[Contribution from L'Institut de Chimie, University of Montreal and the Division of Chemistry of the National Research Council]

THE SYNTHESIS OF *dl*-ARMEPAVINE[1]

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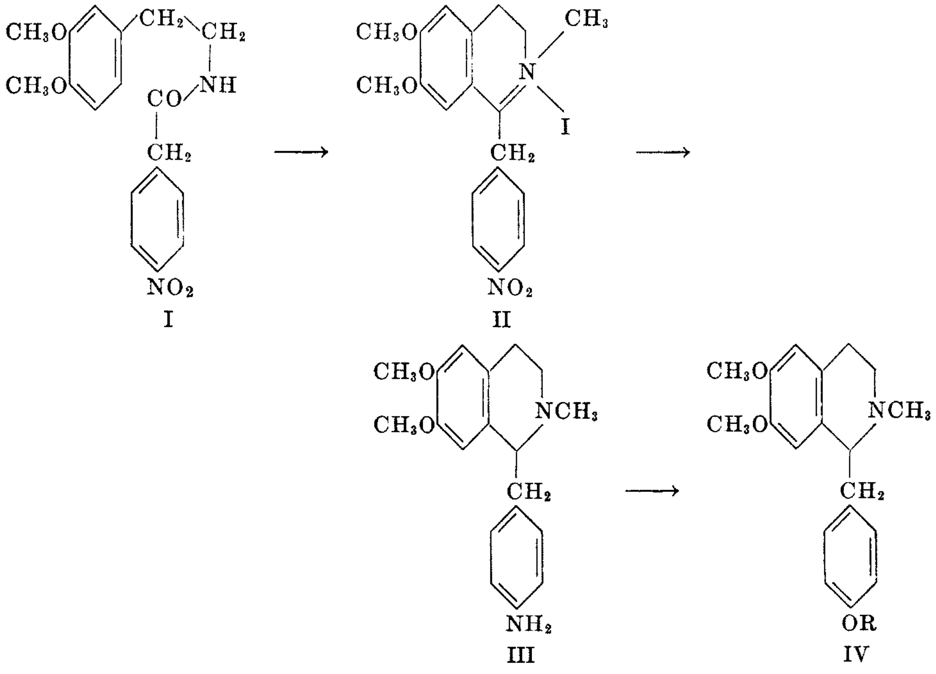
Received September 6, 1949

Armepavine is a levorotatory alkaloid ($C_{19}H_{23}NO_3$) obtainable from two species of *Papaver*, *i.e.*, *P. armeniacum*, Lam., (1) and *P. floribundum*, Desf. (2). On oxidation the base gives rise to 1-keto-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V) (3). Armepavine contains a phenolic hydroxyl and forms a methyl ether which, in the final step of the Hofmann degradation, produces a trimethoxystilbene. The substituted stilbene is scinded by oxidation into anisic acid and *meta*-hemipinic acid. On the basis of these results armepavine has been represented by formula IV (R = H), *i.e.*, 6,7-dimethoxy-1-(*p*-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3). This structure has now been confirmed by a total synthesis of *dl*-armepavine. Although it has not yet proved possible to resolve the racemic base, its degradation to the same products as those obtained from the naturally occurring alkaloid leave no doubt as to the structural identity of the synthetic base with armepavine.

p-Nitrophenylacetyl chloride and 3,4-dimethoxyphenylethylamine were condensed to (*p*-nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide (I) and this was cyclized by the Bischler-Napieralski reaction to 1-(*p*-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. The methiodide (II) of the cyclized product



I

II

III

IV

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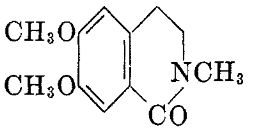
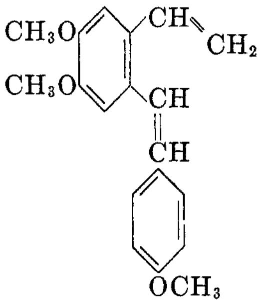
[1] Published as National Research Council Bull. No. 2052.

was reduced to 1-(*p*-aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III) which was diazotized and converted to *dl*-armepavine (IV, R = H).

Oxidation of the racemic base with potassium permanganate produced the expected 1-keto-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V). Synthetic armepavine formed an O-methyl derivative (IV, R = CH_3), the methiodide of which was converted by the action of alkali to *des*-O,N-dimethylarmepavine.



