The Alkaloids of *Margaritaria indica*. Part 2.[1] The Structures of 4-Epiphyllanthine, Margaritarine and the Structural Revision of Securinol A

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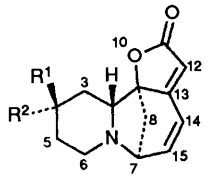
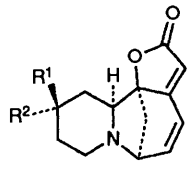
Extraction of the bark of *Margaritaria indica* has yielded the new alkaloids (4α)-4-methoxysecurinan-11-one **3** and 3-{*N*-[(2α,15α)-14,15-dihydro-11-oxosecurinan-15-yl]-2-aminoethyl}-1*H*-indole **10**. Their structures followed from their spectroscopic properties. High field NMR spectra for the known *Securinega* alkaloids (4β)-4-methoxysecurinan-11-one **2** and (2α,4α)-4-methoxysecurinan-11-one **5** were recorded and interpreted. The structure of the known alkaloid securinol A is revised to **17** as a result of an X-ray crystal structure determination of its hydrobromide.

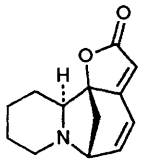
The *Securinega* alkaloids[2] are a small group of bases which are derived biosynthetically from tyrosine and lysine.[3,4] They are of some stereochemical complexity: securinan-11-one (securinine) **1** and its epimer at C-2, (2α)-sucurinan-11-one (allosecurinine, phyllochrysine) **4** occur in *Securinega suffructicosa*,[5] whilst their optical antipodes (2α,7β,9β)-securinan-11-one (virosecurinine) **6** and (7β,9β)-securinan-11-one (viroallosecurinine) **7** occur in *S. virosa*.[6] The conformations of these alkaloids are of interest since securinine **1** has proved to be a GABA receptor antagonist.[7]



1 $R^1 = R^2 = H$
2 $R^1 = OMe$, $R^2 = H$
3 $R^1 = H$, $R^2 = OMe$



4 $R^1 = R^2 = H$
5 $R^1 = H$, $R^2 = OMe$



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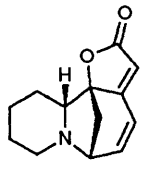

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In continuation of our work[1] on the alkaloids of *Margaritaria indica* we now report on the constitution and stereochemistry of the minor bases of the bark of this West Sumatran tree. In addition to the known compounds securinine **1**, allosecurinine **4** and (2α,15α)-14,15-dihydro-15-methoxysecurinan-11-one (14,15-dihydro-15α-methoxyphyllochrysine) **11**, the isolation of which we have reported previously,[1] we also isolated the known compounds (4β)-4-methoxysecurinan-11-one (phyllanthine) **2**[8,9] and (2α,4α)-4-methoxysecurinan-11-one (securitinine) **5**[10] which were identified by their physical and spectroscopic properties which were in accord with those recorded in the literature. We have also isolated the known alkaloid securinol A which was originally assigned structure **14** but as a result of the present work is now allocated structure **17**. We also report on the structures of the new alkaloids (4α)-4-methoxysecurinan-11-one (4-epiphyllanthine) **3** and 3-{*N*-[(2α,15α)-14,15-dihydro-11-oxosecurinan-15-yl]-2-aminoethyl}-1*H*-indole **10**, for which we suggest the trivial name margaritarine.

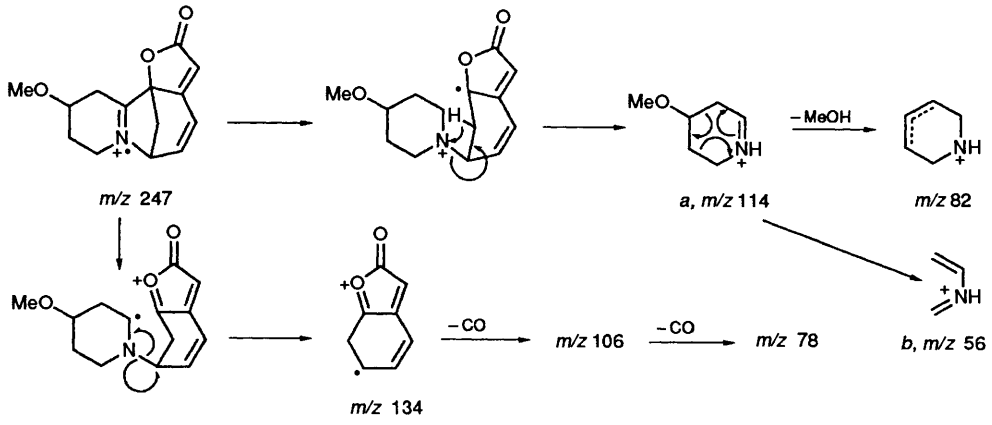
Table 1 ^{13}C and ^1H NMR data for 4-epiphyllanthine **3**

Carbon no.	δ_C	δ_H, multiplicity, coupling constants (Hz)
2	59.81	2.09, dd, $J_{2,3\alpha}$ 11.2, $J_{2,3\beta}$ 2.0
3	32.41	1.45, apparent q, $J_{3\alpha,2}$ 11.2, $J_{3\alpha,3\beta} = J_{3\alpha,4}$ 10.9, 2.15, m, 3β-H
4	77.99	3.12, apparent tt, $J_{4,3\alpha}$ 10.9, $J_{4,5\alpha}$ 10.2, $J_{4,3\beta}$ 4.0, $J_{4,5\beta}$ 4.0.
5	32.36	1.57, dddd, $J_{5\alpha,5\beta}$ 12.5, $J_{5\alpha,6\beta}$ 10.9, $J_{5\alpha,4}$ 10.2, $J_{5\alpha,6\alpha}$ 5.3, 1.97, m, 5β-H
6	45.56	3.00, ddd, $J_{6\alpha,6\beta}$ 10.9, $J_{6\alpha,5\alpha}$ 5.3, $J_{6\alpha,5\beta}$ 3.1, 2.42, dt, $J_{6\beta,6\alpha}$ 10.9, $J_{6\beta,5\alpha}$ 10.9, $J_{6\beta,5\beta}$ 2.9
7	58.21	3.81, t, $J_{7,15}$ 4.6, $J_{7,8\alpha}$ 4.6
8	42.29	2.54, dd, $J_{8\alpha,8\beta}$ 9.4, $J_{8\alpha,7}$ 4.6, 1.81 d, $J_{8\beta,8\alpha}$ 9.4
9	89.17	
11	173.36	
12	105.53	5.56, s
13	169.66	
14	121.46	6.59, d, $J_{14,15}$ 9.2
15	140.16	6.45, dd, $J_{15,14}$ 9.2, $J_{15,7}$ 4.6
OMe	55.75	3.32, s

