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THE STRUCTURE OF SPECIOFOLINE AND "STIPULATINE" (ROTUNDIFOLINE)

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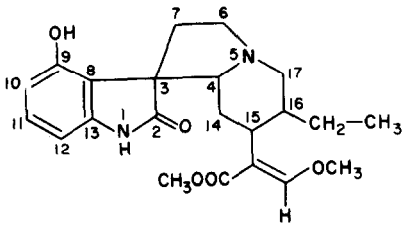
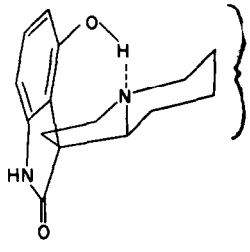
A new oxindole alkaloid designated speciofoline was recently isolated from leaves of Mitragyna speciosa from Malaya[1]. We have assigned structure (I) to this alkaloid on the following evidence.



I



II

Speciofoline ($C_{22}H_{28}N_2O_5$)*, colourless needles, m.p. 202-204°, pKa 6.3 (H_2O), $[\alpha]_D^{22}$ -103 (C, 2 in $CHCl_3$), has infra-red, ultra-violet and nuclear magnetic resonance spectra similar to those of rotundifoline † and "mitragynol" (isorotundifoline†) (Table I) whose structures have been recently briefly reported[2].

*

Analyses	C	H	N	OCH_3	Eq. Wt.**
Speciofoline requires for $C_{22}H_{28}N_2O_5$	66.0	7.0	7.0	15.5	400
Found,	66.2	6.8	7.5	15.0	394

** Titration in non-aqueous media

† Rotundifoline is a known alkaloid and the name isorotundifoline was used for its isomer without reference to the stereochemistry recently established for the iso-compounds of rhynchophylline and mitraphylline.[3]

TABLE I. SPECTRAL DATA ON SOME MITRAGYNA ALKALOIDS

N.M.R. SPECTRA (in $CDCl_3$ at 60 Mc in p.p.m. from TMS)

PROTONS	ROTUNDIFOLINE	STIPULATINE[3]	ISOROTUNDIFOLINE	SPECIOFOLINE
$-CH_3$	0.88 triplet	0.88 triplet	0.87 triplet	0.93 triplet
$-OCH_3$	3.60 singlet	3.62 singlet	3.70 singlet	3.66 singlet
$-\overset{O}{\overset{\|}{C}}-OCH_3$	3.70 singlet	3.70 singlet	3.80 singlet	3.78 singlet
Two aromatic protons	6.50 triplet	6.47 triplet	6.42 triplet	6.45 triplet
One aromatic proton	7.09 triplet	7.45 triplet?	7.02 triplet	7.08 triplet
Olefinic H	7.28 singlet	7.23 singlet	7.33 singlet	7.40 singlet
-N-	9.29 singlet*	9.16 singlet*	8.78 singlet*	8.48 singlet*
OH†	ca 12.00*	not given	ca 13.70*	ca 12.50*
ULTRAVIOLET SPECTRA IN ABSOLUTE ETHANOL				
	mμ log ε	mμ log ε	mμ** log ε	mμ log ε
Shoulder	223 4.36	222 4.35	222 4.43	223 4.47
	ca 242 4.15	240 4.13	ca 242 4.13	ca 242 4.27
	ca 292 3.42	292 3.44	ca 290 3.49	ca 290 3.49
INFRARED SPECTRA IN cm^{-1} (Nujol mulls)				
-N- H	3260	not given	3300	3280
OH .... N	2450 (weak,broad)	not given	--	2500 (weak,broad)
ester and oxindole carbonyl	1710	1715	1695	1705
oxindole and double bond	1630	1626	1630	1625

