Revised Structure of Kribine

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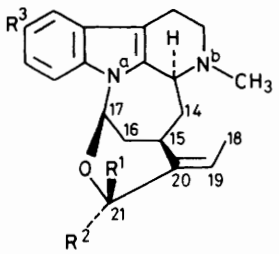
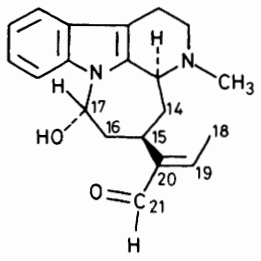
Based on extensive high-resolution ^{1}H n.m.r. experiments, revised structures for the indole alkaloid kribine (**8**) and its derivatives are proposed.

Kribine is an indole alkaloid found in several *Strychnos* species.[1–3] Rolfsen *et al.*[1] were the first to report its isolation. Based on chemical correlation with akagerine (**6**) and its spectral data, structure (**1**) was postulated for kribine, being a mixture of two epimers. The *O*-methyl compounds of the two epimers, (**2**) and (**3**), were also isolated.[1] The 10-hydroxy derivatives of the *O*-methyl epimers, (**4**) and (**5**), have also been reported.[4] The isolation of the alkaloid decussine (**7**)[5,6] from the same plant as the akagerine- and kribine-type alkaloids led to the question of whether these alkaloids were the precursors of the decussine-type alkaloids. As there were some similarities in the spectral data of the decussine series and those of kribine it was decided to reinvestigate the structure of kribine with the aid of high-resolution n.m.r. techniques. As small amounts of 21-*O*-methylkribine only were available, this alkaloid was studied in detail.

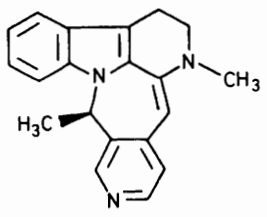


(**1**) R^1 = H, R^2 = OH (⇌ R^1 = OH, R^2 = H), R^3 = H
(**2**) R^1 = OCH_3, R^2 = R^3 = H
(**3**) R^1 = H, R^2 = OCH_3, R^3 = H
(**4**) R^1 = OCH_3, R^2 = H, R^3 = OH
(**5**) R^1 = H, R^2 = OCH_3, R^3 = OH

Old structure assignments of kribine and derivatives as described in the text



(**6**) Akagerine

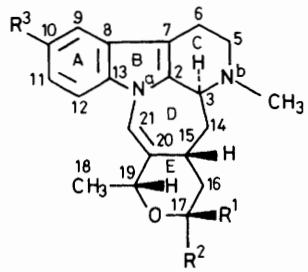


(**7**) Decussine

First a selective heteronuclear decoupling experiment was performed, in order to determine whether the quartet observed at δ_H 4.54 (assigned to 19-H in the original structure) in the ^{1}H n.m.r. spectrum is a strongly shielded vinylic proton or a deshielded aliphatic proton. Not one of the low-field signals in the ^{13}C n.m.r. spectrum (δ_C 98.4—137.8 p.p.m.) was reduced to a singlet. In fact a strongly reduced coupling was observed for the δ_C 66.4 p.p.m. doublet. The quartet thus belongs to an aliphatic proton, which does not agree with structure (**2**).

Further high-resolution ^{1}H n.m.r. studies were made to establish the correct structure of *O*-methylkribine. In a 300 MHz ^{1}H n.m.r. spectrum run in $CDCl_3$ not all the protons were resolved completely. However, some important information could be obtained with some n.O.e.-difference experiments. Irradiation of the singlet at δ_H 6.90 resulted in a n.O.e. for 12-H and the 18-methyl group (δ_H 1.47). Irradiation of the 18-methyl group resulted in a n.O.e. for the quartet at δ_H 4.54 and the singlet at δ_H 6.90. This means that the proton observed at δ_H 6.90 in the molecule must be situated between the 12-H and 18-methyl.

As kribine is formed from akagerine by opening of the C(17)–N^a bond and the conversion of kribine into akagerine is also possible,[1] the number of possible structures for kribine is limited. Only one of the possible structures for *O*-methylkribine fits the n.O.e. results [structure (**9**)].



(**8**) Kribine R^1 = OH, R^2 = H (⇌ R^1 = H, R^2 = OH), R^3 = H
(**9**) 17-*O*-Methylkribine R^1 = OCH_3, R^2 = R^3 = H
(**10**) Epi-17-*O*-methylkribine R^1 = H, R^2 = OCH_3, R^3 = H
(**11**) 10-Hydroxy-17-*O*-methylkribine R^1 = OCH_3, R^2 = H, R^3 = OH
(**12**) 10-Hydroxy-epi-17-*O*-methylkribine R^1 = H, R^2 = OCH_3, R^3 = OH

The incomplete resolution of the protons in the 300 MHz spectrum did not allow the determination of all coupling constants; all signals could, however, be assigned to the various protons in structure (**9**). Couplings between the various protons were established by means of a homonuclear-shift-correlated 2D spectrum (COSY-45). To be able to calculate the various coupling constants, a 500 MHz spectrum was recorded as well, but some signals still overlapped partly (14-H_α, 16-H_α, and 14-H_β, 3-H and *O*-methyl). By running the ^{1}H n.m.r. spectrum (300 MHz) in [$^2H_6$]benzene these protons could be resolved, although the 15-H signal was covered completely by those of 6-H_α and 5-H_α. A series of decoupling experiments and a homonuclear-shift-correlated 2D spectrum in [$^2H_6$]benzene finally enabled the complete assignment of the ^{1}H n.m.r. signals (Table 1).

