclusive production of the benzylisoquinoline alkaloid, coclanoline. Only when the reaction was carried out with zinc powder could they obtain the related aporphine base laurifoline. On the other hand, it is of interest that Hey and Lobo[1] and Hey and Palluel[4] have prepared aporphines by the Pschorr reaction, employing copper powder as catalyst.

EXPERIMENTAL

All the ultraviolet spectra were recorded in 96% ethanol. Melting points are uncorrected.

4-Benzyloxy-3-methoxy-2-nitro-phenylacetic acid. Ten grams of 4-hydroxy-3-methoxy-2-nitro-phenylacetic acid[8] were partially dissolved in 40 ml. of dioxane, 8.5 ml. of benzyl chloride and 5 g. of potassium carbonate were added, and the mixture was boiled for 1.5 hr. with agitation. One hundred ml. of water was then added and steam was passed

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through the solution to eliminate dioxane and benzyl chloride. A heavy dark brown oil and a water phase remained. Upon storing at 0° the oil crystallized. The crystals of crude benzyl ester of 4-benzyloxy-5-methoxy-2-nitrophenylacetic acid were filtered and hydrolyzed by boiling for 30 min. in 20 ml. ethanol with 20 ml. 4*N* potassium hydroxide. The solution was acidified with 2*N* hydrochloric acid, whereupon light brown crystals separated. Recrystallized from ethanol-water, 1.2 g. of white needles was collected which, after drying at 100°, melted 144°.

The water filtrate from the ester was cooled thoroughly and acidified with 2*N* hydrochloric acid. There was produced a crystalline precipitate which, after filtering and recrystallizing from ethanol-water, yielded 8.5 g. of the dried acid, m.p. 144°. The total yield was 9.7 g. (55%). Gulland[9] gives m.p. 144°.

4-Benzyloxy-3-methoxy-2-nitrophenylacetyl chloride. Five grams of the acid was dissolved in 50 ml. chloroform, 20 ml. thionyl chloride was added, and the mixture was boiled for 1.5 hr. on a water bath. The excess chloroform and thionyl chloride were removed *in vacuo* and the red oil remaining was extracted five times with 100 ml. of boiling petroleum ether (66–72°) leaving an insoluble dark residue. The petroleum ether solution was diluted to 700 ml. and left at 5° whereupon the chloride crystallized as long white needles (3.9 g., 75%), m.p. 133–134°. The m.p. was not improved by further recrystallization.

Anal. Calcd. for $C_{16}H_{14}ClNO_5$: Cl, 11.56. Found: Cl, 11.11.

1-(4′-Benzyloxy-3′-methoxy-2′-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline methiodide (II). The necessary 4′-benzyloxy-3′-methoxy-2′-nitrophenyl-*N*-2-(3,4-dimethoxyphenyl)ethylacetamide, m.p. 112°, was prepared by the method of Gulland and co-workers,[6] using chloroform instead of benzene as solvent. It was cyclized to 1-(4′-benzyloxy-3′-methoxy-2′-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (I), m.p. 230–232°, in 85% yield, by a slight modification of the method of Gulland[6]; λ_{max} 276 mμ (log ε 3.85); 312 mμ (log ε 3.86).

The hydrochloride was transformed into the free base by treatment of its solution in ethanol with ammonia. The crystalline base melted 144–145°, decomposed easily, and was not analyzed (Gulland *et al.*[6] give m.p. 119°). By boiling 11.8 g. of the free base with 120 ml. methyl iodide and 20 ml. ethanol for 30 min., 14 g. of yellow long rectangular plates of the methiodide were obtained. M.p. 193–194°, unchanged by recrystallization. Gulland *et al.*[6] give 108° as the m.p. of the methiodide with decomposition at 200°.

Anal. Calcd. for $C_{26}H_{26}N_2O_6 \cdot ICH_3$: C, 52.70; H, 4.50; N, 4.63; I, 21.00. Found: C, 53.40; H, 4.63; N, 4.85; I, 21.15.

1-(4′-Benzyloxy-3′-methoxy-2′-nitrobenzyl)-N-methyltetrahydroisoquinoline hydriodide. Three grams of the former methiodide were dissolved in 180 ml. of absolute ethanol by heating, and the solution was allowed to cool at room temperature and reduced at atmospheric pressure employing 300 mg. platinum dioxide catalyst. During the reduction, white needles of the hydriodide precipitated. When the absorption of hydrogen was complete, the hydriodide was dissolved by heating, the catalyst filtered, and the yellow-green solution concentrated to 120 ml., whereupon crystallization started. After standing for 24 hr. at 5°, the crystals were filtered and recrystallized from absolute ethanol. White needles (2.4 g.), m.p. 162°, were obtained (yield: 81%).

