4.50; N, 5.69. Found: C, 53.48; H, 4.62; N, 5.80.

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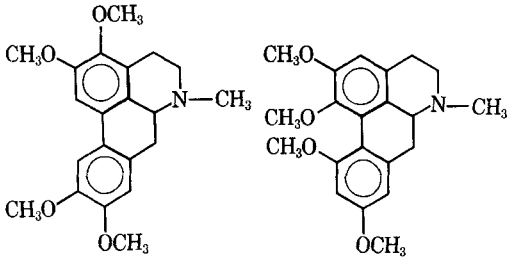
Structure of Argemonine

Identification as (−)-*N*-Methylpavine

By MICHAEL J. MARTELL, JR.*, TAITO O. SOINE, and LEMONT B. KIER†

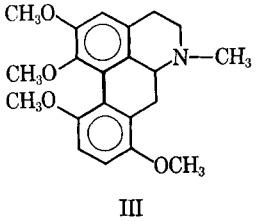
The structure of argemonine has been shown to be (−)-*N*-methylpavine both by chemical evidence and spectral evidence. Racemic *N*-methylpavine has been deracemized as the bitartrates and the base obtained from the D-bitartrate has been shown to be identical with argemonine. The question of whether argemonine is an artifact obtained by cyclization of *N*-methyl-1,2-dihydropapaverine during isolation procedures has been examined, and there appears to be no basis for such conversion.

EARLIER WORK in these laboratories (1, 2) had led to a tentative aporphine-type structural assignment (I) for the alkaloid, argemonine (3). The proposed structure admittedly was biogenetically unfeasible, and Shamma (4), basing his reasoning on the lower than expected intensity of the ultraviolet absorption maxima, suggested alternate formulations (II and III) imposing a 1:11 methoxyl interaction to accentuate the known twist of the biphenyl moiety in aporphines. The resultant reduction in coplanarity would, of necessity, reduce absorption.

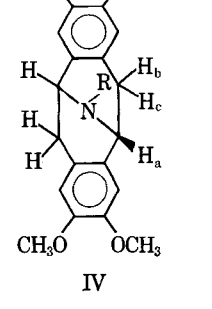


I

II



III



IV

To examine the structural problem further and, initially, to determine the validity of structures I, II, or III, an oxidation of norargemonine ethyl

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ether seemed indicated [as discussed in an earlier communication from these laboratories (3)]. *O*-Ethylnorargemonine, obtained by diazoethylation, was oxidized under mild conditions with manganese dioxide in diluted sulfuric acid, a procedure that previously had yielded 4,5-dimethoxy-*N*-methylphthalimide and 4,5-dimethoxyphthalic acid from argemonine (2). The oxidation yielded four products—namely, 4,5-dimethoxyphthalic acid and its *N*-methylimide as well as 4-ethoxy-5-methoxyphthalic acid and its *N*-methylimide. On this basis, structures I, II, and III were all shown to be untenable (3). Reassurance, however, of the $C_{20}H_{23}NO_4$ molecular formula of norargemonine was obtained by mass spectral analysis, and the molecular formula of argemonine, $C_{21}H_{25}NO_4$, was confirmed as well. The mass spectrum of argemonine showed a large peak at *m/e* 204, corresponding to a *N*-methyl-6,7-dimethoxyisoquinolinium cation (5). For a more extensive treatment of the mass spectra of the pavine type alkaloids, see *Reference 5*.

At this point, nuclear magnetic resonance (NMR) studies were initiated which, aside from showing a far more symmetrical absorption pattern than expected, indicated the presence of *two pairs* of identical aromatic protons, rather than the *three* nonidentical protons expected in an aporphine formulation. This rendered untenable any aporphine formulation and a review of all previously known naturally-occurring alkaloidal types based on the isoquinoline moiety indicated that none of them could be entertained as structural candidates. The high degree of symmetry of the NMR spectrum suggested a symmetrical molecule, and yet the optical activity suggested asymmetry. Both of these requirements could be sustained in the *N*-methylpavine (IV, R = CH_3) structure, since, in spite of the obvious symmetry of the molecule, the asymmetric bridgehead carbons would have the same relative configuration and thus contribute optical activity. The NMR spectrum was explicable in light of the structure of IV (R = CH_3) and is, in part, an ABX system (6) in which protons H_a couple only with H_b[1] and appear as a doublet centering at 5.92 τ (J_{ab} = 6 c.p.s.).