Table 1. ^{1}H N.m.r. data of 17-*O*-methylkribine (δ in p.p.m. relative to $SiMe_4$, coupling constants in Hz)

	Spectrum in $CDCl_3$ (500 MHz)			Spectrum in hexadeuteriobenzene (300 MHz)		
Proton	δ	Multiplicity	Coupling constants	δ	Multiplicity	Coupling constants
3-H	3.44	m		3.18	dddd	$J_{3.6\alpha}$ 1.1, $J_{3.6\beta}$ 2.5, $J_{3.14\alpha}$ 2.5, $J_{3.14\beta}$ 10.2
5-H_α	2.68	ddd	$J_{5\alpha.5\beta}$ 11.8, $J_{5\alpha.6\alpha}$ 4.0, $J_{5\alpha.6\beta}$ 10.5[a]	2.44	ddd	$J_{5\alpha.5\beta}$ 11.5, $J_{5\alpha.6\alpha}$ 5.5, $J_{5\alpha.6\beta}$ 10.5
5-H_β	3.14	ddd	$J_{5\alpha.5\beta}$ 11.8, $J_{5\beta.6\alpha}$ 2.5, $J_{5\beta.6\beta}$ 4.0	2.85	ddd	$J_{4\alpha.5\beta}$ 11.5, $J_{5\beta.6\alpha}$ 2.5, $J_{5\beta.6\beta}$ 5.0
6-H_α	2.75	dddd	$J_{6\alpha.6\beta}$ 15.5, $J_{6\alpha.5\alpha}$ 5.0, $J_{6\alpha.5\beta}$ 2.5, $J_{6\alpha.3}$ 2	2.57	dddd	$J_{6\alpha.6\beta}$ 15, $J_{6\alpha.5\alpha}$ 5.5, $J_{6\alpha.5\beta}$ 2.5 $J_{6\alpha.3}$ 1.1
6-H_β	2.92	dddd	$J_{6\alpha.6\beta}$ 15.5, $J_{6\beta.5\alpha}$ 10.5, $J_{6\beta.5\beta}$ 5.0, $J_{6\beta.3}$ 2.5	2.89	dddd	$J_{6\alpha.6\beta}$ 15, $J_{6\beta.5\alpha}$ 10.5, $J_{6\beta.5\beta}$ 5.0, $J_{6\beta.3}$ 2.5
9-H	7.48	br d	$J_{9.10}$ 7.6	7.57	m	
10-H	7.15	dd	$J_{9.10} = J_{10.11} = 7.6$			
11-H	7.21	ddd	$J_{10.11}$ 7.6, $J_{11.12}$ 8.1, $J_{9.11}$ 1.1	7.26	m	
12-H	7.33	d	$J_{11.12}$ 8.1			
14-H_α	2.10	ddd	$J_{14\alpha.14\beta}$ 13.5, $J_{14\alpha.3}$ 2.0, $J_{14\alpha.15}$ 3.5	1.84	ddd	$J_{14\alpha.14\beta}$ 13.5, $J_{14\alpha.3}$ 2.5, $J_{14\alpha.15}$ 3.5
14-H_β	2.16	ddd	$J_{14\alpha.14\beta}$ 13.5, $J_{14\beta.3}$ 10.2, $J_{14\beta.15}$ 5.0	2.01	ddd	$J_{14\alpha.14\beta}$ 13.5, $J_{14\beta.3}$ 10.2, $J_{14\beta.15}$ 5.2
15-H	3.08	m		2.81—2.95	m	
16-H_α	2.15	ddd	$J_{16\alpha.16\beta}$ 12.9, $J_{16\alpha.15}$ 12.1, $J_{16\alpha.17}$ 4.0	1.90	ddd	$J_{16\alpha.16\beta}$ 12.9, $J_{16\alpha.15}$ 12.5, $J_{16\alpha.17}$ 4.0
16-H_β	1.78	ddd	$J_{16\alpha.16\beta}$ 12.9, $J_{16\beta.15}$ 4.0, $J_{16\beta.17}$ 1.8	1.53	ddd	$J_{16\alpha.16\beta}$ 12.9, $J_{16\beta.15}$ 2.5, $J_{16\beta.17}$ 2.0
17-H	4.89	dd	$J_{17.16\alpha}$ 4.0, $J_{17.16\beta}$ 1.8	4.72	dd	$J_{17.16\alpha}$ 4.0, $J_{17.16\beta}$ 2.0
18-H_3	1.47	d	$J_{18.19}$ 6.2	1.31	d	$J_{18.19}$ 6.2
19-H	4.54	q	$J_{18.19}$ 6.2	4.38	q	$J_{18.19}$ 6.2
21-H	6.90	s		6.75	s	(weak coupling with 15-H and 19-H according to COSY-45)
OCH_3	3.45	s		3.27	s	
NCH_3	2.52	s		2.21	s	

[a] All coupling confirmed by homonuclear-shift-correlated 2D spectra, some also by decoupling experiments.

