The Structure of Kreysiginine (Alkaloid CC-21)

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THREE of the major alkaloids from *Kreysigia multiflora* Reichb. (Liliaceae) have been proved[1] to be homoaporphines and so to be members of the growing new class[2] of 1-phenethylisoquinoline alkaloids. The spectroscopic data for kreysiginine, a further alkaloid from this plant,[3] clearly showed it to be of a different type. Moreover, kreysiginine has now been found to be structurally identical but enantiomeric with alkaloid CC-21 from *Colchicum cornigerum*[4†] (Sweinf.) Täckh. et Drar. (Liliaceae). Our results establish structure (I) for (+)-kreysiginine which is a further 1-phenethylisoquinoline derivative and related, as a ring B homologue, to the morphine group of alkaloids [*cf.* thebaine(II)].

Mass spectrometry supported the molecular formula[3] $C_{21}H_{27}NO_5$ for kreysiginine (M^+ 373),

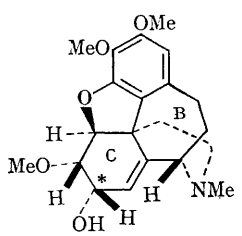
N.m.r. spectra; τ values (CDCl$_3$)

Substance	N–Me	O–Me	$-CH_BOMe$	$-CH_COR$	$-CH_AO-$	$CH_D=C$	Aromatic
Kreysiginine (I)	7·45	6·51, 6·24, 6·13	6·81, 6·78, 6·27, 6·68 J_{AB} 9·5, J_{BC} 4·0	5·81, 5·77, 5·75, 5·71 J_{BC} 4·0, J_{CD} 6·0	5·45, 5·36 J_{AB} 9·5	4·37, 4·31 J_{CD} 6·0	3·86
Couplings demonstrated for above case			⟷	⟷		⟷	
			⟷	⟷			
O-Acetylkreysiginine	7·42	6·61, 6·23, 6·11	Obscured by OMe 6·71, 6·68 J_{BC} 4·0	4·59, 4·55, 4·53, 4·49 J_{BC} 4·0, J_{CD} 6·0	5·48, 5·39 J_{AB} 9·5	4·37, 4·31 J_{CD} 6·0	3·85

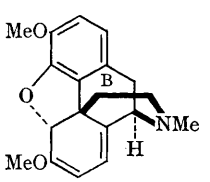
n.m.r. confirmed the presence of one *N*-methyl and three *O*-methyl groups (Table), and i.r. proved the absence of carbonyl groups. A set of coupled signals was present in the 100 Mc./sec. spectrum which established the sequence (III); double-resonance experiments demonstrated all the spin–spin couplings indicated in the Table. Acetylation of kreysiginine proved its nitrogen to be tertiary and the n.m.r. spectrum of the resultant *O*-acetylkreysiginine (M^+ 415) confirmed sequence (III) by showing the expected downfield shift of the signal assigned to >CHOAc. Kreysiginine shows u.v. absorption corresponding to a 1,2,3-trialkoxybenzene chromophore and it possesses only one aromatic proton; partial structure (IV), or an isomer, is thus indicated. The foregoing functional groups and the molecular formula require kreysiginine to be pentacyclic and one of these rings is assigned to a cyclic ether system involving the oxygen X–O–CH of (III) in accordance with the inert nature of this residue.

When partial structures (III) and (IV) are considered biogenetically, constitution (I) becomes a probable one for kreysiginine; proof of this structure was obtained as follows. Mild Jones oxidation of kreysiginine afforded dehydro-kreysiginine (V) showing enone absorption (ν_{max} 1690 cm.$^{-1}$). Treatment of the enone with base opened the oxide bridge yielding a dienone (VI, M^+ 371·1733; $C_{21}H_{25}NO_5$, 371·1724), ν_{max} 1663, 1638, 1613 cm.$^{-1}$, which was *O*-methylated with trimethylanilinium hydroxide to generate the ether (VII, M^+ 385·1888; $C_{22}H_{27}NO_5$, 385·1889). This product, $[\alpha]_D$ −169° ($CHCl_3$), was identical by full spectroscopic and chromatographic comparison with *O*-methylandrocymbine,[2] $[\alpha]_D$ −295° ($CHCl_3$) of rigorously established structure and absolute configuration (VII). Structure (I) thus represents (+)-kreysiginine with the relative configurations still to be considered. The difference in optical rotation for the product (VII) prepared from androcymbine[2] (VIII) and from kreysiginine is a reflection of the partial racemic nature of the latter whose $[\alpha]_D$ has varied over the range +29 to +89° for different batches. Similarly, alkaloid CC–21† is a partial racemate with $[\alpha]_D$ −42° ($CHCl_3$) for the only specimen available; this alkaloid thus contains the enantiomer of structure (I) in admixture with some (+)-form.

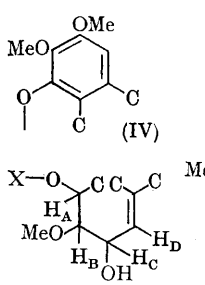
The large coupling (9·5 c./sec.) between H_A and



(I)

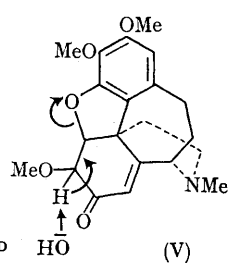


(II)

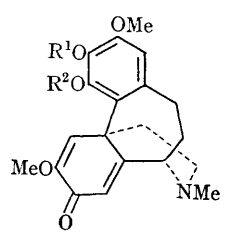


(IV)

(III)



(V)



(VI; R^1 = Me, R^2 = H)
(VII; R^1 = R^2 = Me)
(VIII; R^1 = H, R^2 = Me)

† Isolation and elucidation of the structures of many other alkaloids from *C. cornigerum* will be described in a joint paper from the Olomouc and Liverpool groups.

H_B of kreysiginine (see III) requires a *trans*-diaxial relationship for these protons which is in agreement with the illustrated configurations on a half-chair ring c. The hydroxy-group must then be set axial to account for J_{BC} 4 c./sec. (H_B and H_C in axial–equatorial relationship) and this agrees with J_{CD} 6·0 c./sec., the dihedral angle H_C—H_D being *ca.* 30°. Structure (I) is now a compete representation for (+)-kreysiginine.

Retention of oxygen at the starred carbon of ring c (I) for a molecule having an oxide bridge is in contrast to the situation obtaining in the morphine group of alkaloids.[5] The biosynthetic implications of this observation are being explored by tracer experiments with *K. multiflora*.

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