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THE STEREOCHEMISTRY OF PTEROPODINE AND ISOPTEROPODINE

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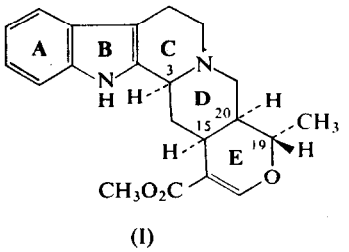
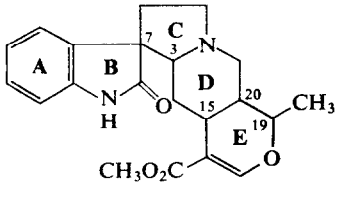
Abstract—Tetrahydroalstonine (I) has been isolated from an unknown *Uncaria* species. By the oxidative rearrangement, it was converted to isopteropodine (II). Utilizing this information and other observations, the detailed stereochemistry of pteropodine (III) and isopteropodine (IV) was deduced.

INTRODUCTION

IN THE course of our screening program for alkaloid-bearing Malayan plants,[1] we have noted the presence of alkaloids in a number of unknown *Uncaria* species. In particular, one bearing our Herbarium No. P.C.S.M. 2475,* was found to be exceedingly rich in alkaloids. In examining the alcoholic extracts of this species, only one crystalline alkaloid was isolated in excellent yield (0·96 per cent) and on further investigation proved to be tetrahydroalstonine whose absolute structure has been well established.[2]



(I)



(II)

Earlier work on *Uncaria pteropoda* Miq. has led to the isolation of two isomeric oxindole alkaloids, pteropodine and isopteropodine,[3a,b] the structures of which have been established as (II) without stereochemical assignments.

This paper reports the facile conversion of tetrahydroalstonine (I) to isopteropodine (II) by the well known oxidative rearrangement procedure which has generally been used in the

* This may well be a new *Uncaria* species. It is to be noted that *Uncaria* species are not easily identified without examining the flowers, fruits or both; and they flower very occasionally.

[1] J. CARRICK, K. C. CHAN and H. T. CHEUNG, *Chem. Pharm. Bull.* (*Tokyo*), in press.
[2] R. H. F. MANSKE, in *The Alkaloids* Vol. VIII (edited by R. H. F. MANSKE), p. 693, Chapter 20, Academic Press, New York, (1965), and references contained therein.
[3] (a) K. C. CHAN, F. MORSINGH and G. B. YEOH, *Tetrahedron Letters* 9, 931 (1966); (b) *J. Chem. Soc.* (*C*) 2245 (1967).

conversion of indole alkaloids to their oxindole analogues (Table 1).[4a–e] Thus the results showed that tetrahydroalstonine, pteropodine and isopteropodine have the same stereochemistry in rings D and E.

TABLE 1. OXIDATIVE REARRANGEMENTS OF INDOLE ALKALOIDS TO THEIR OXINDOLE ANALOGUES

Indole alkaloids	Equivalent oxindole alkaloids	References
Yohimbine	Yohimbine oxindole-B Yohimbine oxindole-A	4b,c,
Methyl isodeserpidate	Methyl isodeserpidate oxindole-B Methyl isodeserpidate oxindole-A	4c
Ajmalicine	Mitraphylline Isomitraphylline	4b,c,e
Dihydrocorynantheine	Rhyncophylline Isorhyncophylline	4c
Yohimbane	Yohimbane oxindole-B Yohimbane oxindole-A	4b
Tetrahydroalstonine	—	4d

Since completion of this work there have been several papers pertaining to the stereochemistry of these alkaloids. In particular, a paper by Pousset and his colleagues[5] describes the stereochemistry of isopteropodine and from the mass spectroscopic data,[6] it has been found that isopteropodine contains the *allo*-α-C_{19}-CH_3 group. Both these papers are in complete accord with our findings.

RESULTS AND DISCUSSION

By a procedure, based in part upon that employed by Chan *et al.*[3b] in their investigation of *Uncaria pteropoda* and outlined in the Experimental, we have been able to isolate from the unknown *Uncaria* species (P.C.S.M. 2475) only tetrahydroalstonine which had m.p. 229–231° (dec.) and was identical in all respects with an authentic sample.

Treatment of tetrahydroalstonine with lead tetraacetate gave the indolenine of acetoxytetrahydroalstonine which, on acid hydrolysis, with weak acetic acid afforded a gum. Chromatography of the gum on neutral alumina furnished isopteropodine, the identity of which was established by spectroscopic and chromatographic comparisons with naturally occurring substance.

