

The Constitution of Androcymbine

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Androcymbium melanthioides contains androcymbine as the major alkaloid together with colchicine (VI; R = R' = Me), 3-demethylcolchicine (VI; R = H, R' = Me) and *N*-formyldeacetylcolchicine¹ (VI; R = Me, R' = H). We now outline the essential data which prove that androcymbine is

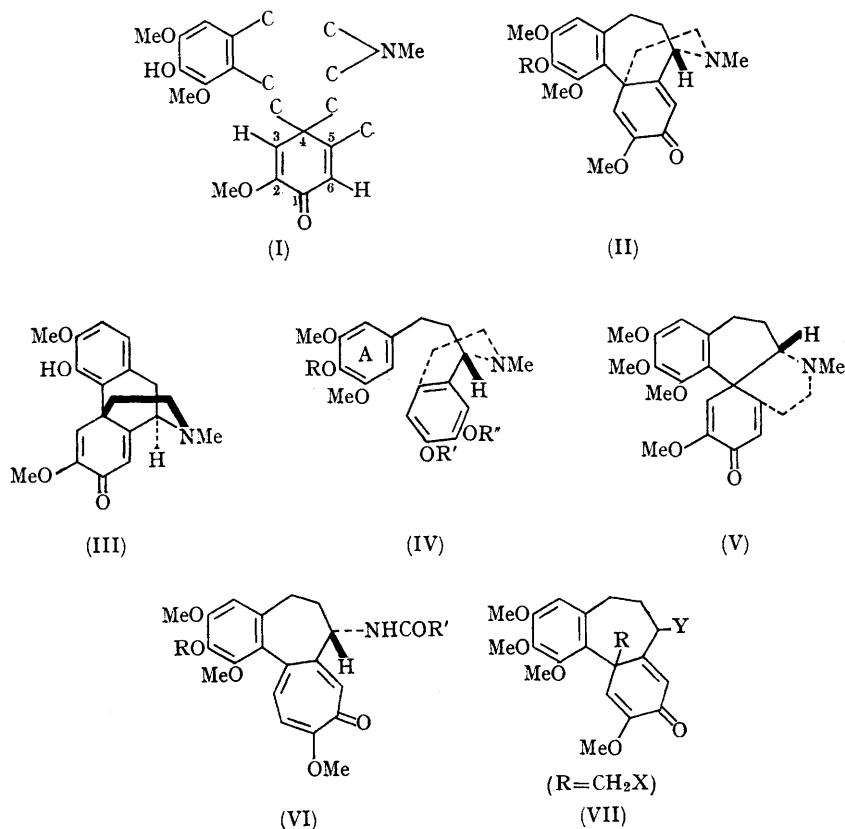
a new type of alkaloid having structure (II; R = H).

Mass spectrometry confirmed the molecular formula C₂₁H₂₅NO₅ for androcymbine (parent, *m/e* 371). The nitrogen is tertiary (acetylation, methiodide formation) and one oxygen is present

as a phenolic hydroxyl group from which can be derived *O*-acetylandrocymbine (parent, *m/e* 413) and *O*-methylandrocymbine (parent, *m/e* 385). Oxidation of the latter afforded 3,4,5-trimethoxyphthalic anhydride. The infrared spectrum of

ultraviolet spectrum of androcymbine which has absorptions at 216, 240, and 278 $m\mu$.

The integrated n.m.r. spectrum of androcymbine established the presence of three methoxyl groups (τ 6.37, 6.18, and 5.98), one *N*-methyl group



androcymbine shows bands at 1665, 1635, and 1615 cm^{-1} , characteristic of a cross-conjugated cyclohexadienone system; these bands are closely similar to the corresponding absorptions of salutaridine² (III) and orientalinone.³ The 1665 cm^{-1} absorption was absent from the spectra of the products obtained by reduction of androcymbine with borohydride or catalytically (uptake 2 mol. rapidly and 1 mol. slowly). Isolated aromatic and dienone chromophores are apparent in the

(τ 7.64), one aromatic proton (singlet, τ 3.73, shifted in $\text{NaOD-D}_2\text{O}$), and two olefinic protons (singlets at τ 3.73 and 3.17). These values and the absence of splitting in the olefinic signals support the partial formula (I) for the alkaloid; adjacent protons on a cyclohexadienone ring and those placed at the 2- and 6- or 3- and 5-positions show spin-spin coupling.^{4-6,3} The spectrum also shows unresolved signals corresponding to *ca.* nine protons, *ca.* five of which have chemical shifts

² D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, 2423.

