

## Melanthioidine: a Second 1-Phenethylisoquinoline Alkaloid

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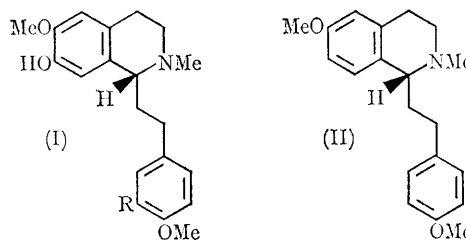
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RECENTLY we reported<sup>1</sup> that androcymbine from *Androcymbium melanthioides* has a novel structure based upon the 1-phenethylisoquinoline system. The same plant contains other alkaloids,<sup>2</sup> among them melanthioidine considered<sup>3</sup> on the basis of elemental analysis to be  $C_{42}H_{50}N_2O_7$ . Melanthioidine has now been shown by means of the following essential data to possess the structure (III, R = H) and thus to be the second representative of the 1-phenethylisoquinoline class.

High-resolution mass spectrometry established the molecular formula  $C_{38}H_{42}N_2O_6$  ( $m/e$  622) for melanthioidine; the fragmentation pattern is considered later. The presence of two phenolic hydroxyl groups was proved by the infrared spectrum, by shift of the ultraviolet spectrum in base, and by the formation of an *OO*-diacetate ( $m/e$  706; single  $\nu_{\max}$  1760  $\text{cm}^{-1}$ ) and *OO*-dimethyl ether ( $m/e$  650). Melanthioidine was shown to be a symmetrical molecule by the striking simplicity of its n.m.r. spectrum which revealed two *N*-methyl groups (singlet,  $\tau$  7.56), two *O*-methyl groups (singlet,  $\tau$  6.21), 10 aryl protons in the region  $\tau$  3.1–3.5 and unresolved signals corresponding to 18 protons ( $\tau$  6.0–9.0). The spectrum was similar to that of 1-phenethylisoquinolines<sup>1</sup> and consideration of this together with the foregoing information, suggested that melanthioidine is a bisphenethylisoquinoline alkaloid. In agreement, the ultraviolet spectrum was closely similar to that of the bisbenzylisoquinoline alkaloid, curine.<sup>3</sup>

Reductive cleavage<sup>4</sup> of *OO*-dimethylmelanthioidine with sodium in liquid ammonia afforded almost exclusively one phenol shown by mass spectrometry ( $M^+$ ,  $m/e$  327; base peak  $m/e$  192) and unambiguous synthesis to have structure (I, R = H). This product has the *R*-configuration (as I) since the first Cotton effect was negative<sup>3,5</sup>;

the o.r.d. curve was kindly determined by Professor W. Klyne and Dr. P. M. Scopes. The symmetry of melanthioidine and all the experimental data can be accommodated by structure (III, R = Me) for *OO*-dimethylmelanthioidine. Two very minor products were isolated from the metal-ammonia reduction and by considering their mass spectra in relation to the established structure of the major reduction product, they can be assigned the structures (I, R = OH) and (II). The former showed  $M^+$ ,  $m/e$  343 (base peak,  $m/e$  192) whilst the latter had  $M^+$ ,  $m/e$  311 (base peak  $m/e$  176). Cleavage of *OO*-dimethylmelanthioidine to a small extent at (a)–(b') [ $\equiv$  (a')–(b)] would yield both bases. Such minor products have been obtained from other diaryl ethers.<sup>6</sup>



The foregoing evidence does not rigorously exclude linkage of the ether bridges *meta* to the methoxyl groups on rings c and c' of *OO*-dimethylmelanthioidine (III). However, the illustrated arrangement is strongly favoured on biogenetic grounds and because this structure would be expected to yield (I, R = H) as the main reduction product whereas the alternative one would not.<sup>6,7</sup>

Major fragment ions appear at  $m/e$  312 and 310 in the mass spectrum of melanthioidine. These correspond to the favoured cleavage<sup>8</sup> at (c)–(c')

<sup>1</sup> A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.

<sup>2</sup> J. Hrbek, jun., and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1962, 27, 255.

<sup>3</sup> A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J. Chem. Soc.*, 1965, 2239.

<sup>4</sup> E. g. M. Tomita, E. Fujita, and F. Murai, *J. Pharm. Soc. Japan*, 1951, 71, 226.

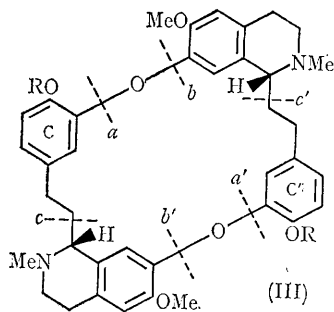
<sup>5</sup> A. Brossi and F. Burkhardt, *Helv. Chim. Acta*, 1961, 44, 1558; A. Rheiner and A. Brossi, *Experientia*, 1964, 20, 488.

<sup>6</sup> D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 1954, 669; C. Djerassi, H. W. Brewer, C. Clarke, and L. J. Durham, *J. Amer. Chem. Soc.*, 1962, 84, 3210.

<sup>7</sup> A. L. Kranzfelker, J. J. Verbanc, and F. J. Sowa, *J. Amer. Chem. Soc.*, 1937, 59, 1488.

<sup>8</sup> H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I. Holden-Day, San Francisco, 1964.

with hydrogen transfer. A further important fragment at  $m/e$  485 corresponds to the loss of  $C_8H_9O_2$  from the parent ion. This fragment supports the structure (III, R = H) for melanthioidine since its formation can then be explained



by fission at  $(b)-(c)$  [ $\equiv (b')-(c')$ ], again with hydrogen transfer; the composition of these fragment ions was determined by accurate mass measurement with errors  $<10$  p.p.m. The fission at  $(b)-(c)$  was confirmed by the appearance of strong peaks at  $m/e$  499 and 527, respectively, in the mass spectra of the *OO*-dimethyl and *OO*-diacetyl derivatives of melanthioidine. The two hydroxyl groups of melanthioidine are thus proved to be located on rings *c* and *c'* and the alkaloid can thus be assigned the structure (III, R = H).

With androcymbine and melanthioidine proved to be 1-phenethylisoquinoline alkaloids analogous to similar substances in the 1-benzylisoquinoline series, a search for the analogues of aporphines, protoberberines, and the morphine alkaloids is justified; this is in progress.

(Received, August 10th, 1965; Com. 500.)