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RELATIVE CONFIGURATION OF THE ALKALOID AUGUSTAMINE*

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Key Word Index—*Crinum augustum*, Amaryllidaceae, alkaloid, augustamine, relative configuration, ^{1}H NMR, ^{13}C NMR, high resolution mass spectrometry

Abstract—Structure and relative configuration of the alkaloid augustamine were established by full spectral analysis

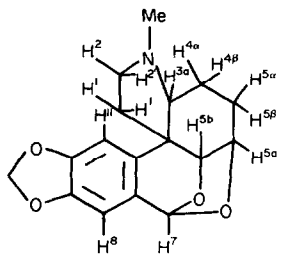
INTRODUCTION

The new alkaloid augustamine has been isolated from *Crinum augustum* Rox and its purification and brief characterization as new base '2' has been published in [1] A six-membered alkaloidal ring system, containing a methylenedioxy phenyl system, with sum formula $C_{17}H_{19}NO_4$ was derived from UV, IR, mass spectral and 60 MHz ^{1}H NMR data It did not belong to the epoxy alkaloid family. The 300 MHz ^{1}H NMR and 20 MHz ^{13}C NMR studies of augustamine have now been completed, the results of which led to the structure and relative configuration of augustamine presented in this paper Augustamine has a specific rotation of $[\alpha]_D^{20} = -83\ 0°$ ($CHCl_3$, *c* 1 4)

RESULTS AND DISCUSSION

The 300 MHz ^{1}H NMR spectra of augustamine allow the identification of a seven-, a four- and a one-spin system in addition to the signals for methylene dioxy, two *para*-positioned aryl- and three N-Me-protons identified in [1] Together with the information from the ^{13}C NMR spectra, which reveal signals for five quaternary (*s*), six tertiary (*d*), five secondary (*t*) and one primary (*q*) carbons, six structural fragments could be derived in accordance with the sum formula $C_{17}H_{19}NO_4$ (Scheme 1)

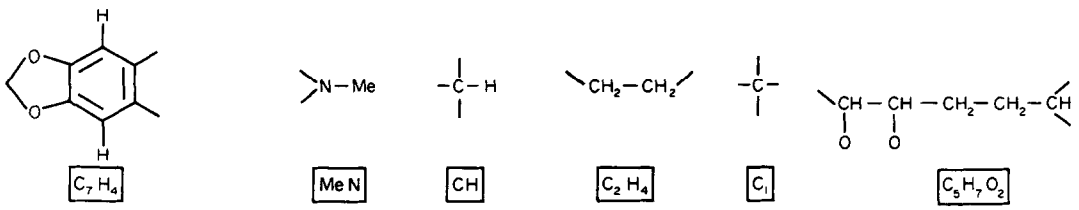
The systematic combination of these fragments taking advantage of all spectral information led to the planar formula of the required six-membered ring system of augustamine as **1**



1

The proton signal assignment to specific protons has been done on the basis of their shifts, multiplicities and their couplings Proton–proton interactions have been evaluated by selective decoupling as well as by

*Part 4 in the series "Alkaloids of *Crinum augustum*" For Part 3 see Frahm, A W, Ali, A A and Kating, H (1981) *Phytochemistry* **20**, 1735