4-Epiphyllanthine **3** gave a molecular ion in its high resolution mass spectrum consistent with the molecular formula $C_{14}H_{17}NO_3$, isomeric with both phyllanthine **2** and securitinine **5**. The infrared spectrum was similar to that of its isomers and revealed the presence of an αβ-unsaturated lactone characterized by bands at 1740 and 1625 cm^{-1}, which was confirmed by the ^1H NMR spectrum which exhibited a singlet at δ_H 5.56 (12-H) and there was evidently another double bond in the molecule since in this spectrum there was a doublet at δ_H 6.59 (14-H, $J_{14,15}$ 9.2 Hz) and a doublet of doublets at δ_H 6.45 (15-H, $J_{15,14}$ 9.2, $J_{15,7}$ 4.6 Hz). Appropriate signals for these functionalities were also detected in the ^{13}C NMR spectrum (see Table 1). The presence of a methoxy group was evident from a 3 proton singlet at δ_H 3.32 in the ^1H NMR spectrum and corresponding signal at δ_C 55.75 in ^{13}C NMR spectrum.

The mass spectrum of the new base (see Scheme 1), rationalized in terms of structure **3**, was very similar to that of both phyllanthine **2** and securitinine **5**. The base peak *a* is indicative of the methoxy group being located on the piperidine ring and the production of the ion *b* means that its location cannot be at C-3 or C-6.

The definition of the exact location of the methoxy group and



Scheme 1

Table 2 ^{13}C and ^{1}H NMR data for phyllanthine **2**

Carbon no.	δ_C	δ_H, multiplicity, coupling constants (Hz)
2	56.20	2.59, dd, $J_{2,3\alpha}$ 12.2, $J_{2,3\beta}$ 2.4
3	31.06	1.68, ddd, $J_{3\alpha,3\beta}$ 13.1, $J_{3\alpha,2}$ 12.2, $J_{3\alpha,4}$ 2.9, 1.95, dddd, $J_{3\beta,3\alpha}$ 13.1, $J_{3\beta,4}$ 2.6, $J_{3\beta,2}$ 2.4, $J_{3\beta,5\beta}$ 1.4
4	74.20	3.63, dddd, $J_{4,5\beta}$ *ca.* 3, $J_{4,5\alpha}$ *ca.* 3, $J_{4,3\alpha}$ 2.9, $J_{4,3\beta}$ 2.6
5	30.61	1.70–1.90, m, 5α- and 5β-H
6	44.52	2.79, ddd, $J_{6\alpha,6\beta}$ 10.4, $J_{6\alpha,5\alpha}$ 5.3, $J_{6\alpha,5\beta}$ 3.4, 2.67, dt, $J_{6\beta,6\alpha}$ 10.4, $J_{6\beta,5\beta}$ 3.4, $J_{6\beta,5\alpha}$ 10.4
7	58.75	3.81, dd, $J_{7,15}$ 5.3, $J_{7,8\alpha}$ 4.2
8	41.92	2.52, dd, $J_{8\alpha,8\beta}$ 9.4, $J_{8\alpha,7}$ 4.2, 1.78, d, $J_{8\beta,8\alpha}$ 9.4
9	89.28	
11	173.58	
12	105.35	5.55, s
13	170.05	
14	121.58	6.58, d, $J_{14,15}$ 9.1
15	140.33	6.43, dd, $J_{15,14}$ 9.1, $J_{15,7}$ 5.3
OMe	56.01	3.27, s

Table 3 ^{13}C and ^{1}H NMR data for securitinine **5**

Carbon no.	δ_C	δ_H, multiplicity, coupling constants (Hz)
2	55.88	3.90, dd, $J_{2,3\beta}$ 13.5, $J_{2,3\alpha}$ 3.5
3	26.32	1.57–1.68, m, 3α- and 5α-H, 1.20, dt, $J_{3\beta,3\alpha}$ 14.0, $J_{3\beta,2}$ 13.5, $J_{3\beta,4}$ 4.4
4	72.75	3.65, dddd, $J_{4,5\beta}$ 8.8, $J_{4,5\alpha}$ 6.0, $J_{4,3\beta}$ 4.4, $J_{4,3\alpha}$ 1.7
5	30.57	1.57–1.68, m, 3α- and 5α-H, 2.16, dddd, $J_{5\beta,5\alpha}$ 14.0, $J_{5\beta,4}$ 8.8, $J_{5\beta,6\alpha}$ 4.0, $J_{5\beta,6\beta}$ 2.5
6	42.18	2.83, dt, $J_{6\alpha,6\beta}$ 10.5, $J_{6\alpha,5\beta}$ 4.0, $J_{6\alpha,5\alpha}$ 4.0, 2.61, ddd, $J_{6\beta,5\alpha}$ 13.0, $J_{6\beta,6\alpha}$ 10.5, $J_{6\beta,5\beta}$ 2.5
7	58.68	3.93, dd, $J_{7,15}$ 5.3, $J_{7,8\alpha}$ 4.5
8	42.82	2.72, dd, $J_{8\alpha,8\beta}$ 9.8, $J_{8\alpha,7}$ 4.5, 1.94, d, $J_{8\beta,8\alpha}$ 9.8
9	91.43	
11	172.47	
12	109.34	5.75, s
13	167.29	
14	122.89	6.67, dd, $J_{14,15}$ 9.1, $J_{14,7}$ 1.0
15	148.61	6.80, dd, $J_{15,14}$ 9.1, $J_{15,7}$ 5.3
OMe	55.88	3.24, s

the stereochemical features of the molecule came from a detailed examination of its NMR spectra in comparison with those of phyllanthine **2** (see Table 2) and securitinine **5** (see Table 3), which are now reported for the first time at high field. All the proton spectra reported for the alkaloids in this paper were analysed by double irradiation and by COSY proton–proton correlation and all the ^{13}C NMR spectra were analysed by the DEPT technique and by the use of HETCOR proton–carbon correlations.

