

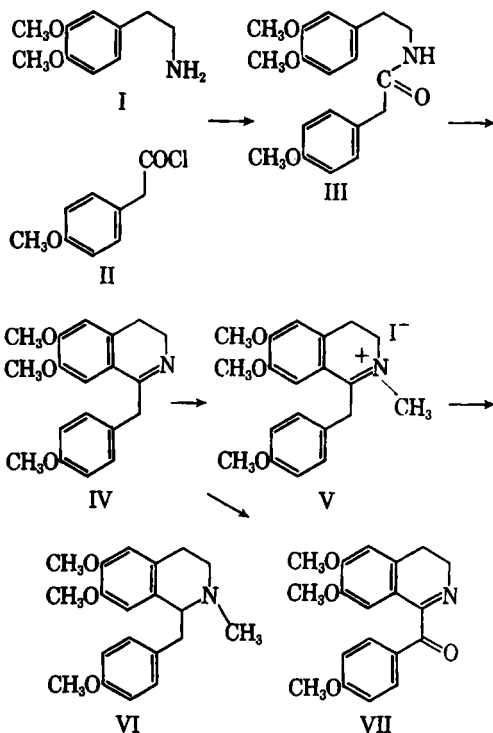
Synthesis of *dl*-*O*-Methylarmepavine

Sir:

In a continuation of studies on the alkaloids of *Magnolia acuminata* L. (1, 2), what appears to be the first isolation and characterization of *d*-*O*-methylarmepavine from plant was reported. For purposes of comparison, a reference sample of the alkaloid was required. The *dl* form of the base was synthesized by a method differing from that reported by Marion *et al.* (3) and Tomita and Yamaguchi (4).

In a series of five steps, Marion and co-workers obtained armepavine starting from homoveratrylamine and 4-nitrophenylacetyl chloride. The phenolic base was methylated with diazomethane to yield *dl*-*O*-methylarmepavine, m.p. 92°. Tomita and Yamaguchi (4) condensed homoveratrylamine with 4-benzyloxyphenylacetyl chloride to yield armepavine in a series of four steps. Methylation of the phenolic alkaloid with diazomethane yielded its *O*-methyl ether, m.p. 62°. Since the melting point of this synthetic compound and that reported by Marion and co-workers was different, Tomita and Yamaguchi considered erroneous the melting point of 92° for *dl*-*O*-methylarmepavine.

In our synthesis of *dl*-*O*-methylarmepavine, homoveratrylamine (I) and 4-methoxyphenylacetyl chloride (II) were condensed to yield the amide (III), m.p. 126–128° [reported m.p. 123.5° (5)]. Cyclization of III under Bishler-Napieralski conditions (4), using phosphorus oxychloride and toluene, yielded from the reaction a white product (IVa), m.p. 145–147° (petroleum ether-chloroform). This product was shaken with water, basified with ammonia, and extracted with chloroform in an atmosphere of nitrogen. The chloroform extracts, on evaporation, yielded presumably IV as a syrupy mass. The mass was treated with methyl iodide to obtain the methiodide (V), m.p. 126–128° (petroleum ether-chloroform). The methiodide (V) was reduced with zinc and hydrochloric acid to yield, after basifying with ammonia and extraction with chloroform, a light brown mass. Crystallization of this mass using ether-petroleum ether gave a colorless compound (VI), m.p. 60–61°. The compound was left overnight *in vacuo* (0.500 mm. pressure) and the melting point



again recorded. The compound (VI) now melted at 89–90°. This change of ~30° in melting point was again observed when a second crop was obtained and left *in vacuo* as previously.

Reduction of methiodide (V) was also performed with sodium borohydride in methanol (6) to afford a yellowish product. Crystallization of this product with benzene-petroleum ether and seeding with crystals, m.p. 89–90°, from zinc hydrochloric acid reduction yielded VI, m.p. 89–90°.

The synthetic *dl*-*O*-methylarmepavine, m.p. 89–90°, yielded a crystalline picrate, m.p. 172–173° [reported m.p. 170–172° (7)], and the methiodide, m.p. 138–139° (softens 135°) [reported 135–136° (3)]. The I.R. spectra of this methiodide and methiodide prepared from authentic *l*-*O*-methylarmepavine were identical. Paper, thin-layer, and gas-liquid chromatographic data and I.R. and U.V. spectra of the crystalline *dl*-*O*-methylarmepavine, m.p. 89–90°, were identical to authentic *l*-*O*-methylarmepavine. The NMR spectrum of the synthetic compound, m.p. 89–90°, was the same as that of *d*-*O*-methylarmepavine isolated from *M. acuminata* leaves (2).

Anal.—Calcd. for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.80; H, 7.86; N, 4.62.

In a separate experiment, preparation of Schiff base (IV) was attempted under the following conditions.

The white product (IVa) was shaken with water, basified with ammonia, and extracted with benzene. The benzene extracts, on evaporation, yielded a light orange mass. A colorless crystalline compound, m.p. 101–102° [$\lambda_{\text{max}}^{\text{EtOH}}$ 226 $m\mu$ (ϵ 23,400), 290 (20,600)]; on addition of dilute hydrochloric acid, the peaks shifted to 248 (14,720), 308 (18,900), and 373 (10,500)] was isolated from the product. The I.R. spectrum of the compound indicated a carbonyl peak at 1667 cm^{-1} . An A_2B_2 system in the NMR $\delta = 8.04$ and 6.98 p.p.m. also suggested the presence of an anisoyl moiety. The presence of 3,4-dihydroisoquinoline was shown by a four proton complex near $\delta = 2.8$. This compound yielded a semicarbazone, m.p. 200–202°, and the picrate, m.p. 229–230° dec. (darkens 220°). Evidently the reported (8–11) aerial oxidation of 1-benzyl-3,4-dihydroisoquinoline (IV) to 1-benzoyl-3,4-dihydroisoquinoline (VII) had occurred during extraction from alkaline solution with benzene.

Anal.—Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.58; H, 5.79; N, 4.06. Mol. wt. 325.35. Found: 324 (± 4) (vapor pressure osmometer).

Govindachari and Nagarajan (12) reported preparation of VII by oxidizing an alcoholic solution of IV by prolonged exposure to air or with iodine. The melting points reported for the base (VII) and its picrate were 110–112° and 220° dec., respectively.

The observation of the change in the melting point of the *dl*-*O*-methylnarmepavine indicates that the alkaloid exists in polymorphic forms.

This alteration in the melting point might explain the discrepancy in the melting point of synthetic *O*-methylnarmepavine, m.p. 92°, reported by Marion *et al.* (3) and for *dl* form of the alkaloid, m.p. 62°, synthesized by Tomita and Yamaguchi (4).

Details of the synthesis reported here will be published at a later date.

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