Protons H_c couple only with protons H_b and are a doublet centering at 7.38 τ (J_{bc} = 17 c.p.s.). Protons H_b are split by H_a and H_c and are a pair of doublets centering at 6.47 and 6.58 τ. The aromatic protons are singlets of intensity two each at 3.24 and 3.41 τ and the methoxyl groups are singlets at 6.08 and 6.16 τ. The *N*-methyl group is a singlet at 7.43 τ. Comparison of the spectrum with that of (±)-pavine[2] (IV, R = H) indicated a remarkable similarity, except that the bridgehead protons are shifted downfield to a doublet centering at 5.55 τ and protons H_c occur as a doublet shifted downfield to 7.25 τ. The *N*-methyl group is absent, of course, and the NH appears as a singlet at 7.87 τ.

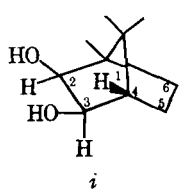
In order to permit direct comparison with authentic *N*-methylpavine it was synthesized by the usual procedure (7) from *N*-methyl-1,2-dihydropapaverine to provide the racemic base. The NMR spectrum of the synthetic base was superimposable on that of argemonine, indicating structural identity. The racemic base was then deracemized by conversion to the bitartrate salts of (+)-L- and (−)-D-tartaric acid. The levorotatory form, obtained from the (−)-D-bitartrate salt, was identical to natural argemonine in every respect.

The possibility that argemonine, isolated from plant material, was an artifact arising from the cyclization of *N*-methyl-1,2-dihydropapaverine due to acid treatment during isolation was considered. It seemed unlikely in view of the work of Knabe *et al.* (8), who showed that dilute acid treatment of this compound results in migration of the 1-homoveratryl group to the 3-position, rather than ring closure. Furthermore, Schermerhorn and Soine (1) had isolated argemonine earlier in a procedure scrupulously avoiding mineral acids. However, to eliminate any doubt on this point, a sample of *N*-methyl-1,2-dihydropapaverine was dissolved in 10% tartaric acid and the ultraviolet spectra of samples withdrawn at various times over a period of 72 hr. were observed. No conversion to *N* methylpavine was noted.

Argemonine, therefore, is the naturally-occurring form of *N*-methylpavine, and this is the first instance of this tetracyclic system being observed in a plant alkaloid. Further examples of the pavine types of alkaloids have been recently described in the literature (5, 9).

In addition, the absolute configuration of argemonine has been determined (10).

[1] This phenomenon has been investigated by Anet, F. A. L. [*Can. J. Chem.*, 39, 789(1961), and references contained therein] as applied to the bicyclo[2.2.1]heptane system. Thus, 2-exo,3-exo-camphane-2,3-diol (*i*) exhibits a bridgehead coupling constant of zero ($J_{3,4}$ = 0) with the adjacent proton, as predicted by the Karplus equation [Karplus, M., *J. Chem. Phys.*, 30, 11(1959)] where the dihedral angle is 79°.



i

[2] Kindly supplied by Professor A. R. Battersby, University of Liverpool, Liverpool, England.

EXPERIMENTAL

Oxidation of O-Ethylnorargemonine—Norargemonine (1 Gm., 0.003 mole) was dissolved in a mixture of 200 ml. of dichloromethane and 50 ml. of absolute methanol. The solution was cooled in an ice bath to 5° and to it was added an excess of diazoethane[3] (1.68 Gm., 0.03 mole) in ether. The mixture was then allowed to come to room temperature gradually over a period of several hours, after which the solvent was stripped off on a steam bath. The residue was dissolved in 100 ml. of 2% (w/v) hydrochloric acid and then alkalinized with enough 10% (w/v) sodium hydroxide solution to make the final solution about 4% (w/v) in sodium hydroxide. The alkaline solution was extracted with several 50-ml. portions of ether until the extracts were negative to Valser's reagent. The combined ethereal extracts were washed twice with 50-ml. portions of distilled water, dried over anhydrous sodium sulfate, and then stripped of solvent under reduced pressure to leave an amorphous yellow residue. The crude ethylated product, without further purification, was dissolved in 100 ml. of 2.5% (w/v) sulfuric acid and refluxed with 1 Gm. of manganese dioxide for 5 hr. The reaction mixture was filtered while hot, cooled, and then extracted for 3 days continuously with ether in a liquid–liquid extractor. The ethereal extract was dried over anhydrous magnesium sulfate and then stripped of solvent to leave a yellowish residue. The residue was warmed with 5% (w/v) sodium carbonate solution (20 ml.) upon which a portion of the residue dissolved, the remaining residue being termed the "neutral fraction" and the dissolved portion the "acidic fraction."

