[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, PRESIDENCY COLLEGE]

SYNTHESIS OF *dl*-4,5,6-TRIMETHOXYAPORPHINE

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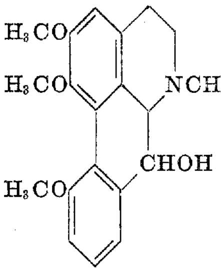
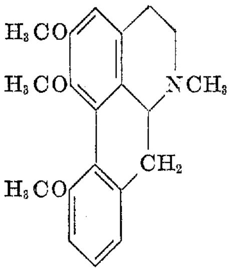
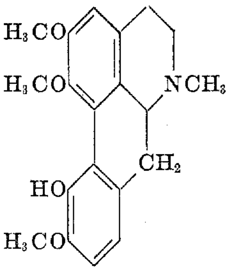
The principal alkaloid from *Artabotrys suaveolens* Bl. was considered to be 4,5,6-trimethoxy-10-hydroxyaporphine (I) by Barger and Sargent (1) on the assumption that it was non-phenolic and on the basis of degradation studies. While attempts to synthesize a molecule of this structure were in progress, it was considered that it would be of interest to synthesize also 4,5,6-trimethoxyaporphine (II). Molecules having structures I and II would be expected to have almost identical ultraviolet absorption spectra, since the alcoholic hydroxyl in the former would hardly have any effect on absorption in the ultraviolet region.



I



II



III

dl-4,5,6-Trimethoxyaporphine was accordingly synthesized by the classical procedure of Gulland and Haworth (2) and its absorption spectrum was determined (Fig. 1). The base has absorption maxima at 275 mμ and 300 mμ and minima at 250 mμ and 285 mμ. Barger and Sargent (1) record the alkaloid from *Artabotrys suaveolens* Bl. (called artabotrine) as having absorption maxima at 3210 and 3490 and minima at 3745 and 3990 expressed as 'frequency'. From a study of this paper and a paper by Girardet (3) on the absorption spectra of aporphine alkaloids and by redetermination of the absorption spectrum of thebaine for which values are recorded by Giradet (3), we have to conclude that these authors imply by the term 'frequency', wave numbers expressed in mm^{-1}. Expressed in terms of wave length, Barger and Sargent's values become 267 mμ and 311 mμ for the maxima and 251 mμ and 287 mμ for the minima. There is a significant divergence from the absorption maxima determined by us for 4,5,6-trimethoxyaporphine.

Recently, Schlittler and Huber (4) have shown that the principal alkaloid from *Artabotrys suaveolens* Bl., till now called artabotrine, is identical with isocorydine (III).

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EXPERIMENTAL

Ultraviolet absorption spectra were determined with a Model DUV-Beckman spectrophotometer in 1-cm. silica cells.

2-Nitro-3-methoxyphenylacetic acid was prepared essentially according to Blaikie and Perkin (5).

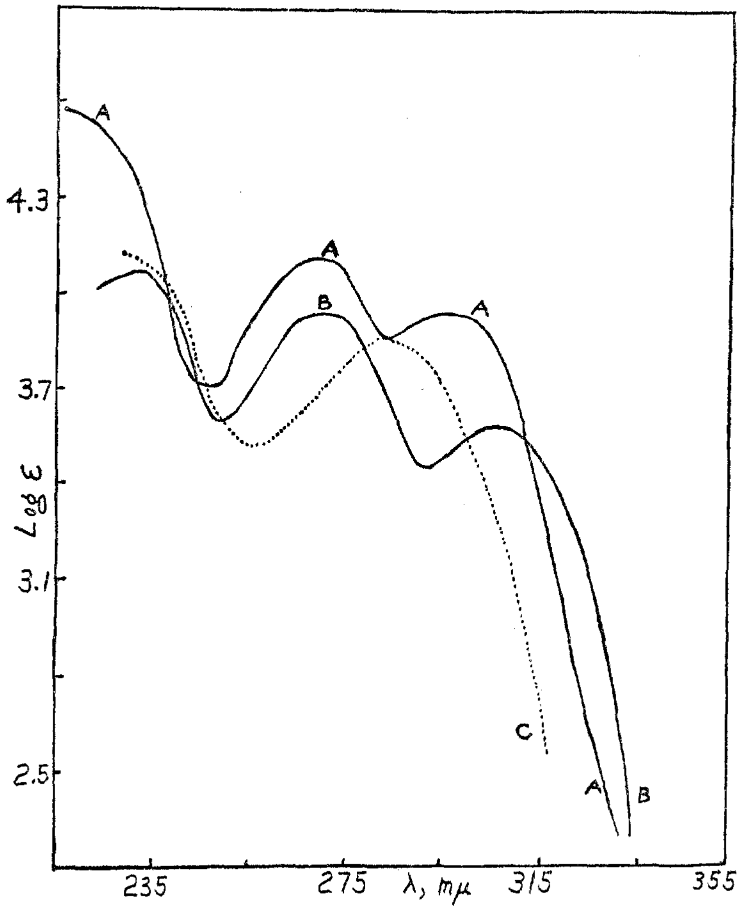

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF: (A) 4,5,6-Trimethoxyaporphine; (B) Bulbocapnine; (C) Thebaine.