Table 4 Comparison of ^{13}C NMR data for the αβγδ-unsaturated lactone systems of securinine **1**, phyllanthine **2**, 4-epiphyllanthine **3**, allosecurine **4** and securitinine **5**

Carbon no.	δ_C				
	1[a]	**2**	**3**	**4**[a]	**5**
9	89.4	89.28	89.17	91.7	91.43
11	173.5	173.58	173.36	172.6	172.47
12	104.9	105.35	105.53	108.9	109.34
13	170.0	170.05	169.66	167.5	167.29
14	121.3	121.58	121.46	122.6	122.89
15	140.2	140.33	140.16	148.6	148.61

[a] Ref. 13.

The overall similarity of the spectra for all three compounds is strong evidence that they all possess the basic securinan-11-one ring system rather than the neosecurinan-12-one ring system (see below). Treatment of phyllanthine **2** with zinc and sulphuric acid followed by reduction of the intermediate lactam with lithium aluminium hydride furnishes the benzoquinolizidine **8**[8] whereas similar treatment of securitinine **5** furnishes the enantiomeric base **9**.[10] The production of these degradation products from the neosecurinan-12-one skeleton does not appear to be possible.

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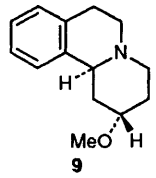

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The assignment of the absolute stereochemistry of both phyllanthine **2** and securitinine **5** is based on a combination of evidence adduced from degradative, synthetic, spectroscopic and chiroptical data. Similar methods were applied to the parent compounds securinine **1** and allosecurinine **4** and, in the case of securinine, its absolute stereochemistry is consistent with that obtained by the X-ray method applied to its hydrobromide[11] and, in the case of allosecurinine **4**, the relative stereochemistry was similarly confirmed by using its methiodide.[12] It is by no means certain whether the conformations adopted by these crystalline derivatives are the same as those adopted by the free bases in solution.

Table 4 shows the carbon chemical shifts of the αβγδ-

Table 5 ^{13}C and ^{1}H NMR data for margaritarine **10**

Carbon no.	δ_C	δ_H, multiplicity, coupling constants (Hz)
2′	67.77	2.82, dd, $J_{2',3'\beta}$ 11.5, $J_{2',3'\alpha}$ 2.0
3′	23.94	1.40, br dd, $J_{3'\alpha,3'\beta}$ 11.5, $J_{3'\alpha,2'}$ 2.0, 0.77, dddd, $J_{3'\beta,2'} = J_{3'\beta,3'\alpha} = J_{3'\beta,4'\alpha}$ 11.5, $J_{3'\beta,4'\beta}$ 3.5
4′	23.91	1.06, m, 4′α-H
		1.64, m, 4′β-H
5′	26.53	0.89, m, 5′α-H
		1.18, m, 5′β-H
6′	52.40	1.93, br d, $J_{6'\alpha,6'\beta}$ 11
		2.29, ddd, $J_{6'\beta,6'\alpha} = J_{6'\beta,5'\alpha}$ = 11, $J_{6'\beta,5'\beta}$ 2.6
7′	56.68	3.22, br d, $J_{7',8'\alpha}$ 6.7
8′	38.21	2.43, dd, $J_{8'\alpha,8'\beta}$ 10.6, $J_{8'\alpha,7'}$ 6.7
		1.40, d, $_{8'\beta,8'\alpha}$ 10.6
9′	89.52	
11′	173.08	
12′	111.72	5.61, d, $J_{12',14'\beta}$ 2.3
13′	171.16	
14′	32.41	2.92–3.08, m, 14′α-H
		2.27, ddd, $J_{14'\beta,14'\alpha}$ 16.0, $J_{14'\beta,15'}$ 9.1, $J_{14'\beta,12'}$ 2.3
15′	61.43	2.68, ddd, $J_{15',14'\beta}$ 9.1, $J_{15',14'\alpha}$ 6.0, $J_{15',7'}$ 1.3
2	122.07	7.06, d, $J_{2,NH}$ 2.2
3	113.42	
α	25.81	3.03–3.16, m, 2.82–2.96, m
β	46.27	2.76–3.10, m
3a	127.10	
4	118.59	7.61, br d, $J_{4,5}$ 7.6
5	119.32	7.10, ddd, $J_{5,4}$ 7.6, $J_{5,6}$ 7.0, $J_{5,7}$ 1.0
6	122.11	7.18, ddd, $J_{6,7}$ 8.0, $J_{6,5}$ 7.0, $J_{6,4}$ 1.0
7	111.21	7.34, br d, $J_{7,6}$ 8.0
7a	136.46	
1-NH		8.16, br
NH		1.92, br, D_2O exchangeable.

Table 6 Comparison of ^{13}C NMR data for the lactone systems of margaritarine **10**, 14,15-dihydro-15α-methoxyphyllochrysine **11**, 14,15-dihydroallosecurinine **12** and 14,15-dihydrosecurinine **13**

Carbon no.	δ_C			
	10	**11**	**12**[a]	**13**[a]
9	89.52	89.84	89.7	91.0
11	173.08	172.78	172.7	175.4
12	111.72	112.99	111.6	109.1

[a] Ref. 14.

unsaturated lactone systems for securinine **1** and allosecurinine **4** compared with the methoxy derivatives phyllanthine **2**, 4-epiphyllanthine **3**, and securitinine **5**. By a combination of molecular mechanics calculations and NMR spectral analysis Livant and Beutler[13] have suggested that securinine **1** adopts a chair conformation for the piperidine ring in which the 2-H and the nitrogen lone pair are in an *anti* relationship whereas the piperidine ring of allosecurinine **4** adopts a twist-boat conformation in which the 2-H and the nitrogen lone pair are in a *gauche* relationship. This is reflected in the marked difference of the carbon chemical shifts of the αβγδ-unsaturated lactone system for securinine **1** and allosecurinine **4**. There are also differences in the chemical shifts of the carbons of the piperidine ring. The difference in stereochemistry is also reflected in the chemical shift of the 2-H in the ^{1}H NMR spectra of these compounds; that in securinine **1** (δ_H 2.10) being at higher field than that in allosecurinine **4** (δ_H 3.65).[13] Examination of the data in Table 4 clearly indicates that both phyllanthine **2** and epiphyllanthine **3** belong to the securinine series and that securitinine **5** belongs to the *allo*-series. This is also confirmed by the chemical shifts of the 2-H in the ^{1}H NMR spectra of these compounds; those in phyllanthine **2** (δ_H 2.59) and 4-epiphyllanthine **3** (δ_H 2.09) being at higher field than that in securitinine **5** (δ_H 3.90).