* disappears with a drop of D_2O

† all broad low singlets

** corrected from Reference 2 misprint

The presence of two methoxy-groups is indicated by Zeisel determinations* and by three-proton singlets at 3.66 p.p.m. and 3.78 p.p.m. in the N.M.R. spectrum. The methyl group of the C-ethyl function was shown by the three-proton triplet at 0.93 p.p.m. similar to that of rhynchophylline (0.87 p.p.m.), isorhynchophylline (0.88 p.p.m.), rotundifoline and isorotundifoline (Table I). A 9-substituent in the benzene ring is indicated by the splitting of the aromatic protons into two sets of triplets at 6.45 p.p.m. (2 protons) and 7.08 p.p.m. (1 proton) similar to those of rotundifoline and isorotundifoline (Table I) (see Hendrickson and Sims[3] for discussion). The hydroxyl group is shown by the analysis, phenol tests (Table II), the absence of the three-proton singlet for a methoxy substituent on an indole at 3.86 p.p.m. and the -OH .... N bond around 2500 cm^{-1} in the infra red spectrum. Presence of active hydrogen on indolic nitrogen and phenolic oxygen is shown by the disappearance of the singlets at 8.48 p.p.m. and 12.50 p.p.m. (very low and broad band) respectively upon addition of D_2O.

The ester-enol-ether function of speciofoline is indicated in the ultra-violet spectrum (Table I) c.f. discussion by Janot and Goutarel[4] similar to that of rotundifoline and isorotundifoline; the infra-red peaks at 1705 cm^{-1} and 1625 cm^{-1} are in support of this assignment[4].

The low broad infra-red peak centred at 2500 cm^{-1} is similar to that observed in rotundifoline (not isorotundifoline)[2]; OH .... N bonding is thus indicated in speciofoline . The N.M.R. data show the presence of the hydroxy-group in the 9-position and models demonstrate that the 9-position is the only one where the hydroxyl group may intramolecularly bond with the N_5 nitrogen. This bonding is shown by insolubility in 5% sodium hydroxide for speciofoline and rotundifoline and not for isorotundifoline. The lack of an appreciable change in the U.V. spectrum of the hydrogen bonded isomers in alkaline solution compared with neutral solution contrasts with the bathochromic shift of the 290 mμ peak (18 mμ) in the non intramolecularly bonded isorotundifoline. In acid the low wavelength peak undergoes a hypsochromic shift (ca 4 mμ) in

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* See previous footnote

TABLE II. PHYSICAL AND CHEMICAL PROPERTIES OF SOME MITRAGYNA ALKALOIDS

	ROTUNDIFOLINE	STIPULATINE[3]	ISOROTUNDIFOLINE	SPECIOFOLINE
Analysis - All calculated and found values agree for $C_{22}H_{28}N_2O_5$(I)				
Eq.wt. found ($C_{22}H_{28}N_2O_5$=400)	400[a]	400[a]	402[b]	394[b]
Melting point	238-40°	238-40°	131-32°	202-204°
$[\alpha]_D$(C,2 in $CHCl_3$)	+125°(19°)	+108°(27°no c)	-7°(23°)	-103°(22°)
pKa	5.3 (HOH)	5.2(50%C_2H_5OH)	7.4 (HOH)	6.3 (HOH)
Phenol tests:				
1. ($FeCl_3$ in acetone)	+ red	+ red ($FeCl_3$ in pyridine)		
2. Libermann's reaction	+ orange	not given	+ orange	+ orange
Rf (Thin layer)[c]				
1. alumina/$CHCl_3$	0.64	not given	0.59	0.65
2. silica gel $CHCl_3$/acetone 5 / 4	0.69	not given	0.47	0.64

a By mass spectrometry
b Titration in non-aqueous media
c Approximate values measured to centre of spot