V



VI

This last compound, in turn, formed a methiodide which, by the action of hot alkali, gave rise to 4,4′,5-trimethoxy-2-vinylstilbene (VI). The structure of this substituted stilbene was confirmed by its oxidation with potassium permanganate to anisic acid and *meta*-hemipinic acid. These various degradative reactions have all been carried out previously with the naturally occurring alkaloid (3) and the properties of the many compounds isolated in the course of these degradations agree with those already on record (3).

Acknowledgment. The authors wish to express their gratefulness to the National Research Council of Canada for the award of a Fellowship to one of them (V. P.).

EXPERIMENTAL

The synthesis first involved the preparation of the starting materials. 3,4-Dimethoxyphenylethylamine was prepared from veratraldehyde by the method used by Marion and Grassie for the synthesis of 3,4-methylenedioxyphenylethylamine (4). *p*-Nitrophenylacetic acid was obtained from benzyl chloride by standard procedures (5, 6).

(p-Nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide (I). To a solution of *p*-nitrophenylacetic acid (7.3 g.) in chloroform (53 cc.), phosphorus pentachloride (18.7 g.) was added gradually. The resulting solution was added dropwise to a mixture of 3,4-dimethoxyphenylethylamine (9 g.), chloroform (45 cc.), 2 *N* aqueous sodium hydroxide (240 cc.), and water (375 cc.), kept stirred mechanically and cooled under the tap. After completion of the addition, stirring was continued for 30 minutes. The chloroform layer was separated and the aqueous solution was extracted with three more portions of chloroform. Successively, the combined chloroform extract was washed with 1:1-hydrochloric acid, with a saturated sodium carbonate solution, and with water; dried over sodium sulfate and distilled to dryness. The residual amide was crystallized twice from boiling methanol from which it separated as colorless scales, melting at 120°,[2] wt. 8.7 g., average yield, 65%.

Anal. Calc'd for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.81; N, 8.11.
Found: C, 62.81, 62.70; H, 5.77, 5.93; N, 7.98, 7.94.

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[2] All melting points are corrected.

1-(p-Nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. To the above amide (5 g.) dissolved in chloroform (20 cc.) was added phosphorus oxychloride (15 cc.) and the resulting solution allowed to stand at room temperature for one week. The chloroform and excess phosphorus oxychloride were evaporated under diminished pressure and the light yellow solid residue was dissolved in warm dilute (1:1) hydrochloric acid. The solution was diluted with water, filtered to remove a small quantity of gum, and alkalized with ammonium hydroxide to liberate the base. The precipitated base was filtered, washed with water, and crystallized from boiling methanol from which it separated as small colorless needles, m.p. 122°; yield, 71%.

Anal. Calc'd for $C_{18}H_{18}N_2O_4$: C, 66.26; H, 5.52; N, 8.59.
Found: C, 66.10; H, 5.52; N, 8.38.

1-(p-Nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (II). A mixture of the substituted dihydroisoquinoline (5 g.), methyl iodide (25 cc.), and methanol (75 cc.) was refluxed on the steam-bath for six hours. The crystalline methiodide which separated was filtered and washed with absolute ether. After recrystallization from boiling methanol it consisted of small yellow prismatic needles, m.p. 194°. Yield, 95%.

Anal. Calc'd for $C_{19}H_{21}IN_2O_4$: C, 48.71; H, 4.49.
Found: C, 48.80, 48.78; H, 4.63, 4.63.

1-(p-Aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride. The methiodide (II) (10 g.) was dissolved in a mixture of water (100 cc.) and conc'd hydrochloric acid (200 cc.) with the aid of heat. To the solution kept mechanically stirred on the steam-bath, zinc dust (30 g.) was added in small quantities in the course of 45 minutes. The resulting mixture was filtered, the cooled filtrate alkalized with ammonium hydroxide, and extracted with four portions of ether. The combined extract was dried over potassium hydroxide pellets and the solvent subsequently distilled off on the steam-bath. The white, crystalline, residual base was immediately dissolved in a mixture of absolute methanol and absolute ether and the solution saturated with dry hydrogen chloride. The precipitated dihydrochloride was filtered and recrystallized from methanol-acetone from which it separated as small, colorless prisms, m.p. 268°. Yield, 70%.