The conformation of the D-ring can be deduced from the coupling constants of 3-H with 14-H_α and 14-H_β and of 15-H with 14-H_α and 14-H_β. Considering the strong coupling between 16-H_α and 15-H (J 12.5 Hz) and the small couplings between 17-H and both 16-H_α and 16-H_β, the conformation of the E-ring must be a chair form with the 17-*O*-methyl in the axial position. The n.O.e. observed for 19-H upon irradiation of the *O*-methyl group places the 19-H in the axial position as well. The 18-methyl group is then in the same plane as the 21-H, explaining the n.O.e.s observed for these protons. The stereochemistry at C-19 is thus established as *R* and at C-17 as *S*. The stereochemistry of the structure of *O*-methylkribine is thus presented in the Figure.

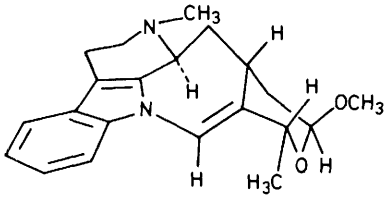


Figure. Stereochemistry of 17-*O*-methylkribine

As no epi-21-*O*-methylkribine was available no further studies of that alkaloid could be made. However, from the known n.m.r. data [1,4] it is clear that the 17-*O*-methyl group is in an equatorial position, resulting in a large and a small coupling, respectively, of 17-H with 16-H_α and 16-H_β. The further upfield position of 17-H, if compared with the 17-H signal in *O*-methylkribine, also confirms the axial position of this proton in epi-*O*-methylkribine; similar shifts have been reported for the two epimers of the *O*-methyl derivative of the Wieland Gumlich aldehyde.[7] The large difference in [α] for *O*-methylkribine (−52°) and its epimer (−212°) also agrees with the proposed conformations.[7]

Finally a comparison of the ^{13}C n.m.r. spectra of the two epimers (Table 2) clearly proves the E-ring stereochemistry. In *O*-methylkribine C-17, bearing an axial *O*-methyl group, is more upfield (Δδ 4.2 p.p.m.) then in epi-*O*-methylkribine which bears an equatorial *O*-methyl group.[8] Furthermore the carbons C-15 and C-19 are more upfield in *O*-methylkribine than in its epimer (Δδ respectively 3.8 and 6.3 p.p.m.) owing to shielding of the axial *O*-methyl group. Thus the structures of *O*-methyl- and epi-*O*-methyl-kribine are established as (**9**) and (**10**). Consequently, the names of 21-*O*-methyl- and epi-21-*O*-methylkribine have to be changed to 17-*O*-methyl- and epi-17-*O*-methyl-kribine. The structures of kribine, 10-hydroxy-17-*O*-methylkribine, and 10-hydroxy-epi-17-methylkribine are thus revised to (**8**), (**11**), and (**12**).

Table 2. ^{13}C N.m.r. data of 17-*O*-methylkribine (**9**) and epi-17-*O*-methylkribine (**10**) (δ in p.p.m. relative to $SiMe_4$)

Carbon	(**9**)	(**10**)	Carbon	(**9**)	(**10**)
2	136.5[a]	136.8[a]	14	36.0	36.1
3	56.6	57.1	15	32.9	36.7
5	52.5	52.9	16	38.0	39.7
6	20.9	21.0	17	98.4	102.6
7	108.6	108.8	18	17.6	17.7
8	127.0	127.1	19	66.4	72.7
9	118.2	118.4	20	125.2	123.1
10	121.6[b]	121.9[b]	21	116.3	117.1
11	120.3[b]	120.6[b]	OCH_3	54.5	56.1
12	109.1	109.1	NCH_3	42.6	42.8
13	137.8[a]	138.1[a]			

[a,b] Signals may be interchanged.

Experimental

For details on the isolation of the alkaloids and their spectral data see ref. 1. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ or benzene solution with $SiMe_4$ as internal standard on a Bruker

WM 300 or WM 500 apparatus. In n.O.e.-difference experiments, peaks of protons were irradiated for a period of 1.0 s, using sufficient irradiation power to cause complete saturation of the signal. A control spectrum was recorded with the decoupler offset in a blank region. The FID signals of both spectra were subtracted to yield the n.O.e.-difference spectrum.

Acknowledgements

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