Acidic Fraction—The sodium carbonate solution was acidified with 5% (w/v) hydrochloric acid and then extracted continuously with ether in a liquid–liquid extractor for 2 days. The ethereal extract was dried and stripped of solvent, the residue was dissolved in 5 ml. of 33% aqueous ethylamine, and the solution was concentrated to dryness. The residue was heated at 180° for 10 min. and then sublimed at 170–185°/1 mm. to yield 50 mg. of sublimate. The sublimate was crystallized from methanol to yield 20 mg. of white needles, m.p. 223–224°, which failed to depress the melting point of authentic 4,5-dimethoxy-*N*-ethylphthalimide. The mother liquor from the first crystallization was allowed to stand and slowly concentrate, upon which a white crystalline residue, m.p. 189–195°, separated (14 mg.). Recrystallization of this residue yielded 5 mg. of product, m.p. 200–202°, which failed to depress the melting point of authentic 4-ethoxy-5-methoxy-*N*-ethylphthalimide.[4]

Neutral Fraction—This residue was washed with water, dried, and sublimed at 170–185°/0.1 mm. to give a yellowish-white sublimate with a melting range of 200–256°. Crystallization from ethanol yielded 10 mg. of white crystals, m.p. 263–264°, which failed to depress the melting point of authentic 4,5-dimethoxy-*N*-methylphthalimide. The mother liquor, on slow concentration, yielded a white crystalline residue, m.p. 180–200°, which on continued recrystallization yielded 6 mg. of white crystals, m.p. 189–191°. A mixed melting point determination with authentic 4-ethoxy-5-methoxy-*N*-methylphthalimide[5] failed to depress the melting point.

N-Methyl-1,2-dihydropapaverine—Prepared according to the method of Schopf and Thierfelder (11), m.p. 128–130°. [Lit. (11) m.p. 129–130°.]

(±)-N-Methylpavine—This was prepared from *N*-methyl-1,2-dihydropapaverine by the method of Battersby and Binks (7), m.p. 138–140°. [Lit. (7) m.p. 135–140°.]

(+)-N-Methylpavine-(+)-L-bitartrate—(+)-L-Tartaric acid (1.5 Gm., 0.01 mole) was dissolved with heat in 35 ml. of ethanol and added while hot to a hot solution of (±)-*N*-methylpavine (3.55 Gm., 0.01 mole) in ethanol (40 ml.). On cooling, copious crystallization occurred to yield 3.1 Gm. of white crystals. These were recrystallized several times from ethanol to yield 0.4 Gm. of white crystals, m.p. 228–230° (with effervescence and previous softening at 221°); $[\alpha]_D^{29}$ +174.8° (c 2.0, H_2O).

Anal.—Calcd. for $C_{25}H_{31}NO_{10}$: C, 59.40; H, 6.18. Found: C, 59.12; H, 6.31.

(+)-N-Methylpavine—(+)-*N*-Methylpavine-(+)-L-bitartrate (0.3 Gm.) was dissolved in about 25 ml. of water and then alkalinized with 5 ml. of 5% (w/v) aqueous sodium hydroxide. The alkaline solution was then extracted with three portions (15 ml.) of dichloromethane and the combined extracts washed once in a separator with 15 ml. of water. The dichloromethane extract was then dried over anhydrous magnesium sulfate and stripped of solvent to leave a clear glassy, noncrystalline residue. This residue was recrystallized from a dilute ethanolic solution to yield prisms (60 mg.), m.p. 133–145° (with effervescence), $[\alpha]_D^{25}$ +207.8° (c 2.0, C_2H_5OH). When these crystals were powdered and dried in vacuum over phosphorus pentoxide at 100° the melting point changed to 151–153°. Argemonine (20 mg.) and (+)-*N*-methylpavine (20 mg.), both in the dried form, were each dissolved in sufficient dichloromethane to effect complete solution and the solutions combined. The solvent was stripped from the combined solution to leave a colorless gum which solidified and crystallized when rubbed with a small amount of ether, m.p. 136–139°. The melting point was not depressed on admixture with authentic (±)-*N*-methylpavine.

(−)-N-Methylpavine-(−)-D-bitartrate—*From (±)-N-Methylpavine*—This salt was prepared in exactly the same manner as described for (+)-*N*-methylpavine-(+)-L-bitartrate except for the use of (−)-D-tartaric acid ("unnatural") instead of the natural (+)-L-tartaric acid, m.p. 227–230°, $[\alpha]_D^{25}$ −176.5° (c 2.0, H_2O).