Anal. Calc'd for $C_{19}H_{26}Cl_2N_2O_2$: C, 59.21; H, 6.75; Cl, 18.44.
Found: C, 59.61, 59.44; H, 6.82, 6.70; Cl, 17.88, 18.34.

dl-Armepavine (IV, R = H). The amine dihydrochloride (5 g.) was dissolved in sulfuric acid (10 cc.) previously diluted with water (100 cc.) and the solution cooled to 0° in an ice-bath. A cold solution of sodium nitrite (1 g.) in water (50 cc.) was then added at such a rate that the temperature did not rise above 5°. After the addition of the sodium nitrite had been completed the reaction mixture was allowed to stand ten minutes, during which the diazo compound crystallized. The resulting mixture was cautiously added to a boiling mixture of water (375 cc.) and conc'd sulfuric acid (125 cc.) and boiling continued for fifteen minutes after completion of the addition. The solution was cooled, filtered through charcoal to remove a quantity of gum which had separated, and the filtrate alkalized by the slow addition of ammonium hydroxide while cooling and stirring. The liberated base was extracted with four portions of ether and the combined extract dried over sodium sulfate. Distillation of the ether by heating the extract on the steam-bath left a residue consisting of small, yellow prisms. After recrystallization from acetone-ether, synthetic *dl*-armepavine was obtained as small, colorless rhombs, m.p. 166°. Yield, 65%.

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.35; N, 4.47.
Found: C, 72.70, 72.87; H, 7.39, 7.27; N, 4.50, 4.41.

O-Methyl-dl-armepavine (IV, R = OCH_3). A solution of *dl*-armepavine (1.0 g.) in ether, to which an excess of diazomethane had been added, was allowed to stand overnight at room temperature. The ether and excess diazomethane were distilled off on the steam-bath and the residue dissolved in 5% hydrochloric acid (50 cc.). The filtered solution was alkalized with sodium hydroxide and extracted with ether. After removal of the solvent by distillation, the extract yielded an oil which was dissolved in absolute ether. On standing, this solution deposited colorless prismatic needles, m.p. 92°. Wt. 0.82 g.; yield, 78.3%.

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.40; H, 7.64, N, 4.28.
Found: C, 73.51, 73.47; H, 7.59, 7.50; N, 4.19, 4.16.

O-Methyl-dl-armepavine methiodide. O-Methyl-*dl*-armepavine when refluxed for three hours with methanol and excess methyl iodide gave a quantitative yield of the corresponding methiodide which crystallized from methanol as small yellow prisms, m.p. 135–136°.

Anal. Calc'd for $C_{21}H_{28}INO_3$: C, 53.73; H, 5.97; N, 2.98.
Found: C, 53.01, 53.14; H, 6.09, 6.06; N, 3.15.

Des-O,N-dimethylarmepavine. The methiodide of O-methyl-*dl*-armepavine (0.2 g.) was added to methanol (10 cc.) containing sodium hydroxide (0.8 g.) and the solution heated on the steam-bath for ninety minutes. This solution was subsequently evaporated to dryness, the residue dissolved in water (20 cc.), and the resulting aqueous solution extracted with ether. The extract was dried over potassium hydroxide pellets and distilled on the steam-bath to remove the solvent. It yielded a colorless oil (wt. 0.15 g.) which crystallized from petroleum ether as fine colorless needles, m.p. 87°; yield, quantitative. The similar compound obtained from *l*-armepavine had m.p. 86–87° (3).

Anal. Calc'd for $C_{21}H_{27}NO_3$: N, 4.10. Found: N, 4.16, 4.21.

Des-O,N-dimethylarmepavine methiodide. This methiodide was prepared by refluxing a mixture of the above methine (90 mg.), methanol (10 cc.), and methyl iodide (2 cc.) for ninety minutes. The resulting solution was concentrated to a small volume and allowed to stand. The methiodide which separated was recrystallized from methanol after which it consisted of small, colorless prisms, m.p. 234°; wt. 95 mg. The methiodide obtained from the natural base had m.p. 233–234° (3).

Anal. Calc'd for $C_{22}H_{30}INO_3$: C, 54.67; H, 6.22.
Found: C, 54.79, 54.71; H, 6.16, 6.14.

