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POSITION OF THE AROMATIC METHOXYL IN AMARYLLIDACEAE ALKALOIDS RELATED TO POWELLANE

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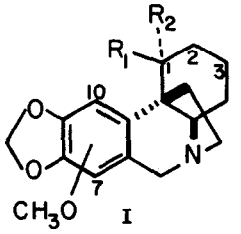
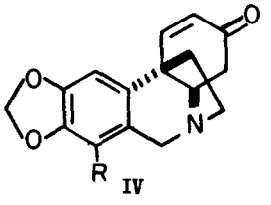
Amaryllidaceae alkaloids related to powellane[1] (I, R_1, R_2 = H) possess a methoxyl group whose position at either C_7 or C_{10} on the aromatic nucleus



I



IV

has been a matter for conjecture. On the basis of the difference in ultraviolet extinction coefficient between derivatives with and without substituents at the C_1 position, Warnhoff and Wildman[2] assigned the methoxyl to the 10-position. As they noted, such a formulation readily fits the biogenetic scheme (cf. II ⟶ III, route A) proposed by Barton and Cohen.[3] However, the

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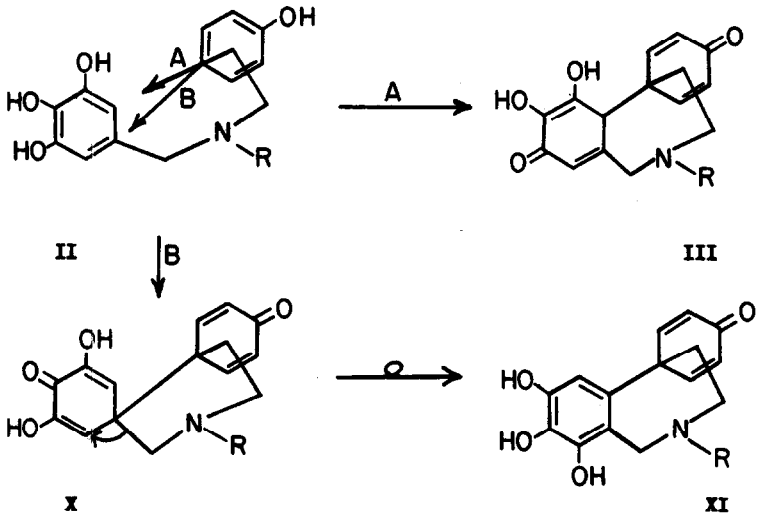
[1] These include powelline, nerbowdine, undulatine, crinamidine and buphanamine; cf. W. C. Wildman, The Alkaloids Vol. VI, p. 289. R. H. F. Manske, ed. Academic Press, Inc., New York, 1960.

[2] E. C. Warnhoff and W. C. Wildman, J. Am. Chem. Soc. 82, 1472 (1960).

[3] D. H. R. Barton and T. Cohen, Festschrift Arthur Stoll ed. by E. Jucker, Birkhauser, Basel, 1957, p. 117.



recent observation that dihydrobuphanamine (I, R_1 = H, R_2 = OH) and epidihydrobuphanamine (I, R_1 = OH, R_2 = H) exhibit hydroxyl stretching frequencies (3599 cm.$^{-1}$ (OH—→π) and 3616 cm.$^{-1}$ (free OH) respectively) nearly identical with their Ar-demethoxy analogues (3602 cm $^{-1}$ (OH—→π) and 3616 cm.$^{-1}$ (free OH) respectively), is not in agreement with this assignment. Molecular models indicate that either configuration of the C_1 hydroxyl should show evidence of hydrogen bonding if the methoxyl is in the 10-position. This evidence supports assignment of the methoxyl to the 7-position.

Comparison of the nuclear magnetic resonance spectra of oxocrinine (IV, R = H)[1] and dihydrooxocrinine (IV, R = H, no double bond at C_1 - C_2) allows the clear differentiation of the absorption from the 7- and 10-protons, for only the latter is appreciably affected by hydrogenation.

Nuclear Magnetic Resonance Data

	Aromatic Protons		Olefinic Protons		Benzylic Protons
	C_7	C_{10}	C_1	C_2	C_6
Oxocrinine	2.66	2.25	1.49	3.09; J=10	4.80, 5.30; J=17
Dihydrooxocrinine	2.68	2.43			4.80, 5.30; J=17
Oxopowelline		2.50	1.53	3.04; J=10	4.90, 5.30; J=17

The spectra were observed at 60 mc., using benzene as an external standard; to convert the data to p.p.m. relative to tetramethylsilane as 10.00 the value of 2.73 p.p.m. was assumed for benzene.[4] The resonance of the sole aromatic proton of oxopowelline (IV, R = OCH_3)[1] is that anticipated for the C_{10} proton, for the shift relative to the proton at C_{10} of oxocrinine corresponds to the observed effect of the aromatic methoxyl (0.23 p.p.m.).[4] The resonance peaks of the olefinic protons of oxopowelline and oxocrinine are essentially the same, although the former would surely be affected by a C_{10} methoxyl. Further, the absorption of one of the benzylic protons of oxopowelline at C_6 shows the effect of the C_7 methoxyl.

