search Fund, administered by the American Chemical Society, for support of this research.

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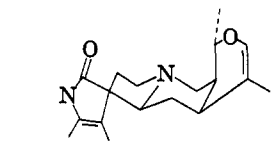
Received December 16, 1966

The Stereochemistry of the Pentacyclic Oxindole Alkaloids

Sir:

The assignment of configurations to the pentacyclic oxindole alkaloids has been one of the paramount problems remaining in alkaloid stereochemistry, and it is the purpose of this communication to describe the configurations of the oxindoles formosanine (uncarine-B), isoformosanine (uncarine-A), pteropodine, isopteropodine, rauniticine-*epiallo*-oxindole-B, rauniticine-*epiallo*-oxindole-A, rauniticine-*allo*-oxindole-B, rauniticine-*allo*-oxindole-A, rauvoxine, and rauvoxinine.[1] Additionally, all the other remaining pentacyclic oxindoles can now be assigned specific configurations by comparison with the bases that will presently be discussed. There are twelve stereochemical groups into which the oxindoles can be classified, and these are shown in the partial diagrams I–VI below.[2]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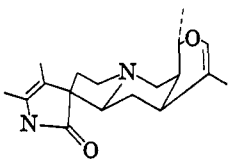
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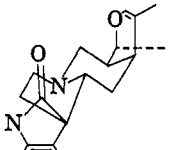
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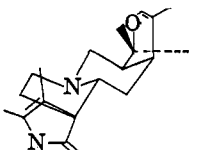
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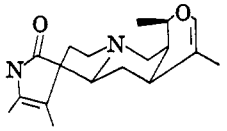
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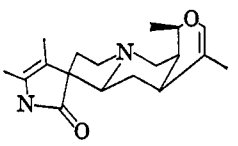
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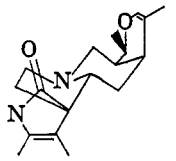
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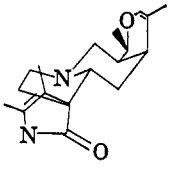
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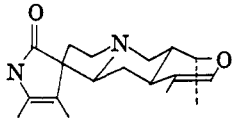
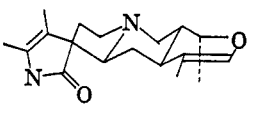
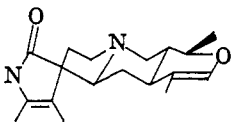
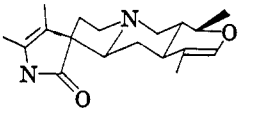
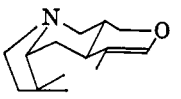
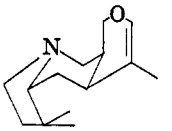

V-B, *normal*


V-A, *normal*


VI-B, *normal*


VI-A, *normal*


VII, *pseudo*


VIII, *epiallo*

Such arrangements as the *pseudo* expression VII need not be considered because of the serious steric interference between the oxindole moiety and the underbelly of ring D. This species would also show a very fast rate of N-methylation,[3] and experimentally no rapid rate was found. It follows that the *epiallo* configuration VIII is not an important one since it is even less favored than VII. The prior assignments of configurations I-B, V-B, and V-A to carapanaubine, mitraphylline, and isomitraphylline, respectively, are based on firm chemical and physical evidence and were reliable guideposts in our work.[1,4]

The pair of alkaloids represented by rauvoxine and rauvoxinine has been chemically related to carapanaubine,[5] and comparison of the chemical shifts of their C-19 methyl groups with that for carapanaubine (I-B) confirms that rauvoxine and rauvoxinine must be *epiallo* rather than *allo*. Rauvoxinine is more stable in acid solution than rauvoxine, so that the former must be represented by II-A and the latter by II-B. The basic nitrogen in II-A is less hindered than in II-B, and this is reflected in the higher rate of quaternization for rauvoxinine (see Table I).

