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KREYSIGININE, A HOMO-MORPHINE ALKALOID FROM *KREYSIGIA MULTIFLORA* REICHB.

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An early investigation of the Australian plant *Kreysigia multiflora* Reichb. (family Liliaceae) revealed the presence of four alkaloids, (±)-kreysigine, (-)-floramultine, (+)-floramultinine and (+)-kreysiginine[1]. Recent studies led to the complete elucidation of the structure of kreysigine and floramultine, which are both homo-aporphine alkaloids and may be assumed to be derived from a 1-phenylethyl-1,2,3,4-tetrahydroisoquinoline precursor[2]. Kreysiginine (I), the structure and absolute stereochemistry of which are now known from an X-ray crystallographic study of kreysiginine methiodide[3], is of interest because it bears a relationship to the morphine alkaloids like that of kreysigine and floramultine to the aporphine alkaloids. Kreysiginine is clearly related to the liliaceous alkaloid androcymbine (II)[4]. The 1-phenylethyl-1,2,3,4-tetrahydroisoquinoline derivative considered to be a precursor of kreysigine and multiflorine can also lead to kreysiginine through appropriate cyclization of an androcymbine-like intermediate.

The novel homo-morphine skeleton of kreysiginine (I) has been established independently from a detailed study by the double resonance technique of the 100 Mc./sec. n.m.r. spectra of kreysiginine (Figure I) and O-acetyl kreysiginine. The n.m.r. data, however, do not enable a distinction to be drawn between (I) and the isomer of opposite absolute configuration, and discussion is restricted to (I) which shows the correct absolute configuration[3]. N.m.r. data reported for the analogous morphine group bases isoneopine (III) and neopine (C-6 epimer of (III)) provide a useful basis for comparison[5].

The molecular formula, $C_{21}H_{27}NO_5$, originally assigned[1] to kreysiginine is confirmed by mass spectrometry (M^+, m/e 373) and the n.m.r. spectrum shows the presence of three methoxyl groups (δ 3.91, 3.81, and 3.53) and an N-methyl group (δ 2.58) as originally suggested. Acetylation of kreysiginine affords an O-acetyl derivative, thereby confirming the presence of an alcohol group, and the fifth and unreactive oxygen atom can be presumed to be present

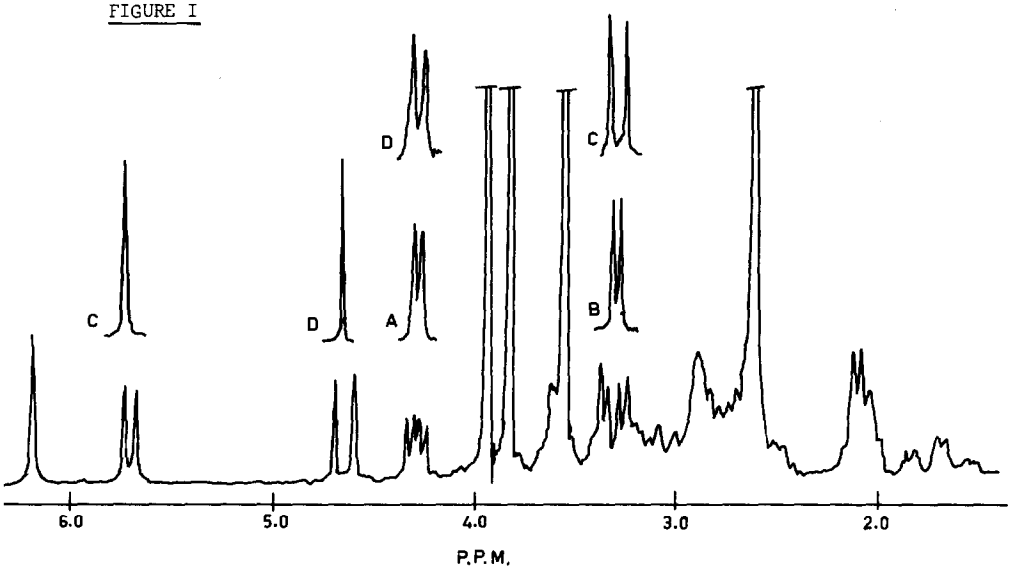
in an ether linkage. The sharp one-proton signal at δ 6.18 is assigned to the aromatic proton at C-1, which, because it is situated on a highly oxygenated aromatic ring, undergoes rapid exchange in the presence of dilute DCl in D_2O at 60°. Under these conditions, the signal at δ 6.18 disappears from the spectrum. Of the methoxyl signals, those at δ 3.91 and δ 3.81 are assigned to the groups at the C-2 and C-3 positions on the aromatic ring, and that at δ 3.53 to the methoxyl group at C-6.

