Tetrahedron Letters No.40, pp. 4883-4888, 1966. Pergamon Press Ltd.
Printed in Great Britain.

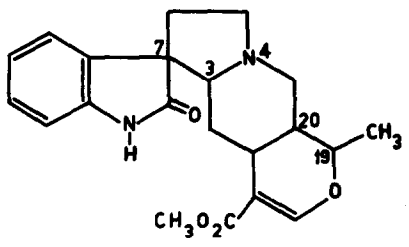
UNCARIA ALKALOIDS: TWO STEREOISOMERS OF MITRAPHYLLINE FROM UNCARIA BERNAYSII F.v.MUELL. AND U. FERREA D.C.

By S. R. Johns and J. A. Lamberton

Division of Organic Chemistry, C.S.I.R.O., Box 4331 G.P.O., Melbourne, Australia.

(Received 29 July 1966)

Uncaria and Mitragyna species of the family Rubiaceae are a source of oxindole alkaloids having the general formula I. The alkaloids of this group are obtained as interconvertible pairs of stereoisomers (mitraphylline and isomitraphylline[1], uncarine A and uncarine B[1], pteropodine and isopteropodine[2]) and equilibration of any one stereoisomer by heating in pyridine or acetic acid gives a mixture of two stereoisomers. We now report that two alkaloids (uncarine C and uncarine D) isolated from both Uncaria bernaysii F.v.Muell. and U. ferrea D.C. (rainforest lianas from New Guinea) are a further pair of interconvertible stereoisomers of I. Speciophylline, from Mitragyna speciosa[3] is reported to be another stereoisomer of I but insufficient



I

details have been published to show whether it may be identical with one of the alkaloids now discussed, and there is no published evidence that speciophylline can be converted into a stereoisomer under equilibration conditions.

Uncarine C and uncarine D were both shown by elemental analyses and their mass spectra to have the formula $C_{21}H_{24}N_2O_4$, and they were characterised as oxindoles of structure I by their spectroscopic properties (i.r. ν max. 1705 ± 1 cm^{-1}, 1627 ± 3 cm^{-1}; u.v., λ max. 245 mμ and n.m.r. spectra (Table I)). Convincing evidence for the close relationship of uncarine C and uncarine D to each other and to mitraphylline[4] was obtained from the mass spectra of the three alkaloids which showed a common fragmentation pattern and only minor differences in relative peak intensities.

Comparison of the properties of uncarine C and uncarine D with those of the other known pairs of stereoisomers of I (Table II) shows marked similarities, but there are, however, significant differences. Equilibration in refluxing pyridine (Table II) leads to the formation of almost 100% of uncarine C, while equilibration in acetic acid affords a mixture consisting of 50% of each stereoisomer. It is apparent that uncarine B (formosanine), pteropodine and uncarine D have closely similar melting points and optical rotations of similar magnitude, but they are not identical (or enantiomeric as the case may be), as they equilibrate with different stereoisomers. Mitraphylline and isomitraphylline have been assigned[5] the structure with rings DE trans and the C_{19}-H trans with respect to the C_{20}-H. Uncarine A and uncarine B are considered[6] to have rings DE cis and the C_{19}-H cis with respect to the C_{20}-H. The stereochemistry of pteropodine and isopteropodine has not been discussed.

TABLE I. N.m.r. spectra (60 Mc/s) in $CDCl_3$ solution

	Mitraphylline	Isomitraphylline	Uncarine B	Uncarine D	Uncarine C
C_{19}-$\underline{CH_3}$	1.11 ($J_{Me,H}$ 6.4)*	1.13 (6.3)*	1.29 (6.1)*	1.22 (6.5)	1.35 (6.5)
C_{19}-H	4.34 ($J_{H,H}$ 2.5)* (J_{CH_3H} 6.4)	4.39 (2.4,6.3)*	3.76 (2.9,6.1)*	4.15 (1.5,6.5)	4.35 (12,6.5)
$\underline{CH_3}O.CO$	3.57	3.54	4.5	3.32	3.55
=C-H	7.39	7.33	7.40	7.31	7.41

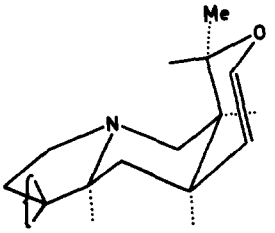
* reference 6

TABLE II

	Mitraph.	Isomitraph.	Unc. B	Unc. A	Pteropod.	Isopteropod.	Unc. D	Unc. C
M.pt.	270°	amorph.	216-217°	amorph.	217-219°	209-211°	183-184°	212-213°
$[\alpha]_D$ $CHCl_3$	-9.8°	+18	+91	+106	-103	-111	+74	-109
$Hg(OAc)_2$ oxidation	slow	fast	-	-	-	-	slow	fast
Pyridine equilibration (%)	20 <------> 80		20 <-----> 80		20 <-------> 80		0 <-----> 100	
HOAc equilibration (%)	50 <------> 50		Major <---> Minor		70 <-------> 30		50 <-----> 50	