Turning now to the *allo–epiallo* system with β-C-19 methyl groups, our starting point was the heteroyohimbine alkaloid rauniticine, of known *allo* β-C-19-methyl stereochemistry.[3] Conversion of this base to its oxindole derivatives[4] gave two major and two minor components which did not correspond to any of the naturally occurring bases we had on hand. The major components were named rauniticine-*epiallo*-oxindole-B and rauniticine-*epiallo*-oxindole-A. Since facile isomerization of the C-3 heteroyohimbine position can occur during oxindole formation, and because in acid solution rauniticine-*epiallo*-oxindole-A is favored over rauniticine-*epiallo*-oxindole-B, these two bases were assigned respectively expressions IV-A and IV-B. Structure IV-A bears a marked relationship to rauvox-

(1) For a recent review on the oxindole alkaloids see J. E. Saxton, *Alkaloids*, **8**, 59 (1965).
(2) Following convention the A notation indicates an α-oxindole carbonyl, and B a β-carbonyl.
(3) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).
(4) N. Finch, C. W. Gemenden, I. H-C. Hsu, and W. I. Taylor, *J. Am. Chem. Soc.*, **85**, 1520 (1963).
(5) J-L. Pousset and J. Poisson, *Compt. Rend.*, **259**, 597 (1964).

Table I. Pentacyclic Oxindoles[a,b]

Stereochemistry	Alkaloid	C_{19}–CH_3, δ	J_{19-20}, cps Found	J_{19-20}, cps Calcd	Main products Py[c]	Main products HOAc[d]	$COOCH_3$, δ	C_{19}–H, δ	$[\alpha]_D$, deg ($CDCl_3$)
I-B	Pteropodine	1.35	9	10 (165°)	I-A	I-B, II-A	3.55	4.49	−103
	Carapanaubine	1.40	9	10 (165°)	I-A	I-B, II-A	3.61	4.46	−115
I-A	Isopteropodine	1.38	9	10 (165°)	I-A	I-B, II-A	3.56	4.31	−111
II-B	Rauvoxine	1.23	1.5	2 (60°)	I-A	I-B, II-A	3.58	4.19	+98
II-A	Rauvoxinine	1.26	1.5	2 (60°)	I-A	I-B, II-A	3.43	4.19	+64
III-B	Rauniticine-*allo*-oxindole-B			5 (35°)	IV-B, III-A	IV-A			
III-A	Rauniticine-*allo*-oxindole-A	1.44	5	5 (35°)	IV-B, III-A	IV-A	3.57	4.34	Very small
IV-B	Rauniticine-*epiallo*-oxindole-B	1.29	1	0 (80°)	IV-B, III-A	IV-A	3.53	4.02	+164
IV-A	Rauniticine-*epiallo*-oxindole-A	1.29	1	0 (80°)	IV-B, III-A	IV-A	3.32	4.13	+143
V-B	Mitraphylline	1.11	Small	0.5 (75°)	V-A	V-B	3.57	4.34	−9.8
V-A	Isomitraphylline	1.13	Small	0.5 (75°)	V-A	V-B	3.54	4.39	+18
VI-B	Formosanine	1.28	9	10 (165°)	VI-A	VI-B	3.52	3.73	+91
VI-A	Isoformosanine	1.30	9	10 (165°)	VI-A	VI-B	3.51	3.75	+106

[a] Mass spectral analyses for the new compounds III-A (mp 199–202°), IV-A (mp 227–229°), and IV-B (amorphous) indicated the expected formula $C_{21}H_{24}N_2O_4$. The tlc system used throughout was $CHCl_3$–CH_3COCH_3–CH_3OH (90:8:2) on silica gel Adsorbil-1. The spin decoupling values were obtained on a 100-Mc Varian unit. [b] The pseudo-first-order rates of methiodide formation in acetonitrile solution at 25° were run on 3-mg samples as per ref 3. All of the rates were very slow ($<2 \times 10^{-4}$ sec^{-1}) except for rauniticine-*epiallo*-oxindole-A (IV-A) and rauvoxinine (II-A) which had values of 8×10^{-4} and 13×10^{-4} sec^{-1}, respectively. [c] Refluxing pyridine, 20 hr. [d] Refluxing 10% HOAc, 12 hr.

inine (II-A), and this is reflected in the relatively fast kinetic result for rauniticine-*epiallo*-oxindole-A.

