Tetrahedron Letters No.11, pp. 1177-1183, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ALKALOIDS OF THE PAPAVERACEAE. III.[1] THE SYNTHESIS AND STRUCTURE OF NORARGEMONINE.

Frank R. Stermitz[2] and James N. Seiber[3]

Department of Chemistry

Utah State University

Logan, Utah

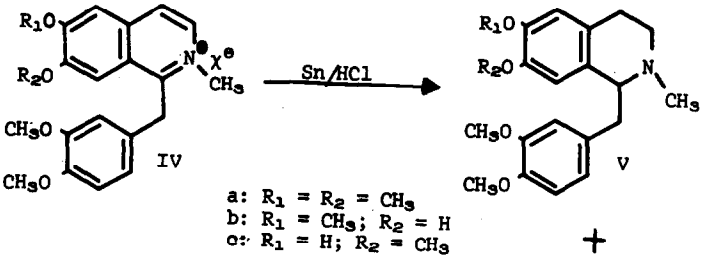
(Received 21 December 1965)

The alkaloid (-)-norargemonine was first isolated by Soine and Gisvold from the desert poppy Argemone hispida[4]. It was shown to be related to (-)-argemonine (I), the structure of which was only recently established,[5,6] by methylation to I with diazomethane[7]. (-)-Norargemonine, $C_{16}H_{10}(OCH_3)_2(OH)NCH_3$, must then be a mono-O-demethyl derivative of I.

With the knowledge of the correct structure of I, it follows that norargemonine must possess either structure II or III. The unusual symmetry of the norargemonine ring system appeared to block degradative attempts at structure proof, so synthesis of both isomers II and III was deemed necessary.

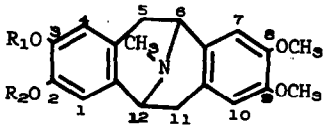
We wish to report the synthesis of both II and III and the identity of norargemonine with II by comparison of the properties of the synthetic (±)-isomer with the natural (-)-alkaloid.

The first direct synthesis of N-methylpavine, which is identical with (±)-argemonine[5,6], was carried out by reduction of N-methylpapaverinium salts (IVa) with tin in hydrochloric acid[6]. This reaction gives, in addition to the cyclic minor product (I), the expected major reduction product (±)-laudanosine (Va). An extension of this reaction to the papaverine derivatives (IVb and IVc) would be expected to result in the production of tetrahydro derivatives (Vb and Vc) along with small amounts of the cyclic compounds (II and III).



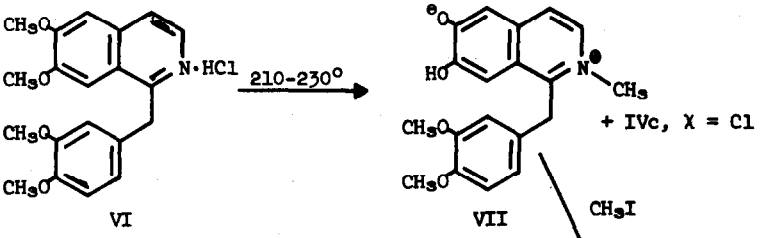
a: $R_1 = R_2 = CH_3$
b: $R_1 = CH_3$; $R_2 = H$
c: $R_1 = H$; $R_2 = CH_3$

+

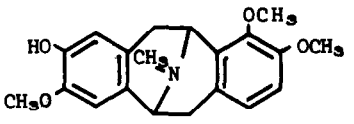


I: $R_1 = R_2 = CH_3$
II: $R_1 = CH_3$; $R_2 = H$
III: $R_1 = H$; $R_2 = CH_3$

Fortunately, both of the isomers IVb and IVc are simply obtained from papaverine hydrochloride (VI) by procedures from the early literature[9]. When papaverine hydrochloride (VI) is heated slightly below its melting point for several minutes it affords a separable mixture of the phenol betaine protopapaverine (VII, 31%) and the salt norpapaverinium betaine hydrochloride (IVc, X = Cl, 28%). Protopapaverine (VII) may be transformed into its methiodide derivative (IVb, X = I) by heating in a sealed tube with methyl iodide.