If the piperidine rings of phyllanthine **2** and securitinine **5** adopt the same conformations as their parent bases, then the axial 4β-methoxy group in phyllanthine will be in close proximity to the 2-H, and the 4α-methoxy group in securitinine will also be in close proximity to the 2-H; this is reflected in the markedly lower field resonances of these protons compared with those of the parent bases. Indeed, a nuclear Overhauser effect was detected between the methoxy group and the 2-H in phyllanthine. The 2-H proton resonance in the spectrum of 4-epiphyllanthine is at higher field than its epimer as expected for an equatorial methoxy group. The assignment of this stereochemistry is supported by the magnitude of the coupling constants for the 2-, 3- and 4-H signals of 4-epiphyllanthine (see Table 1) and these are summarized in Fig. 1.

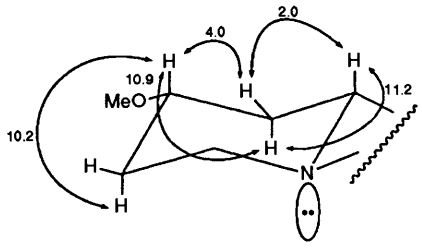


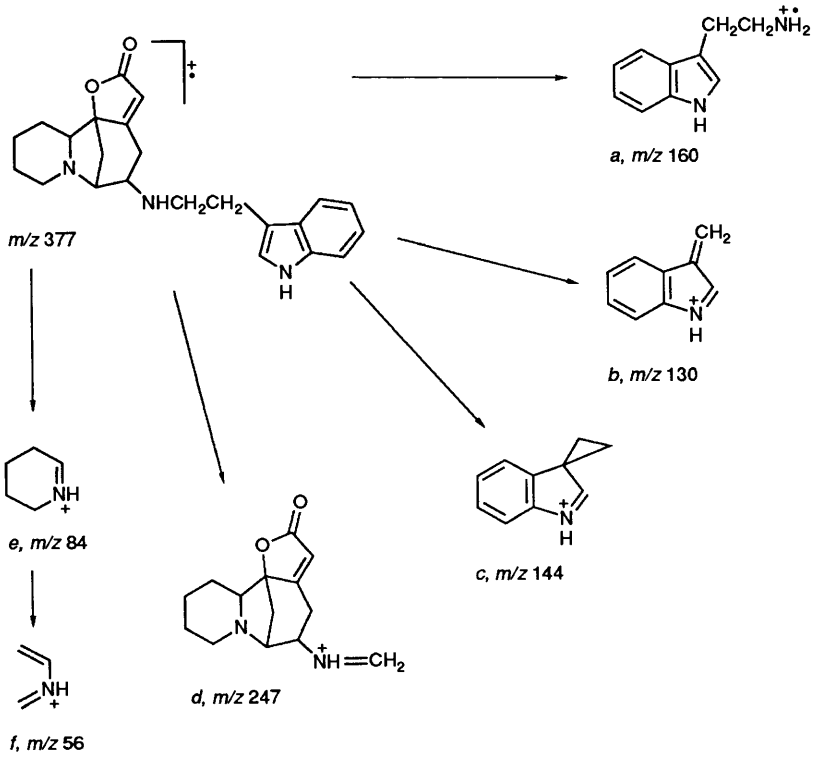
Fig. 1 Coupling constants (Hz) for the piperidine ring of 4-epiphyllanthine **2**

Another minor base isolated from *M. indica* was shown by high resolution mass spectrometry to possess the molecular formula $C_{23}H_{27}N_3O_2$. It was assigned structure **10** on the grounds of the following evidence. Examination of the infrared spectrum suggested the presence of an αβ-unsaturated lactone since it exhibited bands at 1745 and 1630 cm^{-1}, and there were corresponding signals in the ^{13}C NMR spectrum at δ_C 173.08 for the carbonyl group and at δ_C 111.72 for C-12′. The ^{1}H NMR spectrum exhibited a doublet at δ_H 5.61 (12′-H) with allylic coupling to a complex signal at δ_H 2.27 (14′β-H) which was further coupled to a signal at δ_H 2.68 (15′-H). The HETCOR correlation indicated that these last-mentioned signals were related to a methylene and a methine carbon respectively so that the base must belong to the 14,15-dihydrosecurinan-11-one series rather than the neosecurinan-12-one series (see below).

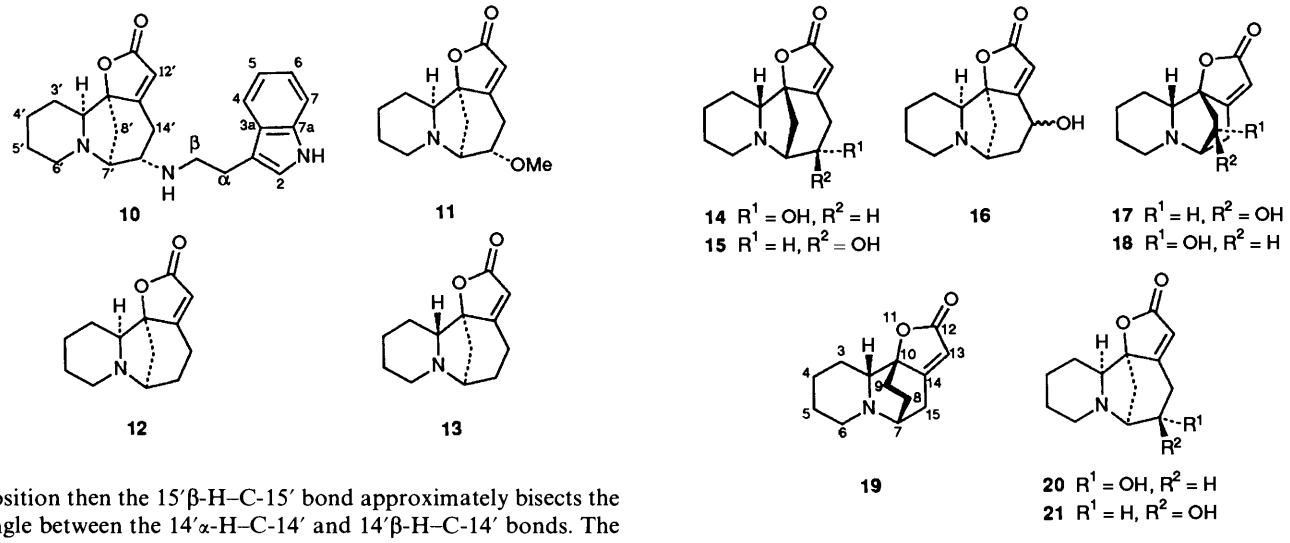
There are also signals in the ^{1}H and ^{13}C NMR spectra which were attributed to a β-substituted indole and the infrared spectrum exhibited a band at 3380 cm^{-1} assigned to NH stretching.