Chemical evidence showing conclusively that the methoxyl group is at the 7- position now has been obtained. (+)-Powellane (V)[5] was converted with sodium in liquid ammonia to the phenol VI,[6] m.p. 245-7°, $[\alpha]_{589}^{24}$ 8.6° (c 0.65, methanol) (Found: C, 73.93; H, 8.12; OCH_3, 11.85. $C_{16}H_{21}NO_2$ requires: C, 74.10; H, 8.16; OCH_3, 11.96). This was converted with diazomethane to the

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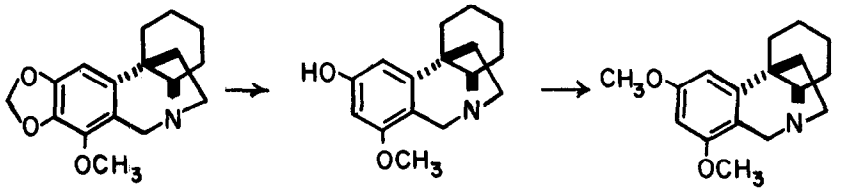
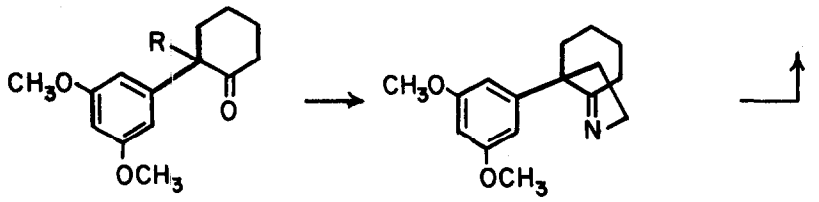
4 L. M. Jackman Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, New York, 1959, p. 63.

5 W. C. Wildman, J. Am. Chem. Soc. 80, 2567 (1958).

6 cf. D. B. Clayson, J. Chem. Soc. 2016, 1949. We are grateful for discussions with Professor A. J. Birch of the University of Manchester concerning the applicability of the method to this problem.



V VI VII



VIII IX

oily ether VII, $[\alpha]_{589}^{24}$ 11.4° (c 0.69, chloroform) (Found: C, 74.25; H, 8.43; OCH_3, 22.95. $C_{17}H_{23}NO_2$ requires: C, 74.69; H, 8.48; 2 OCH_3, 22.71); picrate, m.p. 238-9° (Found: C, 55.09; H, 5.15; N, 11.24. $C_{23}H_{26}O_9N_4$ requires: C, 54.97; H, 5.22; N, 11.15). The ketone VIII (R = H), m.p. 62.5-63° (Found: C, 71.64; H, 8.01; OCH_3, 26.82. $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74; OCH_3, 26.49) was converted to an oily keto ester VIII (R = $CH_2CH_2COOCH_3$) with methyl acrylate (Found: C, 67.61; H, 7.71. $C_{18}H_{24}O_5$ requires: C, 67.48; H, 7.55). This was subjected to a Curtius degradation giving the imine IX, isolated as the picrate, m.p. 164-8° (Found: C, 54.04; H, 4.97; N, 11.46. $C_{22}H_{24}N_4O_9$ requires: C, 54.10; H, 4.95; N, 11.47). The base was reduced to the corresponding secondary amine which was cyclized with formaldehyde furnishing the oily racemate of VII whose infrared spectrum was identical (40 bands) with that of (+)-VII from natural sources (Found: C, 74.77; H, 8.58. $C_{17}H_{23}NO_2$ requires: C, 74.69; H, 8.48). The racemic picrate, m.p. 209-212°, exhibited

an infrared spectrum (KBr) identical with that of (+)- VII. (Found: C, 54.68; H, 5.11; N, 11.06. $C_{23}H_{26}O_9N_4$ requires: C, 54.97; H, 5.22; N, 11.15). Gas chromatographic behavior of the two materials was identical on a 3500 theoretical plate silicone (SE-30) column.

These results lead us to speculate that if the biogenesis proceeds through a precursor such as II, it may involve an alternate mode of coupling of the two rings (cf. II ⟶ X, route B) followed by a dienone-phenol type rearrangement to either of the equivalent unsubstituted positions of ring A to yield XI, which possesses the correct arrangement of oxygen substituents. However, at present the possibility that Ar-methoxylation follows phenol coupling cannot be eliminated.