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THE ABSOLUTE MOLECULAR STRUCTURES OF KREYSIGININE AND OF MORPHINE

by

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X-ray analysis of kreysiginine, from Kreysigia multiflora Reichb (1), has defined its structure and absolute configuration. In the accompanying paper (2), the results of a parallel chemical investigation are reported.

Crystals of kreysiginine methiodide, $C_{21}H_{27}O_5N.CH_3I$, from acetone, are orthorhombic, unit cell dimensions, $\underline{a}$ = 8.366, $\underline{b}$ = 16.349, $\underline{c}$ = 18.606 Å with four molecules in the cell, the space group being $P2_12_12_1$. Intensity data for 2374 reflexions were measured with CuK_α radiation on a Picker automatic single-crystal diffractometer. The iodine sites, located from the three-dimensional vector map, were used to derive an approximate electron-density distribution. Although the first distribution was symmetrized due to the position of the iodine atom with $\underline{x} \sim 0.0$, $\underline{z} \sim 0.0$, the molecular skeleton was gradually built up and refined by subsequent electron-density and difference distributions until the complete structure was revealed.

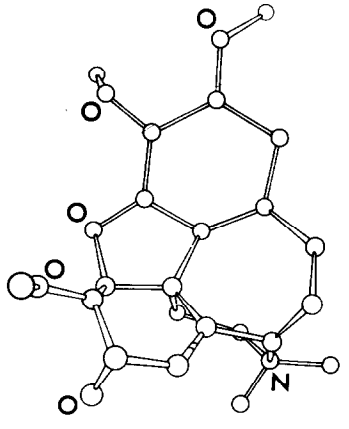


Fig 1

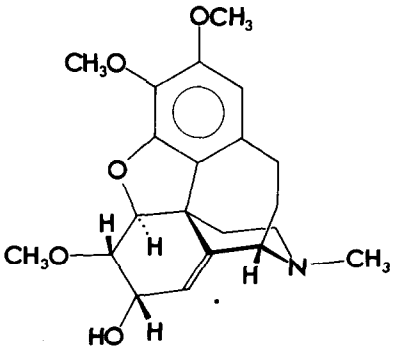


Fig 2

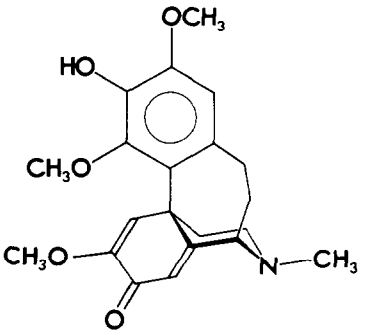
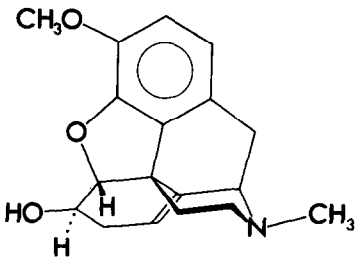


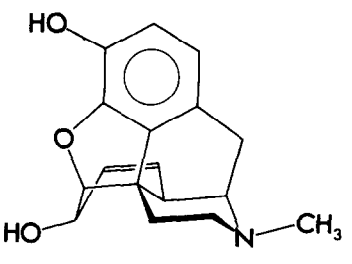
Fig 4

The absolute chirality was then defined by (i) a careful check of selected Bijvoet (3) pairs and (ii) calculation of the reliability index ($R = \Sigma|F_o - F_c|\Sigma|F_o|$) corresponding to each chirality. The conclusions from both were in complete accord. The absolute structure of the organic cation of kreysiginine methiodide is shown in Fig.1. The conventional formulation for kreysiginine is therefore as given in Fig.2.

Kreysiginine is thus a member of the class of homo-morphine alkaloids based on the phenylethylisoquinoline system (4). The position of the double bond relates kreysiginine more closely to neopine, Fig.3a, than to morphine, Fig.3b. A notable result of the analysis is that the absolute chirality of kreysiginine appears to be opposite to that normally ascribed to the morphine group, e.g. Fig.3.



(a)



(b)

Fig 3

To establish this point, the absolute configuration of morphine was determined independently by X-ray examination of selected Bijvoet pairs for morphine hydriodide, utilizing structure parameters reported earlier (5). The result confirmed the absolute structure shown in Fig.3b, the chirality being identical with that of codeine determined also by X-rays (6), the correlation between morphine and codeine being in accord with recent circular dichroism measurements (7).

Kreysiginine is a phenylethylisoquinoline alkaloid with an oxygen bridge, in contrast to androcymbine (4), Fig.4. The absolute chirality of kreysiginine, defined by X-rays, is the same as that of androcymbine, deduced from the mirror relation of its o.r.d. curve to that of the morphine alkaloid, salutaridine (4). That the chirality of the phenylethylisoquinoline alkaloids so far recorded, Figs. 2 and 4, is opposite to that of the main group of benzylisoquinoline alkaloids, as in Fig.3, may represent a consistent and significant pattern. On the other hand, evidence of this type may imply no more significance than the existence of different enzymatic pathways in different plants, as is indicated in the morphine group by the biosynthesis of both salutaridine and its optical isomer, sinoacutine, from the same precursor, reticuline, e.g. see reference (8).

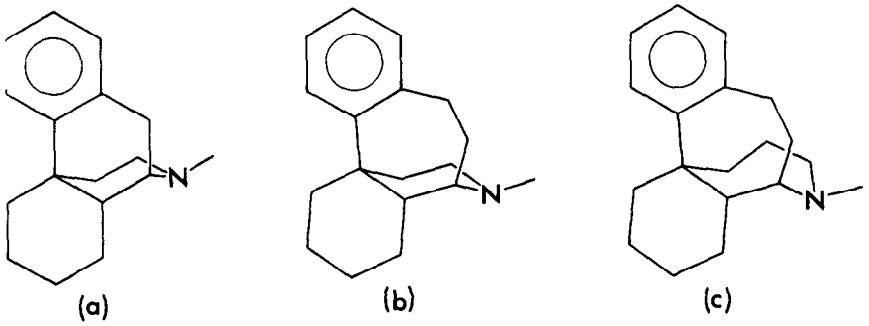


Fig 5

If synthesized by the same basic process (8) as the morphine alkaloids, represented in Fig.5a, the formation of phenylethylisoquinoline alkaloids, Fig.5b, would imply the incorporation of one unit of tyrosine with one unit of γ-phenylbutyrine, $C_6H_5.CH_2.CH_2.CH(NH_2).COOH$, an unusual amino-acid but one already observed in Nasturtium officinale (9). Extrapolation of this possibility would suggest the probable existence (even if in small concentration) of alkaloids based on two units of γ-phenylbutyrine, Fig.5c.

Details of the analysis and of the conformational aspects of the structure will be treated subsequently.

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