A detailed consideration of the mass spectrum of the alkaloid (see Scheme 2) confirmed the presence of a tryptamine residue as indicated by the ions *a*, *b*, *c* and *d*. That the piperidine ring was unsubstituted was apparent from the base peak *e* and the daughter ion *f*. These peaks are also present in the spectra of 14,15-dihydro-15α-methoxyphyllochrysine **11**[1] and 14,15-dihydrosecurinine **13**.[9] In Table 6 a comparison is made of the ^{13}C chemical shifts of the lactone ring of margaritarine **10**, 14,15-dihydro-15-α-methoxyphyllochrysine **11**, 14,15-dihydroallosecurinine **12**,[14] and 14,15-dihydrosecurinine **13**.[14] It is clear from these data that margaritarine **10** belongs to the allosecurinine rather than the securinine stereochemical series. Further evidence of this is the ^{1}H NMR chemical shift of the 2′-H which occurs at δ_H 2.82 in margaritarine **10** and near δ_H 3 in 14,15-dihydro-15α-methoxyphyllochrysine **11**.

The configuration of the tryptamine residue also follows from the ^{1}H NMR spectrum. Examination of a Dreiding model of the alkaloid shows that if the tryptamine residue occupies the 15′α-



Scheme 2



position then the 15′β-H–C-15′ bond approximately bisects the angle between the 14′α-H–C-14′ and 14′β-H–C-14′ bonds. The 15′β-proton thus exhibits coupling constants of 6.0 and 9.1 Hz to 14′α- and 14′β-H respectively as well as a small coupling constant to the 7′-H. The 14′β-H can be clearly identified by its characteristic allylic coupling to the 12′-H.

The stereochemistry of margaritarine **10** is thus the same as that of 14,15-dihydro-15α-methoxyphyllochrysine **11**; the latter was confirmed by a single crystal X-ray structural determination.[1] It is therefore likely that the biosynthesis of margaritarine **10** involves the conjugate addition of tryptamine to allosecurinine **4**.

Securinol A was isolated from a polar fraction in the chromatographic separation of the *Margaritaria* alkaloids. It was identified by its melting point, specific rotation, and ultraviolet, infrared and mass spectra which corresponded to those recorded by Horii and his co-workers[15] who isolated this alkaloid along with its epimer securinol B, and another minor base, securinol C, from *S. suffruticosa*. These workers advanced structures **14**, **15** and **16** for the three alkaloids.[15,16] Treatment of securinol A with methanesulphonyl chloride and pyridine afforded viroallosecurine **7** so that the stereochemistry of the ring system was assumed to be that depicted in structure **14**. The position of the hydroxy group followed from the mass spectrum which exhibited a prominent daughter ion at *m/z* 191, attributed to the loss of CH_2=CHOH from the molecular ion. The stereochemistry of the hydroxy group was based on first order analysis of the ^{1}H NMR spectral signals due to the hydroxymethine proton (δ_H 4.23) and its neighbouring methylene and methine protons, and by application of Brewster's benzoate rule.[15]

Since viroallosecurinine **7** and allosecurinine **4** bear to each other an antipodal relationship, then it follows that 14,15-dihydro-15α-methoxyphyllochrysine **11**, the structure and absolute stereochemistry of which are based on the X-ray method,[1] is the methyl ether of the 15-epimer of the antipode of securinol A. Hence there should be similarity between certain features of their NMR spectra. Livant and Beutler[13] have

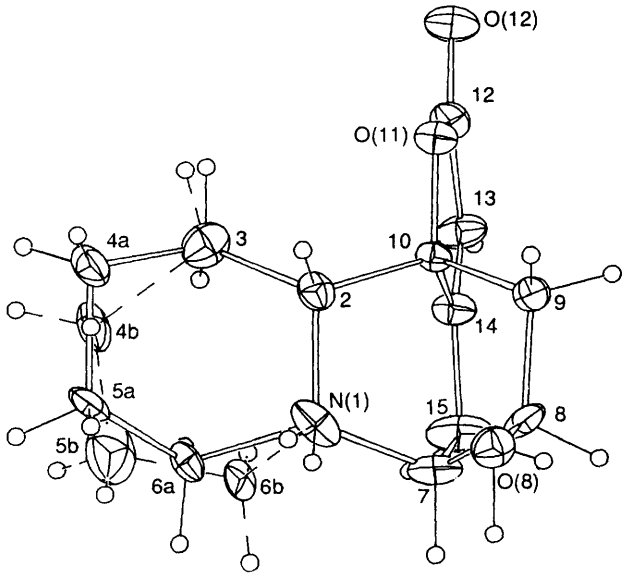


Fig. 2 The cation. 20% Thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have arbitrary radii of 0.1 Å.