The two minor components were rauniticine-*allo*-oxindole-B and rauniticine-*allo*-oxindole-A. The very low C-methyl chemical shift (δ 1.44) of the A isomer caused by the close proximity of the C-methyl to N_b clearly establishes the *allo* stereochemistry,[3] and since this isomer is relatively more stable in pyridine than its companion oxindole, it was assigned the III-A configuration. The J_{19-20} value after spin decoupling was 5 cps, indicating ring E to be twist–boat, and this conformation finds a perfect analogy in the heteroyohimbine series[3] where rauniticine also shows the identical value. The other minor component must therefore correspond to III-B.

Aqueous acetic acid equilibration of either pteropodine or isopteropodine[6] gave four spots on tlc, indicating that these two alkaloids must belong to an *allo–epiallo* system. The two alkaloids were clearly different from any of the rauniticine oxindoles so that they had to belong to the α-C-19-methyl series. Pteropodine was found to have exactly the same stereochemistry as carapanaubine (I-B) on the basis of the near identity of their chemical properties and infrared (near 8.4 μ in $CDCl_3$ solution) and nmr spectra. Isopteropodine must therefore be I-A. Furthermore, oxidative rearrangement of tetrahydroalstonine[3] followed by refluxing in pyridine gave (−)-isopteropodine (I-A) as expected.

Our two remaining alkaloids at this stage were formosanine and isoformosanine, and these must be assigned the normal with β-C-19-methyl configuration. Formosanine is more basic than isoformosanine, so the former must be as in VI-B, and the latter as in VI-A. This assignment is borne out by the fact that the vicinity of the α-C-19 position in the *normal* series is exceptionally highly shielded, as shown by the high-fie'd chemical shifts of the C-19 methyls of mitraphylline (V-B) and isomitraphylline (V-A), and the C-19 hydrogens of formosanine (VI-B) and isoformosanine (VI-A). Thin layer chromatography reveals that oxindoles of the *normal* series give a maximum of two isomers upon acid or base equilibration, while *allo* or *epiallo* oxindoles may yield up to four isomers.

The carbomethoxyl methyls of II-A and IV-A appear relatively upfield because of extra shielding by the benzene ring. Any *anti* oxindole (pair of electrons on N_b and lactam carbonyl on opposite sides), being the weaker base, moves faster on a silica gel (Adsorbosil-1) tlc plate than the corresponding *syn* compound, so that numerical R_f comparisons show I-A > I-B, II-B > II-A, III-A > III-B, IV-B > IV-A, etc. The mercuric acetate test[7] is positive for *anti* compounds (*e.g.*, isomitraphylline, isoformosanine, isopteropodine, and rauvoxine), and negative for *syn* bases (mitraphylline, formosanine, pteropodine, rauvoxinine). J_{19-20} values indicate that ring E is always quasichair, except in the hindered III-A (and presumably III-B) series where it is twist–boat.

(6) G. B. Yeoh, K. C. Chan, and F. Morsingh, *Tetrahedron Letters*, 931 (1966).

(7) H. Zinnes and J. Shavel, *J. Org. Chem.*, 31, 1765 (1966).

(8) M. S. and R. J. S. were supported by National Science Foundation Grant GP-6394.

(9) The authors wish to thank S. B. Penick and Co., Professor E. Wenkert, and Drs. N. Finch, P. Ulshafer, H. Zinnes, and Raymond-Hamet for alkaloidal samples.

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Received December 22, 1966