Structure and Synthesis of Homoaporphines: a New Group of 1-Phenethylisoquinoline Alkaloids

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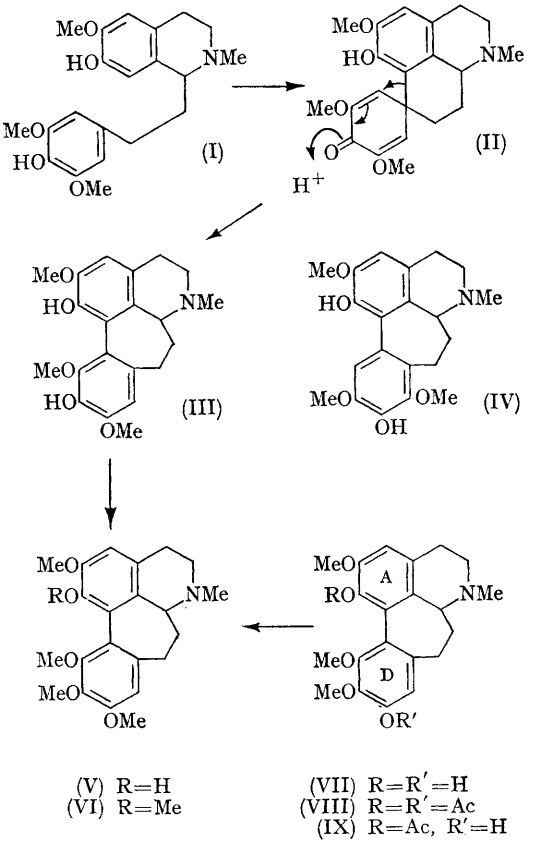
THE recently discovered 1-phenethylisoquinoline class of alkaloids is represented by androcymbine[1] and melanthioidine[2] whilst the biosynthesis of colchicine has been shown[3,4] to involve extensive modification of the 1-phenethylisoquinoline system. The work now outlined adds a further group by deriving homoaporphine structures [*e.g.*, (V)] for three alkaloids from *Kreysigia multiflora* Reichb. (Liliaceae). Repetition of the plant extraction afforded (−)-floramultine and (±)-kreysigine isolated earlier[5] together with many other alkaloids; among these was a new base named multifloramine.

The molecular formula, $C_{22}H_{27}NO_5$, assigned[5] to kreysigine was supported by mass spectrometry (M^+, 385) and n.m.r. confirmed the presence of one *N*-methyl and four *O*-methyl groups; two aromatic protons (singlets, s) appeared at τ 3·41 and 3·46, and signals corresponding to nine further protons were observed over the region τ 6·5—8·1. The remaining oxygen atom is present as a phenolic hydroxyl group (i.r. and u.v. with bathochromic shift in alkali). The data prove kreysigine to be a tetracyclic alkaloid based upon a C_{17} skeleton and containing two aromatic rings; these requirements are met by a dehydro-derivative of 1-phenethylisoquinoline. Two results indicated a homoaporphine system: (*a*) the u.v. spectrum showed conjugation of chromophores, λ_{max} 221, 260, and 293 mμ; (*b*) the signal from one OMe group appeared at higher field, τ 6·41, than the others τ 6·17 (3H), 6·14 (6H) as observed for many aporphines.[6] Structure (V) was therefore considered for kreysigine, the position of the hydroxyl group being selected on the slender evidence[7] that the base peak in the mass spectrum corresponded to $M - 17$. This structure was established by synthesis.

The (±)-diphenol† (I), prepared by standard methods, was oxidised by alkaline ferricyanide in 49% yield to the dienone (II), $C_{21}H_{25}NO_5$, (M^+, 371) which showed the following important n.m.r. signals (τ values): 3·54 (s, 1H) aromatic; 4·07 (d, 1H; J = 2 c./sec.) and 4·22 (d, 1H; J = 2 c./sec.) both olefinic with transannular coupling; 6·29, 6·43, 6·50 (s, 3H each) *O*-methyls; 7·60 (s, 3H) *N*-methyl. Dienone–phenol rearrangement of this product in concentrated sulphuric acid yielded (45%) the (±)-diphenol (III); the alternative structure (IV) was excluded by the appearance of one *O*-methyl signal at high field (τ 6·52) in the n.m.r. spectrum. This product was identical, apart from optical activity, with (−)-multifloramine. Further, methylation of synthetic



(V) R=H
(VI) R=Me

(VII) R=R′=H
(VIII) R=R′=Ac
(IX) R=Ac, R′=H

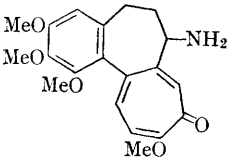
(III) with diazomethane gave a mixture of the di-*O*-methyl ether (VI) and a mono-*O*-methyl ether (V). The former was identical with *O*-methyl-(±)-kreysigine and the latter with (±)-kreysigine itself. Preferential formation of kreysigine (V) by partial methylation of (III) supports the

† Complete spectroscopic and analytical data in agreement with the assigned structures have been obtained for all new compounds.

assigned position of the hydroxyl group in kreysigine because groups *ortho* to the internuclear bond are strongly hindered in such twisted biphenyl systems.[8]

Mass spectrometry showed that the earlier molecular formula[5] for (−)-floramultine must be modified to $C_{21}H_{25}NO_5$ (M^+, 371, base peak at $M - 17$), that is, CH_2 less than for kreysigine. Since (−)-floramultine contains three *O*-methyl groups[5] whereas kreysigine has four, floramultine was methylated with diazomethane to yield (−)-kreysigine (V) and (−)-di-*O*-methylfloramultine (M^+, 399, base peak at $M - 31$). The latter was structurally identical with (±)-*O*-methylkreysigine (VI). Further, *OO*-diacetylfloramultine (VIII) on partial hydrolysis gave the mono-*O*-acetyl derivative (IX), which by *O*-methylation and hydrolysis yielded (−)-kreysigine (V).

(−)-Floramultine is thus a de-*O*-methylkreysigine and since it differs from (−)-multifloramine (III) and shows a high field *O*-methyl n.m.r. signal (τ 6·45), structure (VII) can be assigned to it. A rather unlikely alternative having ring A of (VII) diphenolic and ring D carrying three OMe groups was eliminated by comparing the n.m.r. spectra of mono-*O*-acetylfloramultine [τ 6·12, 6·22 6·59 (OMe); 3·47, 3·33 (aromatic)] and di-*O*-acetylfloramultine [τ 6·18, 6·22, 6·56 (OMe); 3·37, 3·29 (aromatic)] with that of floramultine [τ 6·11, 6·16, 6·45 (OMe); 3·46, 3·41 (aromatic)]. The former two show upfield shifts of the methoxyl signals and downfield shifts of the aromatic signals which establish that the acyl groups in the di-acetyl derivative are attached to different aromatic rings. In addition, the molybdate test for catechol systems was negative when applied to floramultine.



(X)

Kreysigine (V), multifloramine (III), and floramultine (VII) are thus the first examples of homoaporphine alkaloids and their occurrence in *Kreysigia multiflora* is of taxonomic interest. This plant is related botanically to *Colchicum autumnale* and colchicine has recently been detected in *K. multiflora*.[9] We find deacetylcolchicine (X) is also present. The biosynthetic pathways to these different skeleta are being studied by tracer experiments on *K. multiflora*.

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