VI VII



VIII

The reduction of protopapaverine methochloride (IVb, X = Cl) and norpapaverinium betaine hydrochloride (IVc, X = Cl) with tin in hydrochloric acid[8] and catalytically[10], to give the tetrahydro derivatives (±)-codamine (Vb) and (±)-pseudolaudanine (Vc), was also reported. We have repeated the tin in hydrochloric acid reductions and have found, in addition to the compounds Vb and Vc, small amounts of the cyclic isomers II and III.

From the reduction of 2.00 g of IVb (X = Cl) by the procedure of Späth and Epstein[9], there was obtained 0.995 g of a yellow glass. A silica gel G thin-layer chromatographic (TLC) plate (developed in 3:2 benzene-methanol) showed the presence of three components, R_f = 0.70, 0.60, and 0.55, in the approximate ratios 0.5:0.1:10. The glass was separated into petroleum-ether (b.p. 60-70°) soluble and insoluble fractions. From 0.475 g of the former, there was obtained, after treatment with an ethanol solution of picric acid, 0.375 g of the yellow picrate of (±)-codamine (Vb), m.p. 174-8° (m.p. 184-7° after one recrystallization from ethanol; lit.[9] m.p. 187-8°). The free base from the picrate salt agreed in its properties (NMR, IR, and TLC) with those reported for (+)-codamine from opium[11]. From 0.398 g of the petroleum-ether insoluble fraction, separated on preparative TLC, there was obtained 47.6 mg of a fraction containing mainly the base, R_f = 0.7. Seeding an aqueous ethanolic solution of this fraction with a trace of (-)-norargemonine gave 12.8 mg of crystalline material, m.p. 218-20°. One recrystallization from the same solvent gave 8.0 mg of colorless needles, m.p. 222-223° corresponding in its NMR spectrum to structure II. (Anal. Found: C, 70.16; H,6.90; N, 4.28. $C_{20}H_{23}NO_4$ requires: C, 70.36; H, 6.79; N, 4.10).

From the reduction of 2.000 g of IVc (X = Cl) by the procedure of Späth and Epstein[9] there was obtained 1.182 g of a colorless syrup. The TLC plate showed the presence of two compounds, R_f = 0.7 and 0.5, in the approximate ratio of 1:10. From a methanol-ether solution of the crude product there was obtained 0.733 g of colorless crystalline (±)-pseudolaudanine (Vc), m.p. 115-8° (m.p. 117-9° after

one recrystallization from the same solvent; lit.[9] m.p. 120-1°). Evaporation of the mother liquor gave a syrup which, after separation on preparative TLC, produced 0.100 g of a fraction containing mainly the base, R_f = 0.7. Precipitation of this base from methanol solution with ether, followed by sublimation (0.05 mm., 20 hr., 180°) and crystallization of the sublimate from n-heptane, gave colorless plates, m.p. 175-7°, corresponding in its NMR spectrum to structure III. (Anal. Found: C, 69.84; H, 6.95; N, 4.20). In order to rule out the possibility of structure VIII, the alternate cyclization product, for this compound, a small amount was methylated with ethereal diazomethane. The methylated derivative agreed exactly in its properties (IR, TLC) with those of N-methylpavine prepared by the standard procedure[8].

A pure sample of (-)-norargemonine was isolated by a modification of the procedure of Soine and Gisvold[4] from Argemone hispida Gray collected in eastern Wyoming[12]. It agreed in its properties (m.p., optical rotation, and IR) with those reported[4,7] and showed one spot on TLC, R_f = 0.7.

Figure 1 shows the IR spectra (KBr disc) of the synthetic isomers II and III. The spectrum of II was identical in every respect with that of (-)-norargemonine from A. hispida, thus establishing structure II for norargemonine. The NMR spectra (in deuterochloroform, TMS internal standard) shown in Figure 2 confirm this identity and illustrate the close similarity of (±)-norargemonine (II) with (±)-isonorargemonine (III). The only significant difference in the NMR spectra appears in the methoxyl region in which protons of methoxyl groups substituted at positions 2 and 8 appear at 6.16 τ and those substituted at positions 3 and 9 appear at 6.23 τ .