It is known that isomerization of isopteropodine in aqueous acetic acid[3a,b] gave a mixture of isopteropodine and pteropodine. Moreover, Wenkert and his colleagues[7] have suggested

[4] (a) W. H. PERKIN, JR. and S. G. P. PLANT, *J. Chem. Soc.* **123**, 676 (1923); S. G. P. PLANT and R. ROBINSON, *Nature* **165**, 36 (1950); E. E. VAN TAMELEN, K. V. SIEBRASSE and J. B. HESTER, *Chem. & Ind.* 1145 (1956); A. PATCHORNIK, W. B. LAWSON and B. WITKOP, *J. Am. Chem. Soc.* **80**, 4748 (1958), **82**, 5918 (1960); W. B. LAWSON and B. WITKOP, *J. Org. Chem.* **26**, 263 (1961); (b). J. SHAVEL, JR. and H. ZINNES, *J. Am. Chem. Soc.* **84**, 1320 (1962); (c). N. FINCH and W. I. TAYLOR, *ibid.* **84**, 1318, 3871 (1962); (d). N. FINCH, C. W. GEMENDEN, I. H. C. HSU and W. I. TAYLOR, *ibid.* **85**, 1520 (1963); N. FINCH, C. W. GEMENDEN, I. H. C. HSU, A. KERR, G. A. SIM and W. I. TAYLOR, *ibid.* **87**, 2229 (1965); (e). H. ZINNES and J. SHAVEL, JR., *J. Org. Chem.* **31**, 1765 (1966).

[5] J. L. POUSSET, J. POISSON, R. J. SHINE and M. SHAMMA, *Bull. Soc. Chim. Fr.* **8**, 2766 (1967).

[6] M. SHAMMA and K. F. FOLEY, *J. Org. Chem.* **32**, 4141 (1967).

[7] E. WENKERT, B. WICKBERG and C. LEICHT, *Tetrahedron Letters* **22**, 822 (1961).

that such facile isomerization of an interconvertible pair of mitraphylloid-type alkaloids would involve the cleavage and reformation of C_3 and C_7 bond. Further, the existence of a bulky group at C_3 would result, during isomerization, in inversion in configuration at C_7 and retention of the hydrogen at C_3 which assumes the *cis* configuration with respect to the hydrogen at C_{15}. This proposal has been tested and shown to be correct.[4c] Thus pteropodine and isopteropodine must have the same stereochemistry as tetrahydroalstonine having (a) rings D and E *cis*, (b) C_{19}-H *trans* with respect to C_{20}-H, (c) C_3-H *cis* with respect to C_{15}-H[8] and (d) *allo* conformation with respect to yohimbane.[2, 6]

In agreement with (b), the spin–spin decoupling experiments of tetrahydroalstonine showed that irradiation at 1·37 p.p.m. caused collapse of multiplet at 4·45 p.p.m. to doublet (J_{19-20}=9 c/s) and irradiation at 4·45 p.p.m. caused collapse of doublet at 1·37 p.p.m. to singlet, as would be expected. Similarly irradiation at 1·35 and 1·40 p.p.m. caused the respective multiplet of pteropodine and isopteropodine at 4·49 and 4·46 p.p.m. to collapse to doublet, giving the same coupling constant (J_{19-20}=9 c/s; Table 2). The large J_{19-20} value of

TABLE 2. NMR SPECTRA IN $CDCl_3$ AT 60 Mc/sec AND 100 Mc/sec IN p.p.m. FROM TETRAMETHYLSILANE

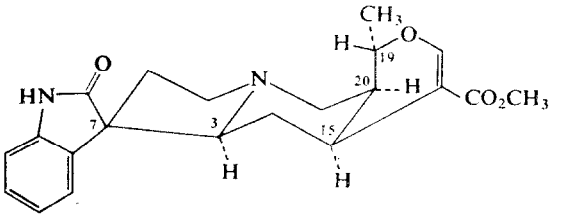
Functional groups	Pteropodine[3a,b]	Isopteropodine[3a,b]	Tetrahydroalstonine
CH_3CHO	1·35(d)* (J=6·0 c/s)	1·40(d)* (J=6·0 c/s)	1·37(d) (J=6·0 c/s)
CH_3CO_2	3·80 (s)	3·82 (s)	3·78 (s)
CH_3CHO	4·49 (m)	4·46 (m)	4·45 (m)
Aromatic H	7·30 (m)	7·28 (m)	7·15 (m)
Olefinic	7·70 (s)	7·72 (s)	7·58 (s)
—NH—	9·47 (s)	9·49 (s)	8·15 (s)
J_{19-20} (Found)	9 c/s	9 c/s	9 c/s
J_{19-20} (Calculated)	10 (165°)	10 (165°)	10 (165°)

* The earlier reported values[3a,b] were proved to be erroneous; s=singlet, d=doublet, m=multiplet.

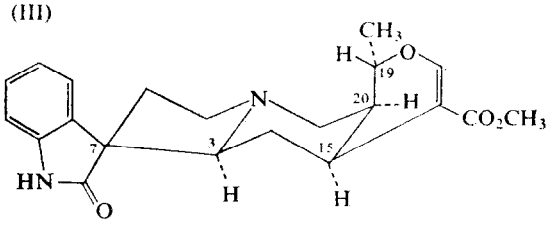
tetrahydroalstonine establishes a C_{19}-H and C_{20}-H *trans* diaxial configuration[9] for this alkaloid, thus implicating also C_{19}-H and C_{20}-H *trans* arrangement for pteropodine and isopteropodine.