Table 7 Non-hydrogen positional parameters

Atom	*x*	*y*	*z*
Br	0.457 69(5)	0.529 9(1)	0.550 9(1)
N(1)	0.363 2(4)	0.127(1)	0.208 1(9)
C(2)	0.314 8(4)	0.123(1)	0.349(1)
C(3)	0.300 5(5)	0.295(1)	0.404(1)
C(4a)*	0.269 1(9)	0.401(3)	0.287(2)
C(5a)*	0.317 3(9)	0.402(3)	0.135(2)
C(6a)*	0.372 0(8)	0.316(2)	0.156(2)
C(4b)*	0.293 9(9)	0.402(3)	0.229(3)
C(5b)*	0.350(1)	0.399(3)	0.121(4)
C(6b)*	0.400 0(9)	0.273(2)	0.190(3)
C(7)	0.414 3(4)	0.009(2)	0.243(1)
C(8)	0.381 6(4)	−0.156(1)	0.255(1)
O(8)	0.346 5(3)	−0.189 4(8)	0.116 0(8)
C(9)	0.341 6(5)	−0.158(1)	0.407(1)
C(10)	0.339 4(3)	0.012(1)	0.477 7(9)
O(11)	0.303 5(2)	0.020 1(8)	0.623 4(7)
C(12)	0.339 8(4)	0.076(1)	0.748(1)
O(12)	0.318 9(3)	0.098(1)	0.882 3(8)
C(13)	0.402 1(4)	0.100(1)	0.684(1)
C(14)	0.402 3(4)	0.062(1)	0.531(1)
C(15)	0.447 1(4)	0.053(2)	0.397(1)
O(0)	0.564 1(3)	0.244(1)	0.612 7(9)

* Site occupancy factor = 0.5.

examined the high field ^{1}H and ^{13}C NMR spectra of impure securinol A and have attempted to interpret them in terms of structure **14**. Armed with a knowledge of the spectral data of 14,15-dihydro-15α-methoxyphyllochrysine **11**, we also attempted to interpret the NMR spectra of pure securinol A in terms of structure **14**. It became apparent that the interpretation of Livant and Beutler was erroneous.[13] In particular, a signal assigned by these authors to C-2 at δ_C 65.2 in the ^{13}C NMR spectrum correlated with a signal at δ_H 2.7 in the proton spectrum, whereas, in the spectra recorded by us, the carbon assigned to C-2 (δ_C 62.84)—the analogous carbon in 14,15-dihydro-15α-methoxyphyllochrysine **11** occurred at δ_C 66.73—correlated with a signal at δ_H 3.23, which brought into question whether securinol A actually belonged to the viroallosecurinine stereochemical series. To fit the values of the proton coupling constants and the proton–carbon correlations in terms of structure **14** for securinol A it was necessary to reverse the

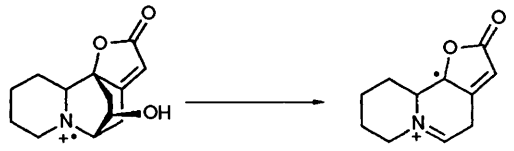
Table 8 ^{13}C and ^{1}H NMR data for securinol A **17**

Carbon no.	δ_C	δ_H, multiplicity, coupling constants (Hz)
2	62.84	3.23, dd, $J_{2,3\alpha}$ 11.3, $J_{2,3\beta}$ 2.2
3	24.20	0.89, dddd, $J_{3\alpha,4\beta} = J_{3\alpha,3\beta} = J_{3\alpha,2} = 11.3$, $J_{3\alpha,4\alpha}$ 4.5, 1.53–1.60, m, 3β- and 5-H
4	22.41	1.79, m, 4α-H, 1.30–1.49, m, 4β-H and 5-H
5	25.62	1.53–1.60, m, 5- and 3β-H, 1.30–1.49, m, 5- and 4-H
6	52.49	2.96–3.00, m, 6-H
7	59.24	3.05, ddd, $J_{7,15}$ 4.4, $J_{7,8}$ 2.9, $J_{7,15'}$ *ca.* 1
8	69.76	4.23, ddd, $J_{8,9\beta}$ 9.1, $J_{8,7}$ 2.9, $J_{8,9\alpha}$ 1.6
9	41.14	2.17, dd, $J_{9\alpha,9\beta}$ 13.2, $J_{9\alpha,8\alpha}$ 1.6, 1.98, dd, $J_{9\beta,9\alpha}$ 13.2, $J_{9\beta,8}$ 9.1
10	84.48	
12	173.63	
13	112.66	5.74, dd, $J_{13,15} = J_{13,15'} = 1.5$ Hz
14	171.78	
15	30.17	2.95, ddd, $J_{15,15'}$ 18.6, $J_{15,7}$ 4.4, $J_{15,13}$ 1.5, 2.44, ddd, $J_{15',15}$ 18.6, $J_{15',13}$ 1.5, $J_{15',7}$ *ca.* 1

assignments of Livant and Beutler[13] for C-7 and C-13. The proton–carbon correlations then meant that the 15-H resonated at δ_H 3.05, a value at too high a field for a hydroxymethine proton (*cf.*, 14,15-dihydro-15α-methoxyphyllochrysine, δ_H 3.58), and the C-15 resonated at δ_C 59.24, a value at too high a field for such a carbon (*cf.*, δ_C 79.76 for 14,15-dihydro-15α-methoxyphyllochrysine). We were therefore suspicious of the structural assignment of Horii and his co-workers.[15]

Since only a limited amount of securinol A was available we had resort to the X-ray method as applied to the hydrobromide of securinol A (Fig. 2) (Table 7). The structure and absolute stereochemistry are thus as depicted in **17**. This skeleton represents a new type for the *Securinega* alkaloids and we propose the trivial name neosecurinan-12-one, as in structure **19**, for this ring system.

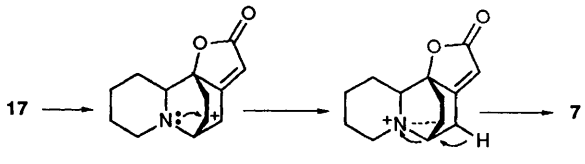
The NMR spectral data (see Table 8) of the alkaloid can now be interpreted in a satisfactory manner in terms of structure **17**, as can the major mass spectral fragmentation which is depicted in Scheme 3. When securinol A is treated with methanesulphonyl



m/z 235 *m/z* 191

Scheme 3

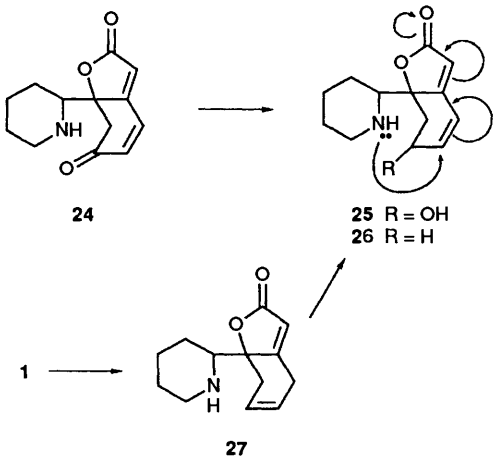
chloride and pyridine it is reasoned that the carbocation **22** is produced (see Scheme 4) which can be captured by the lone pair



22 **23**

Scheme 4

of the nitrogen to produce the aziridinium ion **23**. The ionization of the intermediate mesylate could, of course, be anchimerically assisted by the nitrogen lone pair. Collapse of the intermediate **23** would then supply viroallosecurinine **7**.