³ A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85; A. R. Battersby, J. H. Clements, and T. H. Brown, *J. Chem. Soc.*, 1965, in the press.

⁴ Unpublished work by Dr. W. von Philipsborn (Zürich).

⁵ K. Bernauer, *Helv. Chim. Acta*, 1963, 46, 1783.

⁶ L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *Proc. Chem. Soc.*, 1963, 280.

expected of protons in the benzylic position or on carbon adjacent to nitrogen.

When the foregoing results are taken with biogenetic considerations, partial structure (I) can be expanded to (II; R = H) for androcymbine; the position of the phenolic hydroxyl group is assigned at present by analogy with 3-demethylcolchicine. This structure was tested by sodium-liquid ammonia reduction⁷ of *O*-methylandrocymbine (II; R = Me). The phenolic product (parent, *m/e* 387, base peak *m/e* 192) was proved to have structure (IV; R = R' = Me; R'' = H) by a standard synthesis to be described in our full paper. Further, this phenolic product showed a positive Cotton effect in the 278–265 $m\mu$ region proving⁸ that it has the *S*-configuration (as IV). In support, androcymbine (II, R = H) and salutaridine² (III) show mirror image o.r.d. curves (kindly determined by Professor W. Klyne and Dr. P. M. Scopes).

Structure (V) for *O*-methylandrocymbine can accommodate all the above results save that its sodium-ammonia reduction product would have structure (IV; R = R'' = Me; R' = H). This was also synthesised and it proved to be clearly different from the phenol derived from *O*-methylandrocymbine. Androcymbine is thus proved to have the constitution and absolute stereochemistry

(II; R = H). It is highly probable that androcymbine is biosynthesised by phenol oxidation⁹ from the base (IV; R = R'' = H; R' = Me) or from the isomer having the positions of one methoxyl and the phenolic hydroxyl group reversed on ring A and this will be tested experimentally. Related plants contain similar alkaloids¹⁰ and it is probable that androcymbine is the first representative of a new class of alkaloids based upon the 1-phenethylisoquinoline system.

The sub-family *Wurmbaeoideae* encompasses *Colchicum* species in addition to those of *Androcymbium* and the occurrence of colchicine (VI; R = R' = Me) and its relatives in *A. melanthioides* strengthens this taxonomic link. Recent tracer experiments on the biosynthesis of colchicine¹¹ led to the suggestion¹¹ that the dienone (VII; the nature of X and Y to be determined) is a key intermediate on the pathway to colchicine and this was subsequently supported by a different tracer experiment.¹² Comparison of the postulated intermediate (VII) with androcymbine strongly suggests that colchicine (VI; R = R' = Me) is a modified 1-phenethylisoquinoline alkaloid; the absolute stereochemical relationship of androcymbine and colchicine supports this and the experimental test is in progress.

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⁷ M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffan, and J. A. Weisbach, *Chem. and Ind.*, 1964, 282.

⁸ A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J. Chem. Soc.*, 1965, 2239; A. Brossi and F. Burkhardt, *Helv. Chim. Acta*, 1961, **44**, 1558; A. Rheiner and A. Brossi, *Experientia*, 1964, **20**, 488.

⁹ D. H. R. Barton and T. Cohen, "*Festschrift A. Stoll*," Birkhauser, Basle, 1957, p. 117; H. Erdtman and C. A. Wachtmeister, *ibid.*, p. 144.

¹⁰ M. Saleh, S. El-Ganghi, A. El-Hamidi, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1963, **28**, 3413.

¹¹ A. R. Battersby, R. Binks, and D. A. Yeowell, *Proc. Chem. Soc.*, 1964, 86; A. R. Battersby, R. Binks, J. J. Reynolds, and D. A. Yeowell, *J. Chem. Soc.*, 1964, 4257; A. R. Battersby and R. B. Herbert, *Proc. Chem. Soc.*, 1964, 260.

¹² E. Leete, *Tetrahedron Letters*, 1965, 333.