4,4′,5-Trimethoxy-2-vinylstilbene. *Des-O,N*-dimethylarmepavine methiodide (0.2 g.) was added to methanol (5 cc.) containing potassium hydroxide (1 g.) and heated on the steam-bath for 1¾ hours. The solution was evaporated to dryness, water (15 cc.) was added to the residue, and the mixture extracted with ether (four portions). The combined extract was washed with two 50-cc. portions of 5% hydrochloric acid and with water. It was then dried over potassium hydroxide pellets and evaporated to dryness when it yielded a colorless oil which crystallized in contact with petroleum ether (2–3 cc.). Wt. 0.12 g., yield, 95%. After recrystallization from a mixture of anhydrous ether and petroleum ether, the product consisted of colorless rods, m.p. 79.5°. Literature, m.p. 79–79.5° (3).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.02; H, 6.76.
Found: C, 76.77, 76.95; H, 6.77, 6.75.

Oxidation of 4,4′,5-trimethoxy-2-vinylstilbene. To a stirred solution of the substituted stilbene (0.5 g.) in purified acetone (100 cc.), 1% potassium permanganate in purified acetone (150 cc.) was added in the course of two hours at 20–22°. The reaction mixture was stirred a further two hours after which a little alcohol was added to destroy the excess potassium permanganate. The precipitated manganese dioxide was filtered and washed with hot water (200 cc.). The aqueous washings which had been kept separate were evaporated to dryness *in vacuo* on the steam-bath, the residue shaken with 10% hydrochloric acid (50 cc.), and the mixture extracted with five portions of ether. The combined extract was concentrated to 3–4 cc. and allowed to stand when it deposited a mixture of small, brownish warts and colorless needles. This was shaken with ether until all the needles had dissolved and the mixture filtered to remove the less soluble warts which were washed with a few drops of ether (wt. 0.116 g.). On recrystallization from boiling anhydrous ether, the filtered product yielded small colorless needles, m.p. 185–186° either alone or in admixture with an authentic sample of *meta-hemipinic acid.* The acetone liquor, from which the manganese dioxide had been filtered, was evaporated to dryness *in vacuo.* It left a residue which was shaken with 15% hydrochloric acid (50 cc.); the mixture was extracted with four portions of ether. When concentrated to a small volume, the combined extract deposited a crystalline substance which, after recrystallization from anhydrous ether, consisted of colorless needles (wt. 0.116 g.) m.p. 183.5–184.5° either alone or after admixture with an authentic sample of *anisic acid.*

6,7-Dimethoxy-2-methyl-1-keto-1,2,3,4-tetrahydroisoquinoline (V). To a solution of *dl*-armepavine (0.4 g.) in purified acetone (75 cc.) kept at 25–27°, was added dropwise, in the course of ninety minutes, a solution of potassium permanganate (0.7 g.) in purified acetone (90 cc.). This solution was allowed to stand with occasional stirring for a further hour and the excess potassium permanganate was destroyed by the addition of a little methanol. The manganese dioxide was then filtered and washed with acetone (50 cc.) and the combined filtrate and washings were evaporated to dryness *in vacuo*. A yellowish, solid residue was left which was dissolved in warm 10% hydrochloric acid (100 cc.). The solution was cooled, filtered, alkalized with ammonium hydroxide, and extracted with ethyl acetate. On evaporation to dryness *in vacuo* the extract left a residue which was dissolved in warm 0.5% hydrochloric acid (100 cc.). The solution was cooled, extracted with four portions of ether and the extract dried over potassium hydroxide pellets and distilled to dryness. There was left a crystalline residue which, after recrystallization from anhydrous ether, consisted of small colorless needles, m.p. 124–125°, wt. 0.15 g. Literature, m.p. 124–125° (3).

Anal. Calc'd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33.
Found: C, 65.20; H, 6.92; N, 6.40.

SUMMARY

The structure assigned to armepavine has been confirmed by a total synthesis of the racemic base. This synthesis has been effected from (*p*-nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide which was cyclized to the corresponding dihydroisoquinoline, the methiodide of which was reduced and the product converted to *dl*-armepavine by diazotization. The structural identity of the synthetic base with the naturally occurring alkaloid has been confirmed by a comparison of the properties of the oxidation product and of the products of the Hofmann degradation with the recorded properties of the corresponding derivatives obtained from the alkaloid.

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