Anal. Calcd. for $C_{27}H_{30}N_2O_6 \cdot HI$: C, 53.46; H, 4.14; N, 4.61; I, 20.92. Found: C, 53.75; H, 4.32; N, 4.53; I, 21.87.

The free nitro base was prepared by dissolving 410 mg. of the hydriodide in 10 ml. warm absolute ethanol and adding 2 ml. of concentrated ammonia. A precipitate was obtained which after cooling was filtered and recrystallized from absolute ethanol. The yield was 315 mg. (98%) of rectangular plates, m.p. 138°.

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Anal. Calcd. for $C_{27}H_{30}N_2O_6$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.69; H, 6.22; N, 5.94.

1-(2′-Amino-4′-benzyloxy-3′-methoxybenzyl)-N-methyltetrahydroisoquinoline (III). The reduction of the nitro group was followed by ascending chromatography on Whatman paper No. 1, employing butyl alcohol:acetic-acid:water (80:3:17) as the mobile phase and Dragendorff's reagent for development. The nitro base, R_f 0.77, shows no fluorescence with ultraviolet light and gives an orange spot with the reagent. The amino base, R_f 0.48, shows a strong violet fluorescence and gives a red spot.

From the hydriodide. Two hundred milligrams of the hydriodide of the nitro base (II) was dissolved in 20 ml. methanol, and reduced for 7 hr. at 4 atm. pressure, employing 40 mg. of platinum oxide as catalyst. After filtering and evaporating the solvent, the residue was dissolved in water, and the solution was made alkaline with ammonia and extracted with ether. Evaporation of the ether gave an oily residue which showed a faint spot of the nitro base in the chromatogram. It was dissolved in ethanol and an excess of a solution of picrolonic acid in the same solvent was added. The dipicrolonate (250 mg., 78%), m.p. 208°, was obtained in the usual way. Gulland *et al.*[6] give m.p. 207°.

From the free nitro base. The same result was obtained by hydrogenation of the free nitro base. Five hundred milligrams was suspended in 140 ml. of water and dissolved by adding 0.1*N* sulfuric acid to *p*H 2, and hydrogenated at room pressure and temperature for 60 hr., employing 160 mg. of platinum dioxide as catalyst. After filtering the slightly yellow solution was made alkaline with diluted ammonia and extracted with ether. The dried ethereal extract was evaporated and the residue, dissolved in a small amount of warm absolute ethanol, was transformed into the picrolonate, m.p. 208°, 634 mg. (67.5%).

Benzyl-pseudocorydine hydriodide. The dipicrolonate (1.2 g.) was suspended in 6 ml. of cold methanol, 1.2 ml. of concentrated sulfuric acid dissolved in 6 ml. of cold methanol was added and the insoluble solid was well ground. The base dissolved and the insoluble picrolonic acid was filtered and washed with methanol. The mixed yellow methanolic solutions were cooled to 0° and 84 mg. of sodium nitrite, dissolved in 2.4 ml. of water, was slowly added. After standing overnight at 3–5°, 300 mg. of catalytic copper was added and a strong evolution of nitrogen took place. After 1 hr. at room temperature, with stirring, the suspension was boiled during 30 min. an equal volume of water was added and, when cool, the mixture was extracted twice with ether, and the extract discarded. The solution was then alkalinized with concentrated ammonia and again extracted with ether, until the extract gave a negative Mayer's reaction. The ether solution was well dried and evaporated to dryness and 386 mg. of a dark orange oil was obtained. It was dissolved in a few ml. of benzene and chromatographed by passage through a column of 18 g. of neutral aluminum oxide, activity III. The column was washed with 100 ml. of benzene and eluted with benzene–0.1% ethanol. Fractions of 50 ml. were collected. Fractions 7–12 gave a positive Mayer reaction and fraction 13 was negative. Benzene–1% ethanol was then employed and fractions 14–15 gave a positive reaction, while fraction 16 was again negative.

The oily residue from fractions 7 and 8, with a total weight of 128 mg., were pooled, dissolved in 2 ml. warm methanol, a small amount of acetic acid was added, and the solution was saturated with sodium iodide. Upon cooling, the hydriodide of benzylpseudocorydine crystallized. After recrystallization from methanol, 96 mg. of white prisms, m.p. 237° (dec.) was collected; λ_{max} 270 mμ (log ε 4.20), 299 mμ (log ε 3.77). No crystalline material could be obtained from the other fractions.