The one-proton doublet at δ 4.64 (J 9.0 c./sec.) is assigned to the C-5 proton and this chemical shift is in agreement with that observed for the corresponding proton in the spectra of neopine (δ 4.62) and isoneopine (δ 4.54)[5]. Double irradiation at the resonance frequency of the C-5 proton (Figure I-B) collapses the quartet at δ 3.28 to a doublet (J 4.0 c./sec.) while irradiation at the δ 3.28 signal (Figure I-D) collapses the C-5 doublet to a singlet and the quartet at δ 4.28 to a doublet (J 6.0 c./sec.). Irradiation at the δ 4.28 quartet (Figure (I-C) collapses the δ 3.28 quartet to a doublet (J 9.0 c./sec.) and the doublet at δ 5.70 to a singlet. Finally, irradiation at the δ 5.70 doublet (Figure I-A) collapses the δ 4.28 quartet to a doublet (J 4.0 c./sec.). These data are consistent with the proposed structure (I) for kreysiginine in which the quartet at δ 3.28 is assigned to the C-6 proton ($J_{5,6}$ 9.0 c./sec.; $J_{6,7}$ 4.0 c./sec.), the quartet at δ 4.28 to the C-7 proton ($J_{6,7}$ 4.0 c./sec.; $J_{7,8}$ 6.0 c./sec.), and the doublet at δ 5.70 to the C-8 proton ($J_{7,8}$ 6.0 c./sec.).

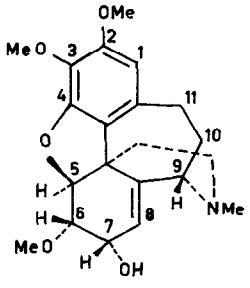
The large C-5, C-6 proton coupling (J 9.0 c./sec.) is consistent with a *trans pseudo* diaxial configuration for these protons (dihedral angle 170°), and establishes the relative configuration C-5-Hα and C-6-Hβ, as shown in (I). The relative configuration of the C-6, C-7 protons can be similarly established by consideration of the coupling constant (J 4.0 c./sec.) which is consistent with a dihedral angle of 45° and indicates a *cis* axial-equatorial configuration with C-7-Hβ. The coupling (J 6.0 c./sec.; dihedral angle, 30°) between C-7-Hβ and the allylic C-8-H is consistent only with a *pseudo*-equatorial configuration for C-7-Hβ. The magnitude of the chemical shift (δ 3.28) assigned to the C-6-H provides further evidence for a *pseudo*-axial configuration, as the *pseudo*-axial C-6-Hα (δ 3.50) in isoneopine resonates at higher field than the *pseudo*-equatorial C-6-Hβ (δ 4.23) of neopine[5]. The presence of an hydroxyl group at C-7 in kreysiginine was confirmed by observing a 1.17 p.p.m. "acylation shift" of the C-7-Hβ quartet in the spectrum of O-acetyl kreysiginine.

The C-9 proton signal is obscured in the spectrum of kreysiginine by the C-6 methoxyl signal, but in the spectrum of O-acetyl kreysiginine, the C-9 proton signal is observed as a

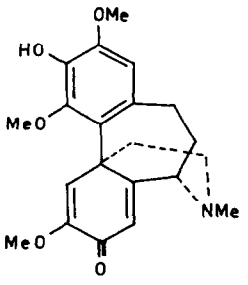
FIGURE I



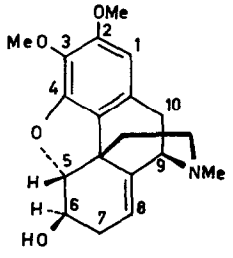
100 Mc./sec. n.m.r. spectrum of kreysiginine in $CDCl_3$ solution. Insets show spin-spin decoupled spectra resulting from irradiation at (A) δ 5.70 doublet, (B) δ 6.46 doublet, (C) δ 4.28 quartet, and (D) δ 3.28 quartet.



I



II



III

quartet at δ 3.53 ($J_{9,10\alpha}$ 1.5 c./sec., $J_{9,10\beta}$ 6.0 c./sec.). Double irradiation at the C-9 quartet simplifies a complex multiplet at δ 1.62 which is the only other signal than can be assigned by first-order inspection of the spectrum. This complex multiplet can be assigned to the C-10α proton, and is broadened by two large and two small couplings. Double irradiation at this multiplet removed the C-9, C-10α coupling, J 1.5 c./sec., $\phi_{9,10\alpha}$ 85°, from the C-9 quartet which collapses to a doublet (J 6.0 c./sec.), as well as collapsing other regions of the spectrum, which allows the assignment of approximate chemical shifts to the C-10β proton (δ 2.55) and to the C-11 protons at δ 2.62 and δ 3.13. The *pseudo* axial C-10α proton resonates at higher field than the *pseudo* equatorial C-10β proton, and by analogy it can be argued that the C-11 proton signal at δ 2.62 can be assigned to the *pseudo* axial C-11β proton, and the δ 3.13 signal to the *pseudo* equatorial C-11α proton. The complexity of the spectrum in these regions prevents the complete analysis of these multiplets.

The occurrence of alkaloids of both the homo-aporphine and homo-morphine types in *Kreysigia multiflora* is of considerable biosynthetic interest, as it has been shown that colchicine and N-formyl-N-desacetylcolchicine also occur in *K. multiflora*[6].

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