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MACRONINE

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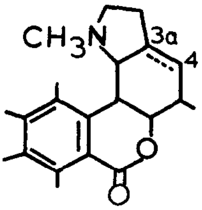
In a recent paper Stauffacher and Hauth (1) reported the isolation of two unknown alkaloids, macronine and macranthine, from Crimum macrantherum Engl. (Amaryllidaceae). The structure of macronine and its relationship to 6-hydroxycrinamine and criwelline are reported in this paper.

Macronine, $C_{18}H_{19}NO_5$, was shown to contain one N-methyl, one O-methyl, and a δ-lactone group in conjugation with a benzene ring containing a methylenedioxy substituent. Hydrogenation experiments were not performed, but the nuclear magnetic resonance spectrum of macronine suggested only one olefinic proton with resonance near 5.95 ppm (1). Several lactonic alkaloids have been isolated from the plant family Amaryllidaceae and all are based on the [2] benzopyrano[3,4g]indole ring system (I). When these alkaloids contain olefinic unsaturation, it



I

occurs at C_{3a}-C_4 (2). All available chemical and spectroscopic evidence would suggest that macronine is a member of the alkaloids of general structure I. Our current interest (3) in the chemistry and biosynthesis of criwelline, $C_{18}H_{21}NO_5$, which also occurs in C. macrantherum, led us to examine lactonic derivatives of criwelline for a possible correlation with macronine.

Methylation of 6-hydroxycrinamine (II) with methyl iodide in acetone provided a methiodide which was transformed into criwelline (III) by dilute alkali (4). If the methylation is carried out with methyl iodide in refluxing methanol, followed by base, an acetal is the major product; m.p. 117-119°; λ_{max}^{EtOH} 290 mμ (log ϵ = 3.61) and 241 mμ (log ϵ = 3.80). The infrared spectrum ($CHCl_3$) showed no hydroxyl bands. The NMR spectrum showed two methoxyl peaks (3.56 and 3.42 ppm), one N-methyl peak (2.50 ppm), one benzylic proton (singlet at 5.51 ppm) and two multiplets centered at 3.92 and 4.27 ppm whose areas correspond to one proton each. The empirical formula, $C_{18}H_{23}NO_5$,* suggested that this compound was O-methylcriwelline; however, the physical and spectral properties were not the same as those reported (4). On the basis of the evidence cited above, IV was an alternative structure to consider. Confirmation of structure IV was obtained in the following manner. Acid cleavage of the acetal followed by basification gave criwelline. Presumably an intermediate aldehyde is formed which is the same intermediate as in the rearrangement of 6-hydroxycrinamine methiodide to criwelline (3). Oxidation of IV with chromium trioxide in

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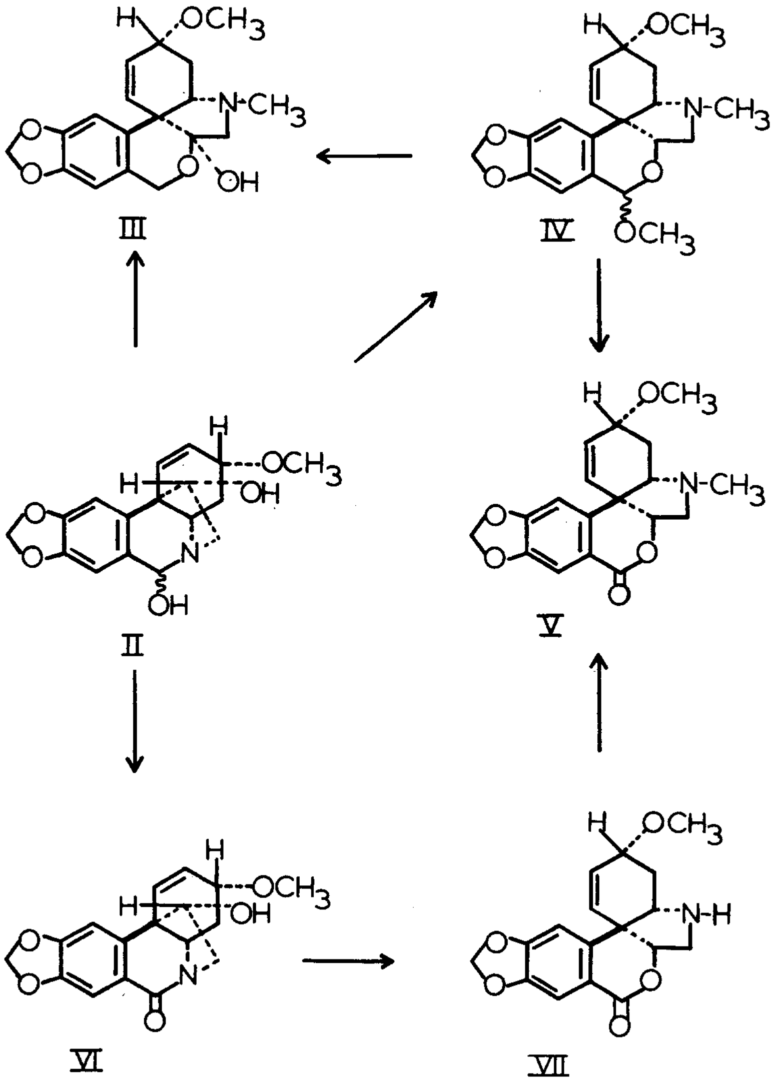
* Satisfactory elemental analyses were obtained for all compounds cited in this communication.


III
IV
II
V
VI
VII
OCH3
N-CH3
N-H
OH

acetic acid gave the lactone V. It is believed that the weakly acidic solution formed a hemiacetal (IV, benzylic OH instead of OCH_3) which was subsequently oxidized. The lactone V (m.p. 199-200°; λ_{max}^{EtOH} 306 mμ (log ϵ = 3.79), 267 mμ (log ϵ = 3.73), 227 mμ (log ϵ = 4.43); infrared absorption (KBr) at 5.86 and 6.17 μ) showed resonances in the NMR at 3.44 ppm (methoxyl), 2.54 ppm (N-methyl), 3.94 and 4.59 ppm (one proton multiplets assigned to the C_3 and C_{6a} protons respectively) and at 6.5-5.7 ppm (multiplets assigned to the olefinic protons). V was found to be identical in all respects to macronine (infrared spectra, melting points and mixture melting point).**

Further support for the structure of macronine was obtained by the hydrolysis of the strained lactam VI to the unstrained lactone VII in a buffered neutral solution (pH 6.80). The product (VII), $C_{17}H_{17}NO_5$, (m.p. 172-174°; λ_{max}^{EtOH} 305 mμ (log ϵ = 3.74), 268 mμ (log ϵ = 3.67) and 228 mμ (log ϵ = 4.43); infrared absorption (KBr) at 5.79 and 6.18 μ) showed N-H absorption in the infrared at 2.95 μ and one proton peak (2.66 ppm) in the NMR spectrum which was removed in the presence of deuterium oxide. Methylation of VII with formaldehyde and sodium borohydride afforded macronine.

From the known structures and stereochemistry of 6-hydroxycrinamine and criwelline (3-5), the structure of macronine is established as V. Thus macronine is the first example of a lactonic Amaryllidaceae alkaloid with the tazettine ring system.

** The authentic sample of macronine was provided through the courtesy of Dr. D. Stauffacher, Sandoz, Ltd., Basel, Switzerland.

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