Anal. Calcd. for $C_{27}H_{29}NO_4 \cdot IH$: C, 57.97; H, 5.41; N, 2.50; I, 22.69. Found: C, 58.04; H, 5.40; N, 2.55; I, 23.02.

Pseudocodamine (V). Fractions 14 and 15 gave 89 mg. of a dark orange oil that was boiled for 45 min. with 15 ml. of 20% hydrochloric acid. After cooling, the solution was ex-

tracted with ether, alkalinized with ammonia and extracted again with ether until a negative Mayer's reaction was obtained. This last ether extract was well dried and a few drops of cyclohexane were added to the oily residue, whereupon it was caused to crystallize by scratching. The filtered crystals, recrystallized from cyclohexane, gave prisms, m.p. 130–131°, undepressed by pseudocodamine, m.p. 130–131°.[7] The picrate melted at 156–157°, and was identical with pseudocodamine picrate.

Pseudocorydine hydrochloride. One hundred milligrams of the former benzyl-pseudocorydine hydriodide was suspended in water, the solution covered with a layer of ethyl ether, made alkaline with saturated sodium hydrogen carbonate solution, and extracted with ether until a negative Mayer reaction was obtained. The ether extracts were dried and on evaporation gave 70 mg. of a brown oily residue. Fifteen ml. of 20% hydrochloric acid was added, and the solution was boiled for 1 hr. and evaporated to dryness, *in vacuo*. A crystalline brown residue was obtained, which was recrystallized by dissolving in ethanol and adding ether to turbidity. Thirty mg. (Vacuum) of white needles, m.p. 268–269° (sintering from 262°), was collected. λ_{max} 272 mμ (4.09); 302 mμ (3.70).

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot ClH$: C, 63.56; H, 6.40; N, 3.70; Cl, 9.38. Found: C, 63.43; H, 6.37; N, 3.77; Cl, 9.37.

Pseudocorydine (IV). The hydrochloride (50 mg.) was dissolved in water, covered with a layer of ethyl ether, made alkaline with diluted ammonia and extracted with ether until a negative Mayer reaction was obtained. The dried extracts on evaporation left a white grayish crystalline solid, very soluble in all organic solvents, excepting cyclohexane and petroleum ether. After several recrystallizations from cyclohexane, white long prisms were obtained, melting 184–185° in vacuum. λ_{max} 272 mμ (log ε 4.04), 302 mμ (log ε 3.66).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.51; H, 6.98; N, 4.07.

Pseudocorydine gives the same color reactions as isocorydine except with Fröhde's reagent which gives a dark purple color with pseudocorydine and a violet one with isocorydine.

Picrate. Prisms from ethanol m.p. 210–211°.

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot C_6H_3N_3O_7$: N, 9.82. Found: N, 9.52.

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Effects of Perfluoroalkyl Groups on Adjacent Functions

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The adjacency of a perfluoroalkyl group can affect the stability of intermediate reaction products in such an adverse way as to render impractical some conventional reactions. Aldehydes and ketones so fluorinated react with diazomethane to give the expected oxides, but these are cleaved by hydrogen to give secondary and tertiary alcohols, instead of primary and secondary alcohols. Pyrolysis of *N,N'*-di(trifluoroacetyl)hydrazine and *N*-benzenesulfonyl-*N'*-trifluoroacetylhydrazine did not give trifluoroacetaldehyde, but its pyrolysis products, carbon monoxide and fluoroform. Hydrogenolysis of the benzyl ester of *N*-heptafluoropropylcarbamic acid gave toluene with hydrogen fluoride and pentafluoropropionamide instead of heptafluoropropylamine.

The adjacency of a perfluoroalkyl group, besides modifying the polarity of a function, can affect the stability of a conventional reaction product in such a favorable way as to render practical certain reactions otherwise not useful, *e.g.*, the preparation of ketones in good yields from perfluorinated acids and Grignard reagents due to the stability of the intermediate.[2–4] This modifying action is not always an aid and may make impractical some convential reactions.

Most aldehydes and ketones react conventionally with diazomethane to give the next higher homologs, or mixtures of them, and substituted ethylene oxides.[5–7] When electron withdrawing groups are present in the alpha position, the oxide is the major or sole product.[8–10] When trifluoroacetaldehyde and trifluoroacetone were used, the reaction proceeded as expected to give the corresponding oxides, 1,2-epoxy-3,3,3-trifluoropropane (I) and 1,2-epoxy-2-methyl-3,3,3-trifluoropropane (II), respectively. On hydrogenation, unfluorinated oxides give primary and secondary alcohols.[11–13] In contrast, hydrogenation with Raney nickel of the fluorinated oxides gave 2-trifluoromethyl-2-propanol, and 1,1,1-

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