Since tetrahydroalstonine was converted to isopteropodine by oxidative rearrangement and since the NMR spectrum (Table 2) indicated close resemblance to pteropodine and isopteropodine it was reasonable to assign structures (III) and its 7-epimer (IV) respectively to these alkaloids. This conclusion is strengthened by the fact that pteropodine (pK_a 4·8) is a stronger base than isopteropodine (pK_a 4·08)[3a,b]; the same criterion[4c] is being employed in assigning the complete stereochemistry of mitraphylline and isomitraphylline.

[8] E. WENKERT and D. K. ROYCHAUDHURI, *J. Am. Chem. Soc.* **80**, 1613 (1958).
[9] Cf. L. M. JACKMAN, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York (1959).



(III)



(IV)

EXPERIMENTAL

All m.p.s were determined on a Kofler hot stage and are uncorrected. Unless stated, i.r. spectra were recorded in $CHCl_3$ on Hilger Watts either a H 800 spectrophotometer or a H 900 Infrascan. U.v. spectrum was measured in $CHCl_3$ with a Perkin-Elmer 137 spectrophotometer. Ascending chromatography was on Whatman No. 1 paper in the upper phase of pentyl alcohol-cyclohexane-acetic acid-water (3:1:3:3 v/v). Merck activity III neutral alumina was used for column chromatography. Microanalysis was by Mr. R. D. MacDonald (Melbourne).

Isolation of Tetrahydroalstonine

Dried ground stem (5 kg) was exhaustively extracted by recycling with methanol for 48 hr. Removal of methanol under reduced pressure gave a dark brown residue which was then stirred vigorously with dil. NH_4OH (10%, 2 l.) and filtered. The alkaline solution was exhaustively extracted with $CHCl_3$. After drying, the solvent was removed and the greenish yellow residue was extracted with successive portions of boiling benzene. Removal of benzene under reduced pressure gave a gum (5·6 g) which readily crystallized from methanol. Repeated recrystallizations from the same solvent furnished tetrahydroalstonine (4·8 g, 0·96 per cent) as colourless *needles*, m.p. 229–231° (dec.), $[\alpha]_D^{22} = -109{\cdot}7°$ (*c* 0·8 in $CHCl_3$), pK_a 5·98 (by titration in 80% methanol with 0·2 N HCl). [lit.[10] m.p. 230–232°, $[\alpha]_D^{25} = -98°$ (*c* 0·2 in $CHCl_3$)]. [Found: C, 71·6; H, 7·2, N, 8·0; OMe 8·5; *M*, 330 (Rast). Calc. for $C_{21}H_{24}N_2O_3$: C, 71·5; H, 6·9; N, 8·0; 1 OMe 8·8 per cent; *M*, 352]. λ_{max} 232, 284, 291 nm (log ϵ 4·57, 3·89 and 3·83). ν_{max} 3430 (NH), 1708 (ester C=O) and 1629 (benzene) cm^{-1}.

The alkaloid obtained was identical in m.p., mixed m.p. and i.r. spectra with the authentic sample.

Oxidative Rearrangement of Tetrahydroalstonine to Isopteropodine

A solution of $Pb(OAc)_4$ (650 mg) in CH_2Cl_2 (25 ml) was added slowly to a solution of tetrahydrostonine (505 mg) in the same solvent (100 ml) at 0° to −5°, until oxidant was consumed (25 min). The CH_2Cl_2 solution was washed with 10% $KHCO_3$ solution, dried ($MgSO_4$), and the solvent was removed. The crude residue (465 mg) was chromatographed on alumina to give a foam, indolenine of acetoxytetrahydroalstonine (412 mg). This material was then dissolved in MeOH (25 ml) containing aq. HOAc (2 ml; 2%) and the mixture was heated under reflux for 2 hr. The cooled solution was basified with dil. NH_4OH, followed by extraction with $CHCl_3$. After drying, the solvent was removed and the gummy residue was chromatographed on alumina. Elution with $CHCl_3$ yielded isopteropodine (78 mg) which crystallized as *needles* from methanol. Its identity was confirmed by m.p. mixed m.p., paper chromatography and i.r. spectra with naturally occurring material.

Acknowledgements—The author thanks Professor R. C. Elderfield (Michigan, USA) for a sample of tetrahydroalstonine, Dr. D. G. Williamson (Aberdeen, UK) and Dr. H. Fales (N.I.H, Bethesda, USA) for NMR spectra, and Mr. J. Carrick (University of Malaya) for plant material.

[10] F. A. HOCHSTEIN, *J. Am. Chem. Soc.* 77, 5744 (1955).