Scheme 5

The intermediate **24** (see Scheme 5) has been postulated by Spenser and his co-workers [3] as being involved at a late stage in the biosynthesis of the *Securinega* alkaloids. Reduction of the carbonyl group and formation of a bond from the nitrogen to the former carbonyl carbon atom, as postulated previously,[2] would yield the securinan-11-one skeleton but reduction of the carbonyl group followed by conjugate addition of the piperidine nitrogen as depicted in **25** would yield either securinol A **17** or its epimer securinol B **18**. Precedent exists for this latter reaction. Securinine **1** on reduction with aluminium amalgam and wet ether yields the piperidinyl lactone **27**.[17] On heating to 150–160 °C, the double bond moves into conjugation and the lactone **26** can be isolated. However, if the temperature is raised to 190 °C the nitrogen lone pair undergoes conjugate addition to the terminus of the unsaturated system thus generating the neosecurinan-12-one system,[18] albeit of antipodal stereochemistry to securinol A.

Horii and his co-workers [16] showed that securinol B yielded viroallosecurinine **7** on treatment of its mesylate with collidine. It is therefore likely that securinol B has structure **18**. Securinol C, however, on similar treatment yielded allosecurinine **4**.[16] It is therefore tempting to postulate that securinol C possesses structure **20** and is therefore related to 14,15-dihydro-15α-methoxyphyllochrysine **11**. The specific rotation of securinol C is small and negative whereas that of compound **11** is small and positive, so that the structural determination of securinol C requires further work.

Mensah *et al.*[20] have recently isolated a new alkaloid from the leaves of *Phyllanthus discoideus* which they claim is a hydroxylated securinine derivative. Since the physical properties of the new base were different from those of securinol A, securinol B and securinol C they proposed structure **21** for this alkaloid. The ^{13}C NMR chemical shifts reported for the base are inconsistent with the assigned structure. The spectroscopic data presented, however, do not allow a definite structural proposal.

Experimental

Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were determined with a Perkin-Elmer model 141 automatic polarimeter. NMR spectra were determined for solutions in deuteriochloroform using a Bruker AM 300 instrument. Infrared spectra were determined for potassium bromide discs using a Perkin-Elmer 283 instrument. Electronic spectra were determined for methanolic solutions using a Hewlett-Packard 8450A spectrophotometer. Mass spectra (35 eV) were measured using a Hewlett-Packard 5896 instrument. High resolution data were obtained through the courtesy of Dr. J. K. McLeod at the Australian National University. Merck silica gel 60 was used for column chromatography and radial chromatography was carried out using a Harrison Research Chromatotron with plates coated with Merck Kieselgel PF_{254} under an atmosphere of nitrogen.

Extraction of Margaritaria indica.—The chopped fresh bark (32 kg) of *Margaritaria indica* (Dalz.) G. L. Webster (Euphorbiaceae) collected at Sijunjung, West Sumatra,[1] was allowed to stand for 5 d with successive portions of methanol (4 × 40 dm^3) and the combined extract was concentrated (1 dm^3) under diminished pressure. The concentrated extract was diluted with sulphuric acid (5%, 2 dm^3) and set aside overnight. The acidic layer was decanted and the residue was washed with sulphuric acid (2%, 2 × 500 cm^3). The combined acidic solution was basified with concentrated ammonia and extracted with chloroform (6 × 1 dm^3). The chloroform extract was washed with saturated brine, dried (Na_2SO_4) and evaporated to dryness under diminished pressure. The crude extract (91 g), so obtained, was crystallized first from dichloromethane–hexane and then from ethyl acetate–hexane to afford (2α)-securinan-11-one (allosecurinine) **4** as yellow plates (21.0 g), m.p. 136–137 °C (lit.,[1] 136–137 °C). The mother liquors were evaporated under reduced pressure and the residue was pre-adsorbed on silica gel (50 g) and chromatographed over the same adsorbent (400 g) with increasing amounts of ether in hexane, containing triethylamine (1%). Fractions which had the same behaviour on TLC were combined. The least polar fraction was crystallized first from dichloromethane–hexane and next from hexane which afforded needles (540 mg) of (2α,15α)-14,15-dihydro-15-methoxysecurinan-11-one **11**, m.p. 141 °C (lit.,[1] 141 °C).* The second most polar fraction was crystallized first from dichloromethane–hexane and next from methanol to afford securinan-11-one (securinine) **1** (2.1 g) as yellow needles, m.p. 143 °C (lit.,[5,19] 141–142 and 145 °C). The third fraction showed many spots on TLC and yielded a brown gum on evaporation (see below). The fourth fraction was crystallized from ethyl acetate–hexane to afford more allosecurinine **4** (11.8 g). The fifth fraction was crystallized from ethyl acetate and yielded yellow plates (1.7 g) of (2α,4α)-4-methoxysecurininan-11-one (securitinine) **5**, m.p. 130 °C (lit.,[10] 129–130 °C); $[\alpha]_D^{20}$ −1015° (*c* 0.17, EtOH) (lit.,[10] −952°, EtOH); λ_{max}/nm 255 (log ε 4.38); ν_{max}/cm^{-1} 3490, 1810, 1755, 1625, 1080, 895 and 850; *m/z* 247 (M^+, 10%), 114 (41), 106 (36), 82 (39), 78 (42), 56 (100) and 55 (15). The third fraction was subjected to radial chromatography with increasing amounts of ether in hexane, containing 1% triethylamine, as eluent. The least polar material crystallized from ethyl acetate–hexane as yellow plates (28 mg) of (4β)-4-methoxysecurinan-11-one (phyllanthine) **2**, m.p. 97–98 °C (lit.,[8] 96–98 °C); $[\alpha]_D^{20}$ −1508° (*c* 0.09, EtOH) (lit.,[8] −898°, $CHCl_3$); ν_{max}/cm^{-1} 1740s, 1625m and 1090m; *m/z* 247 (15%, M^+), 216 (2), 134 (28), 114 (77), 106 (59), 82 (53), 79 (9), 78 (57), 56 (100) and 55 (20). Further elution supplied (4α)-4-*methoxysecurinan*-11-*one* (4-epiphyllanthine) **3** (28 mg) which crystallized from ethyl acetate–hexane as yellow needles, m.p. 82–84 °C; $[\alpha]_D^{20}$ −753° (*c* 0.06, EtOH) (Found: M^+, 247.1207. $^{12}C_{14}{}^{1}H_{17}{}^{14}N^{16}O_3$ requires M, 247.1208); ν_{max}/cm^{-1} 1740s, 1625m and 1090m; *m/z* 247 (M^+, 24%), 216 (2), 134 (52), 114 (100), 107 (11), 106 (74), 82 (56), 79 (20), 78 (66), 56 (96) and 55 (12). Further elution supplied 3-{*N*-[(2α,15α)-14,15-*dihydro*-11-*oxosecurinan*-15-*yl*]-2-*aminoethyl*}-1H-*indole* (margaritarine) **10** (70 mg) as an amorphous solid which softened at 66–68 °C; $[\alpha]_D^{20}$ +106.9° (*c* 0.06, EtOH) (Found: M^+, 377.2103. $^{12}C_{23}{}^{1}H_{27}{}^{14}N_3{}^{16}O_2$ requires M, 377.2103); ν_{max}/cm^{-1} 3380s,