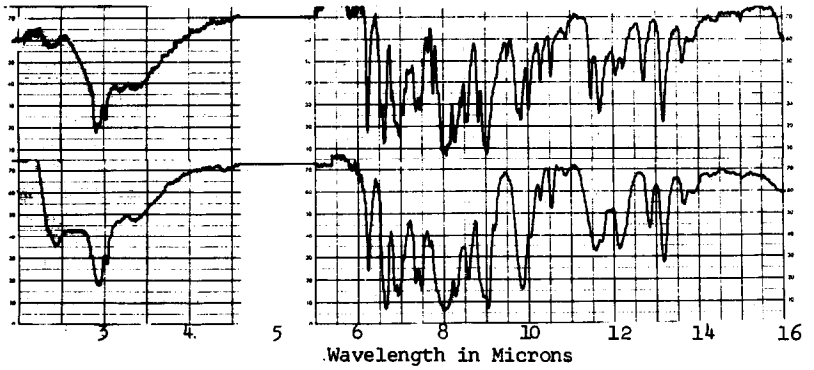


Fig. 1 The Infrared Spectra of (±)-Norargemonine (II)(top), and (±)-Isonorargemonine (III)(bottom).

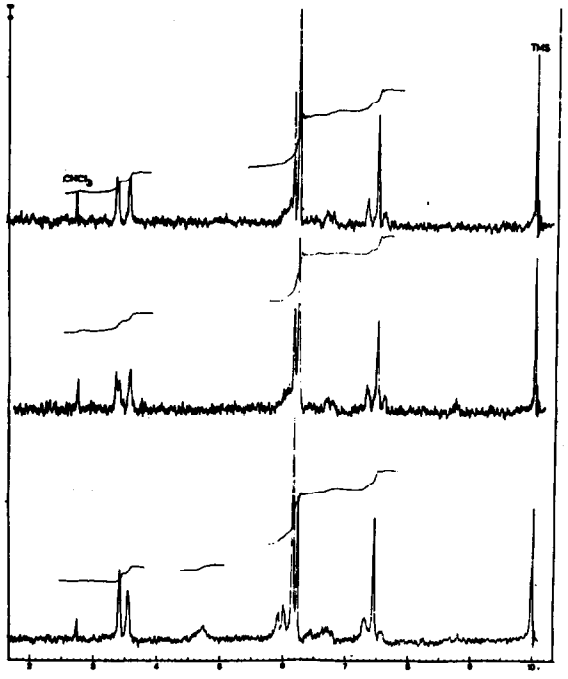


Fig. 2 The NMR Spectra of (Top to Bottom) (-)-Norargemonine, (±)-Norargemonine (II), and (±)-Isonorargemonine (III).

REFERENCES

1. Part II: F. R. Stermitz, L. Chen, and J. White, Tetrahedron, 22, in press (1966).

2. Public Health Service Research Career Development Awardee (5-K3-GM-16, 698) from the NIGMS. This research was also supported by PHS grant GM-09300.

3. Public Health Service Predoctoral Fellow (5-F1-GM20, 217) of the NIGMS, 1963-1965.

4. T. O. Soine and O. Gisvold, J. Am. Pharm. Assoc. Sci. Ed., 33, 185 (1944).

5. M. J. Martell, Jr., T. O. Soine, and L. B. Kier, J. Amer. Chem. Soc., 85, 1022 (1963).

6. F. R. Stermitz, S-Y. Lwo, and G. Kallos, ibid., 85, 1551 (1963).

7. J. W. Schermerhorn and T. O. Soine, J. Am. Pharm. Assoc. Sci. Ed., 40, 19 (1951).

8. F. L. Pyman and W. C. Reynolds, J. Chem. Soc., 97, 1320 (1910).

9. E. Späth and H. Epstein, Ber., 61, 334 (1928), and references contained therein.

10. C. Schöpf and K. Thierfelder, Ann., 537, 143 (1939).

11. E. Brochmann-Hanssen, B. Nielsen, and G. E. Utzinger, J. Pharm. Sci., 54, 1531 (1965).

12. Voucher specimens are deposited in the Intermountain Herbarium, Logan, Utah, under the mounting numbers 107559 and 107560.