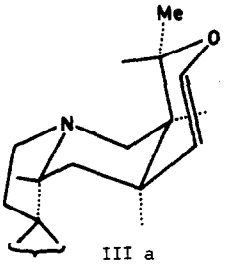
Mitraph. = mitraphylline; Unc. = uncarine; Pteropod. = pteropodine

Equilibration of the interconvertible isomers is considered to occur by cleavage and reformation of the C_3 to C_7 bond[6]. Such a process can result in inversion in configuration at C_3 and/or C_7. Because of the bulk of the group at C_3, Wenkert *et al.*[6] have proposed that isomerisation occurs with inversion of configuration at C_7 and retention at C_3, the C_3-H assuming the *axial* conformation with respect to ring D. The reported similarity of the n.m.r. spectra of the previously described isomeric pairs seems in accord with such a scheme. However, the spectra of uncarine C and uncarine D are different in a number of respects. The coupling constant (J 12 c/s) between the C_{19}-H and C_{20}-H of uncarine C

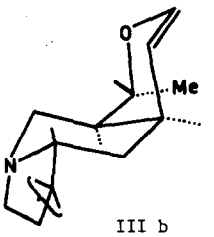


II

DE *cis*; 19H, 20H *trans* *diaxial*



III a



III b

DE *cis*; 19H, 20H *trans*, *diequatorial*

requires a trans diaxial arrangement of the hydrogen atoms whereas in uncarine D the coupling constant (J 1.5 c/s) suggests a trans di-equatorial arrangement. As equilibration conditions are such that no epimerisation can occur at C_{19} a change necessarily takes place at C_{20}. A conformational change at the DE ring junction must therefore be involved and such a change can only occur if the DE ring junction is cis. Consequently, uncarine C is considered to have the DE ring junction cis and C_{19}-H and C_{20}-H trans diaxial (partial structure II). A study of molecular models indicates that equilibration of II involving epimerisation at C_7 produces no marked steric interaction between the C_7-spiro group and N_4 which could produce a change in the conformation of ring D. However, if inversion at C_3 were involved in the conversion of II to uncarine D the less stable structure IIIa is produced with the bulky substituent having an axial conformation. The DE cis ring junction would allow inversion of ring D to produce the more stable structure IIIb (C_3-H axial). Such an inversion of ring D changes the conformation at C_{19} and C_{20} where the hydrogen atoms now have a trans diequatorial arrangement which is in accord with the coupling constant for uncarine D. Structures II and IIIb for uncarine C and uncarine D respectively are in accord with other evidence. In structure IIIb, the C_{19}-CH_3 is oriented in the shielding cone of the ring E double bond while structure II has the C_{19}-CH_3 oriented away from the double bond. As would be expected, the C_{19}-CH_3 signal resonates at higher field in uncarine D (δ 1.22) than in uncarine C (δ 1.35). It has been suggested that the mercuric acetate oxidation of tertiary amines involves an anti coplanar elimination from an N-mercurated complex[7,8]. Structure II has the required stereochemistry about the CD ring junction and, as would be expected, the rate of oxidation of uncarine C with mercuric acetate is much faster than that of uncarine D.

The above evidence suggests that epimerisation takes place at C_3 in the interconversion of uncarine C and uncarine D. Further work is being undertaken to determine whether inversion also takes place at C_7 in these isomers and whether C_3 is involved in the isomerisation of the other mitraphylline isomers.

N.m.r. spectra were recorded on a Varian A60 spectrometer in $CDCl_3$ with TMS as internal standard (δ 0.00).

REFERENCES

(1) J. E. Saxton, "The Alkaloids", Vol.VIII, edit. R. H. F. Manske (Academic Press), p.59. 1965.

(2) G. B. Yeoh, K. C. Chan and F. Morsingh, Tetrahedron Letters, no.9, 931 (1966).

(3) A. A. Beckett, E. J. Shellard, J. D. Phillipson and C. M. Lee, J. Pharm. Pharmacol., 17, 755 (1965).

(4) B. Gilbert, J. A. Brissolese, N. Finch, W. I. Taylor, H. Budzikiewicz, J. M. Wilson and C. Djerassi, J. Amer. Chem. Soc., 85, 1523 (1963).

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

(6) E. Wenkert, B. Wickberg and C. Leicht, Tetrahedron Letters, no.22, 822 (1961).

(7) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, J. Amer. Chem. Soc., 77, 439 (1955).

(8) N. J. Leonard and D. F. Morrow, J. Amer. Chem. Soc., 80, 371, (1958).