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MITRAPHYLLINE AND THE POSSIBLE EXISTENCE OF ITS OPTICAL ANTIPODE

Neville Finch and W. I. Taylor

Research Department, CIBA Pharmaceutical Company
Division of CIBA Corporation, Summit, New Jersey

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MITRAPHYLLINE is one of the apparent exceptions to the rule of the common stereochemical denominator[1] (C_{15}) among the yohimbinoid alkaloids. This base is reported to occur in l-,[2] d-[3,4] and racemic[4,5] forms. The recent conversion of ajmalicine, of known absolute stereochemistry, into l-mitraphylline[6] $\left[[\alpha]_D\ -8^\circ\ (CHCl_3)\right]$ indicates that it is d-mitraphylline which is exceptional.

It is known that oxindole alkaloids of this type very easily equilibrate into a mixture of the parent alkaloid and its epimer.[6,7] In the case of l-mitraphylline, the epimer is an amorphous base, isomitraphylline, which is dextrorotatory $\left[[\alpha]_D\ +18^\circ\ (CHCl_3)\right]$. It is possible, therefore, that the apparent isolation of rac- or d-mitraphylline could

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[1] E. Wenkert and N. V. Bringi, J. Amer. Chem. Soc. 81, 1474, 6535 (1959) and references therein.

[2] For leading references see J. C. Seaton, R. Tondeur and L. Marion, Can. J. Chem. 26, 1031 (1958).

[3] T. Nozoye, Chem. Pharm. Bull. (Japan) 6, 306 (1958).

[4] G. M. Badger, J. W. Cook and P. A. Ongley, J. Chem. Soc. 867 (1950).

[5] L. Michiels, J. Pharm. Belg. 13, 719 (1931).

[6] N. Finch and W. I. Taylor, J. Amer. Chem. Soc. 84, 1318, 3871 (1962).

[7] J. C. Seaton, M. D. Nair, O. E. Edwards and L. Marion, Can. J. Chem. 38, 1035 (1960).

be due to l-mitraphylline being contaminated with the *iso*- base. An alternative explanation depends simply on the errors attendant in measuring a small rotation with an inadequate concentration of the alkaloid.

We have attempted to obtain authentic samples of d- and dl-mitraphylline, *viz.*, Michiels,[5] $[\alpha]_{D}^{20^\circ} \pm 0^\circ$ (c, 0.64 in $CHCl_3$) from *Mitragyna macrophylla*; Badger, Cook and Ongley,[4] $[\alpha]_D \pm 0^\circ$ (no details), $[\alpha]_{D}^{21^\circ}$ $+7.1^\circ$ (c, 1.96 in $CHCl_3$), $+4.6^\circ$ (c, 0.98 in $CHCl_3$) from the leaves and bark of *M. rubrostipulacea*;[8] and Nozoye,[3] $[\alpha]_D$ $+3.8^\circ$ ($CHCl_3$) from *Uncaria kawakamii*. Only Dr. Nozoye was able to provide a sample of original material, and he very kindly furnished us with a 10 mg. sample.

On examination by thin-layer chromatography in a system known to resolve mitraphylline and *iso*mitraphylline (EtOAc|$CHCl_3$, 9:1 on silica gel plates), this material ran as a single spot. It was identical (m.p., mixed m.p., I.R. and p.m.r.[9]) with a sample of synthetic l-mitraphylline. The O.R.D. curve[10] [dioxan (c, 0.069) $[\alpha]_{589}$ $\pm 0^\circ$, (c, 0.0138) $[\alpha]_{298}$ $+1090^\circ$, $[\alpha]_{280}$ -2170°, $[\alpha]_{253}$ $\pm 0^\circ$] possessed the same sign of Cotton effect as that of l-mitraphylline [dioxan (c, 0.097) $[\alpha]_{589}$ $\pm 0^\circ$, (c, 0.0194) $[\alpha]_{302}$ $+1435^\circ$, $[\alpha]_{280}$ -2190°].

This evidence suggests that the remaining d- and dl-mitraphyllines are in reality also l-. This sort of ambiguity with oxindole alkaloids will be minimized in future work, if care is taken to exclude the presence of the *iso*- compound and if rotations are measured in a solvent or at a wavelength which provides an adequate value.

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[8] This work taken at its face value would suggest that the d- alkaloid occurred in the bark, and the l- alkaloid, in the leaves, an observation not substantiated by other workers (ref. 2).

[9] We wish to thank N. S. Bhacca of Varian Associates for obtaining an excellent spectrum on 5 mg. of alkaloid.

[10] These curves were kindly obtained for us by Professor C. Djerassi.