TABLE III. DERIVATIVES OF ROTUNDIFOLINE AND STIPULATINE

	ROTUNDIFOLINE	STIPULATINE[3]
N-ACETYL		
Melting point	171-172°	170-171°
NMR ($CDCl_3$ 60 Mc in p.p.m.)		
N-Acetyl	2.64 (3 proton singlet)	2.67 (3 proton singlet)
aromatic (one proton each)	6.79 (doublet)	6.80 (doublet)
	7.15 (triplet)	7.22 (triplet)
	7.75 (doublet)	7.74 (doublet)
ALDEHYDE		
Melting point	240-241°	"chromatographically pure glass"
Calcd. for $C_{18}H_{24}N_2O_3$		
C 69.49	68.79	68.87
H 7.37	7.54	7.57
N 8.53	8.94	8.85
Molec. weight 328	331[a]	328[b]

a By titration in non-aqueous media
b By mass spectrometry

a hypochromic shift (Ca 4 mμ) in speciofoline and rotundifoline so that the shoulder at 242 mμ becomes a distinct peak; this effect is less pronounced in isorotundifoline (Ca 2 mμ). Speciofoline is therefore a stereoisomer of rotundifoline.

The data briefly reported[2] for rotundifoline and that of Tables I, II and III correspond closely with that recently reported by Hendrickson and Sims[3] for 'stipulatine' from samples of M.speciosa from the Phillipines and also allocated structure I[3].

The properties of the derivatives of rotundifoline correspond with those reported for stipulatine (Table III). Isomerisation may occur in these reactions e.g. rotundifoline and isorotundifoline form the same quaternary methyl iodide[2] whereas the N-acetyl derivative has probably the rotundifoline configuration since the OH .... N bond is still present in this compound.

However, unlike rotundifoline which may be isomerised to substantial proportions of isorotundifoline[2], 'stipulatine' was reported[3] to form an isomer only in minute yield as evidenced by thin layer chromatography. The hydrogen bonding of the phenolic -OH to the basic nitrogen (see II) would be expected to stabilise this isomer (see also Hendrickson and Sims[3]).

However, this hydrogen bonding would only occur under neutral or mildly alkaline conditions. Protonation and solvation of the N-atom would be expected to result in a free OH group and an increase in non-bonded interactions to make isomer II less stable under acidic conditions; the rotundifoline/isorotundifoline ratio observed was 3:1 in pyridine but 2:3 in acetic acid. Rotundifoline and isorotundifoline give only traces of their isomer when the usual conditions[5,6] of refluxing overnight are used. Heating for 48 hours in an oil bath (temperature 130° for 10% acetic acid and 140° for pyridine) is required for complete equilibration starting from either isomer.

The above evidence indicates that 'stipulatine' is probably the known alkaloid rotundifoline.

REFERENCES

1. A.H. Beckett, E.J. Shellard and A.N. Tackie, unpublished work; material authenticated at Kew.

2. A.H. Beckett and A.N. Tackie, Chem. and Ind. 1963, 1122.

3. J.B. Hendrickson and J.J. Sims, Tetrahedron Letters, 14, 929, (1963).

4. M.M. Janot and R. Goutarel, Bull. Soc. Chim. France, 18, 988, (1951).

5. N. Finch and W.I. Taylor, J. Am. Chem. Soc., 84, 3871, (1961).

6. J.C. Seaton, M.D. Nair, O.E. Edwards and L. Marion, Can. J. Chem., 38, 1033, (1960).

7. G.M. Badger, J.W. Cook, and P.A. Ongley, J. Chem. Soc., 1950, 867.

8. G.M. Badger, L.M. Jackman, R. Sklar, and E. Wenkert, Proc. Chem. Soc., 1963, 206.

ADDENDUM

A sample of 'stipulatine' kindly supplied by Dr. Hendrickson has an identical infrared spectrum as rotundifoline. Rotundifoline (silica gel column purification, mp 248-49°) and 'stipulatine' (mp. 245-46°) gave a mixed melting point of 245-46°. Both compounds gave identical Rf values (TLC) in the two systems used (Table II).

Two melting points have been quoted for mitragynol (isorotundifoline) viz. 130° (7) and 200° (8). Our sample of isorotundifoline (130°) can be converted to the higher melting form by heating and by acid-base treatment. The 200° form can be converted to the 130° form by dissolving in $CHCl_3$ and evaporating to dryness.