N-[β-(3,4-dimethoxyphenyl)ethyl]-2-nitro-3-methoxyphenylacetamide. A solution of 14.5 g. of 2-nitro-3-methoxyphenylacetic acid in 75 ml. of chloroform was treated with 45 ml. of thionyl chloride at 40° for two hours, while protected from moisture. The chloroform and thionyl chloride were removed by distillation *in vacuo*, keeping the bath temperature below 40°. The residue was kept over sodium hydroxide *in vacuo* for 24 hours and it set to a red crystalline mass. It was then dissolved in 25 ml. of benzene and added with stirring to a solution of 12 g. of homoveratrylamine in 250 ml. of benzene, cooled in ice. The mixture was stirred for one hour and a cold solution of 2.7 g. of sodium hydroxide in 60 ml. of water was added. After leaving in the ice chest overnight, the solid that had separated was filtered off and purified by grinding successively with dilute hydrochloride acid (2 *N*), dilute sodium carbonate solution (2 *N*), filtering after each operation, and finally washing with water. From the benzene layer, some amide was recovered by removal of solvent. The total yield of amide was 17 g. pure enough for the next step. The amide was recrystallized from benzene, m.p. 126°.

Anal. Calc'd for $C_{19}H_{22}N_2O_6$: N, 7.55. Found: N, 7.49.

1-(2-Nitro-3-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. A solution of 5.5 g. of the amide in 50 ml. of dry chloroform was well cooled in ice and treated cautiously with 6.5 g. of phosphorus pentachloride in small amounts. The reaction mixture was protected from moisture and left for 60 hours at room temperature. Within a few hours of the addition of phosphorus pentachloride a yellow crystalline material separated. After 60 hours, the material was filtered on a sintered glass funnel and washed with dry chloroform. The residue was crystallized from water. From the chloroform filtrate, more of the same material was obtained by removal of chloroform, and this likewise was purified by crystallization from water. The yield of the dihydroisoquinoline hydrochloride was 4.7 g., m.p. 224–226° (decomp.).

Anal. Calc'd for $C_{19}H_{21}ClN_2O_5$: N, 7.14. Found: N, 7.23.

The *free base* was prepared by triturating the hydrochloride with dilute ammonia. The amorphous product so formed was crystallized from ethanol. M.p. 143°.

Anal. Calc'd for $C_{19}H_{20}N_2O_5$: N, 7.87. Found: N, 8.23.

The *methiodide* was prepared by refluxing the dihydroisoquinoline in chloroform solution with excess methyl iodide for four hours. After removal of solvent, the residue was recrystallized from ethanol, m.p. 218°.

Anal. Calc'd for $C_{20}H_{23}IN_2O_5$: N, 5.63. Found, N, 5.84.

1-(2-Amino-3-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride. A suspension of 6 g. of the above methiodide in 60 ml. of concentrated hydrochloric acid and 60 ml. of water was heated on a water-bath with the gradual addition of 18 g. of zinc dust. Addition was completed in 30 minutes during which time the mixture was vigorously shaken. The clear colorless solution was filtered hot from undissolved zinc, cooled, basified, and extracted with ether. The base was extracted from the ether solution by repeated shaking with portions of dilute hydrochloric acid (4 *N*). The acid extract was cooled, basified, and the base again extracted with ether. The ether extract was dried over sodium sulphate. The residue from the dried ether extract was an oil which was dried thoroughly by being kept *in vacuo* over potassium hydroxide. The dry oil was dissolved in anhydrous benzene and saturated with dry hydrogen chloride gas. The precipitated hydrochloride was recrystallized from an absolute alcohol-ether mixture. Yield, 3 g., m.p. 218°.

Anal. Calc'd for $C_{20}H_{25}Cl_2N_2O_3$: C, 57.84; H, 6.75.
Found: C, 57.93; H, 6.88.

dl-4,5,6-Trimethoxyaporphine. A solution of 1 g. of the above dihydrochloride in 10 ml. of dilute sulphuric acid (2 *N*) and 10 ml. of methanol was treated at 0° with 9.5 ml. of a freshly prepared solution of sodium nitrite containing 0.17 g. of sodium nitrite. The solution was kept at 0° for one hour after which it was allowed to rise to room temperature. The solution was then heated on a water-bath until evolution of nitrogen ceased. The red solution which resulted was heated with 0.5 g. of zinc dust and 1 ml. of concentrated hydrochloric acid, when the color was discharged. The solution was filtered hot, cooled well, basified with aqueous ammonia, and extracted with ether. The ether extract was repeatedly shaken with portions of dilute hydrochloric acid. The acid extract was carefully neutralized and treated with a large excess of a saturated solution of potassium iodide. The gummy precipitate thus obtained was freed from mother liquor and rubbed with absolute alcohol, when a crystalline material formed. This was filtered and recrystallized from absolute alcohol. This product is the hydriodide of the aporphine base. Yield, 0.12 g., m.p. 250°.

Anal. Calc'd for $C_{20}H_{24}INO_3$: C, 52.98; H, 5.30; N, 3.09.
Found: C, 53.3; H, 5.45; N, 3.38.

The *free base* was prepared by trituration of the hydriodide with dilute ammonia. It was excessively soluble in almost all organic solvents. It was purified by spontaneous evaporation from a petroleum ether solution, m.p. 98°.

The *picrolonate*, prepared by mixing alcoholic solutions of the base and picrolonic acid, after crystallization from alcohol had m.p. 196°.

Anal. Calc'd for $C_{30}H_{31}N_5O_8$: C, 60.87; H, 4.96; N, 12.09.
Found: C, 61.12; H, 5.26; N, 11.89.

SUMMARY

dl-4,5,6-Trimethoxyaporphine has been synthesized and its absorption spectrum has been determined.

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