* The HETCOR spectrum of this compound showed that the previous assignments[1] of 3α- and 4β-H should be reversed.

1745s, 1630m, 1430m, 1330m, 910m and 735s; *m/z* 377 (M^+, 2%), 247 (24), 218 (7), 217 (7), 203 (15), 174 (18), 160 (17), 144 (19), 134 (11), 131 (53), 130 (92), 106 (31), 97 (44), 96 (12), 84 (100), 82 (13), 78 (24), 77 (16), 56 (10) and 55(12). The most polar fraction afforded securinol A **17** which crystallized from ethyl acetate as plates (15 mg), m.p. 135 °C (lit.,[15] 135–136 °C); $[\alpha]_D^{20}$ +57.1° (*c* 0.13, MeOH) (lit.,[15] +58°, $CHCl_3$); λ_{max}/nm 218 (log ε 4.27); ν_{max}/cm^{-1} 3500br, 1800, 1765 and 1655; *m/z* 235 (M^+, 32%), 206 (10), 192 (12), 191 (100), 176 (14), 163 (17), 162 (11), 140 (34), 135 (16), 134 (27), 110 (37), 84 (14) and 55 (10). The hydrobromide crystallized from ethyl acetate–methanol as stout rods, m.p. 115–120 °C.

Structure determination

Data sets *h,k,l* and $\bar{h},\bar{k},\bar{l}$ were measured at *ca.* 295 K within the limit $2\theta_{max} = 50°$ using an ENRAF-Nonius CAD-4 diffractometer, equipped with monochromatic Mo-Kα radiation source ($\lambda = 0.7107_3$ Å) and operating in conventional $2\theta/\theta$ scan mode; 1514 and 1513 independent reflections were obtained, 1039 and 1057 with $I > 3\sigma(I)$ being considered 'observed' and used in independent full matrix least squares refinements after Gaussian absorption correction and solution of the structure by the heavy atom method. Anisotropic thermal parameters were refined for the non-hydrogen atoms; $(x, y, z, U_{iso})_H$ were included constrained at estimated values. Conventional residuals on $|F|$ at convergence, R,R' were 0.048, 0.049 (*h,k,l*) and 0.052, 0.055 ($\bar{h},\bar{k},\bar{l}$); for the opposite chirality they were 0.062, 0.063 (*h,k,l*) and 0.065, 0.068 ($\bar{h},\bar{k},\bar{l}$). Neutral atom complex scattering factors were employed (Br^- excepted); computation used the XTAL 3.0 program system[21] implemented by S. R. Hall. Pertinent results are presented in the Figures and Tables; material deposited comprises structure factor amplitudes, thermal and hydrogen atom parameters and non-hydrogen atom geometries.*

Crystal Data.—$C_{13}H_{17}NO_3^+ \cdot Br^- \cdot H_2O \equiv C_{18}H_{20}BrNO_4$, M = 334.2. Orthorhombic, space group $P2_12_12_1$ (D_2^4, No. 19), a = 21.876(6), b = 8.243(4), c = 8.157(3) Å, V = 1471(1) $Å^3$, D_c (Z = 4) = 1.51 g cm^{-3}, $F(000)$ = 684, μ_{Mo} = 27.1 cm^{-1}; specimen: 0.30 × 0.14 × 0.25 mm; $A^*_{min,max}$ = 1.37, 1.84.

Abnormal Features.—(i), Atoms C(4,5,6) were disordered over two sets of sites whose populations refined to values not differing significantly from 0.5 and were constrained at the value. Surprisingly, both sets a, b made up rings essentially in similar 'boat' conformations. Consideration of a Dreiding model suggested that the large envelope encompassing C(15) was a foil for disorder of that atom corresponding to two different ring conformations and that, by virtue of close contacts between the two components of H(6B) and H(15B), disorder between the two rings was concerted, further resulting in the enlarged envelope for N(1). This resulted in successful modelling and stable refinement of C(15) as two components separated by *ca.* 0.45 Å, but with R increased from 0.048 to 0.049 and less realistic envelopes for the C(5,6) components. Accordingly, results are presented in terms of the model shown.

(ii), A difference map artefact was modelled as a water molecule oxygen, refining with site occupancy not significantly different from 1, at which value it was constrained. Associated hydrogen atoms were located in difference maps, as was that of the cationic hydroxyl atom.

* For details of the deposition scheme see 'Instructions for Authors,' issue 1, 1991.

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