From Argemonine—Argemonine (0.355 Gm., 0.001 mole) was dissolved in ethanol, and to this solution, while hot, was added 10 ml. of a hot ethanolic solution containing 0.150 Gm. (0.001 mole) of (−)-D-tartaric acid. On cooling, a copious gelatinous residue formed which became crystalline on agitation and warming. Recrystallization of the white crystalline residue from ethanol yielded 350 mg. of crystalline rosettes, m.p. 230–232° (with effervescence and softening at 225°); $[\alpha]_D^{23}$ −188.8°

[3] Prepared from Ethyl Diazald, Aldrich Chemical Co., Milwaukee, Wis.

[4] Prepared by permanganate oxidation of *O*-ethylated boldine and subsequent conversion of the acidic fraction to the *N*-ethylimide.

[5] Prepared by permanganate oxidation of *O*-ethylated boldine and subsequent conversion of the acidic fraction to the *N*-methylimide.

(c 2.5, H_2O). A mixed melting point determination with the same salt prepared by the first method showed no depression of melting point.

Anal.—Calcd. for $C_{25}H_{31}NO_{10}$: C, 59.40; H, 6.18. Found: C, 59.26; H, 6.28.

(−)-N-Methylpavine—The preparation of this base was carried out in exactly the same manner as for (+)-*N*-methylpavine from its bitartrate salt. The product, after recrystallization from aqueous ethanol, possessed a melting point of 130–140° (with effervescence); $[\alpha]_D^{25}$ −209° (c 1.0, C_2H_5OH). On drying the crystals in the same way as for the (+)-rotatory base, the white powder melted at 152–153°. A mixed melting point determination as well as infrared comparison with authentic dried argemonine base showed them to be completely identical.

Spectra

Nuclear Magnetic Resonance—Spectra were obtained in $CDCl_3$ on a Varian A-60 spectrometer using tetramethylsilane as the internal standard.

Mass—Spectra were obtained on a C.E.C.-103-C instrument at 200° using a metal inlet at 70 e.v.

Ultraviolet—*N* - Methyl - 1,2 - dihydropapaverine (100 mg.) was dissolved in 100 ml. of 10% (w/v) aqueous tartaric acid. At various time intervals over a 72-hr. period the spectrum of the solution was examined over the wavelength range of 220–370 mμ to determine whether the characteristic absorption bands for argemonine were appearing in the 275–295-mμ region. The analysis was carried out by diluting 1 ml. of the sample solution to 100 ml. with water and placing this solution in the sample cell. The reference cell was filled with a solution obtained by diluting 1 ml. of the 10% aqueous tartaric acid solution (without sample) to 100 ml. The measurements were carried out on a Bausch & Lomb model 505 recording spectrophotometer and showed no absorption in the region mentioned although maxima developed at 250 and 312 mμ.

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Structures of Some Degradation Products of (±)-*N*-Methylpavine

By MAHMOUD M. ABDEL-MONEM* and TAITO O. SOINE

The structures of three products encountered during structural studies on argemonine and (±)-*N*-methylpavine (I) have been determined. The first of these, obtained by hydrochloric acid treatment of 3-hydroxy-2′:3′:2″:3″-tetramethoxy-1:2-5:6-dibenzoöcta-1:5:7-triene (II), has been determined to be 3-chloromethyl-2′:3′:2″:3″-tetramethoxy-1:2-4:5-dibenzocyclohepta-1:4:6-triene. The second, known as argemoninic acid and resulting from permanganate oxidation of II, has been shown to be 2:2′-dicarboxy-4:5:4′:5′-tetramethoxybenzil. The third product, resulting from alkaline ethyl chloroformate treatment of I, has been shown to be the corresponding *N*-carbethoxy derivative of pavine.

THE ISOLATION of three new alkaloids from *Argemone* species was accomplished in these laboratories (1–3), these alkaloids being named argemonine, norargemonine, and bisnorargemonine. Diazomethylation of the latter two showed them to be the mono- and diphenolic precursors, respectively, of argemonine. After initial studies which led to an erroneous tentative structural postulation for argemonine as an aporphine (3, 4), the correct structure was reported by Martell, Soine, and Kier (5) as being (−)-*N*-methylpavine. The structure of synthetic (±)-*N*-methylpavine (I) had been elucidated in 1955 by Battersby and Binks (6) and the natural product proved to be identical to the synthetic product except for rotatory differences and melting point.

In the course of the early structural work on argemonine a number of degradation products were obtained as shown in Scheme I.

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