Scheme 1 Structural fragments of augustamine

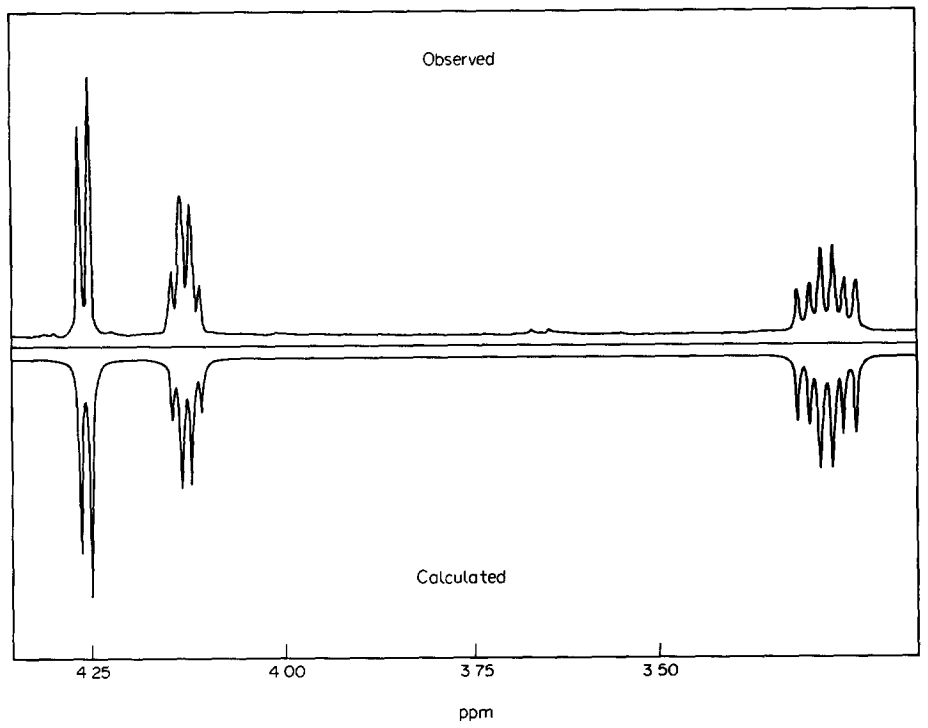
the size of their coupling constants, as far as they could not be derived directly from the normal spectrum or by subspectral analysis In the case of spectral overlapping of parts of the four- and seven-spin systems spectra simulation could overcome these difficulties The complete data set is found in Table 1 There are no exchangable protons The seven-spin system consists of the protons H–5b, H–5a, H–3a, H–5β, H–5α, H–4β and H–4α The signal at δ 4 26 assignable to H–5b is observed as a doublet, coupling with the signal appearing as a multiplet at δ 4 13 belonging to the proton H–5a, which on irradiation causes the H–5b signal to collapse to a singlet Additionally the multiplets at δ 1 84 and 1 67 due to H–5β and H–5α are simplified The residual splittings are missing a 4 0 and 3 4 Hz coupling, respectively The low field shift of the vicinal protons H–5a and H–5b would not fit with an oxiran ring system and must originate from one oxygen substituent each

The signal at δ 2 39 as a doublet of doublets is attributable to H–3a, the irradiation of which induces simplification of both the multiplet signals at δ 1 35 and 1 25 correlated to H–4β and H–4α Selective decoupling of H–4α afforded, as expected, a collapse of the H–3a signal to a doublet The multiplet of H–4β simplified with the disappearance of the large coupling (−14 7 Hz) Furthermore the signals of H–5α and H–5β showed a simplified splitting pattern This is evidence for a vicinal linkage between the geminal protons H–4α and H–4β and H–5α and H–5β, which also show a geminal coupling The four-spin system consists of the H–2, H–2′, H–1 and H–1′ protons, each one of which couples with all three others The low field shift of H–2 and H–2′ in com-

Table 1 300 MHz ^{1}H NMR spectrum of augustamine*

Proton	δ(ppm)	Multiplicity	Coupling protons	J (Hz)
H–11	6 68	*s*	—	—
H–8	6 55	*s*	—	—
O–CH_2–O	5 85	*s*	—	—
H–7	5 78	*s*	—	—
H–5b	4 26	*d*	5b, 5a	4 4
H–5a	4 13	*ddd*	5a, 5b	4 4
			5a, 5α	3 4
			5a, 5β	4 0
H–2	3 27	*ddd*	2, 1	9 0
			2, 2′	9 7
			2, 1′	4 9
H–2′	2 47	*ddd*	2′, 1′	11 0
			2′, 2	−9 7
			2′, 1	6 0
H–3a	2 39	*dd*	3a, 4α	3 6
		broadened lines	3a, 4β	3 5
H–1	2 25	*ddd*	1, 1′	−13 4
			1, 2	9 0
			1, 2′	6 0
N–Me	2 20	*s*	—	—
H–1′	1 91	*ddd*	1′, 1	−13 4
			1′, 2′	11 0
			1′, 2	4 9
H–5β	1 84	*dddd*	5β, 5α	−14 6
			5β, 4α	12 3
			5β, 4β	4 2
			5β, 5a	4 0
H–5α	1 67	*dddd*	5α, 5β	−14 6
			5α, 4α	4 3
			5α, 4β	3 9
			5α, 5a	3 4
H–4β	1 35	*dddd*	4β, 4α	−14 7
			4β, 5α	3 9
			4β, 5β	4 2
			4β, 3a	3 5
H–4α	1 25	*dddd*	4α, 4β	14 7
			4α, 5β	12 3
			4α, 5α	4 3
			4α, 3a	3 6

*Solvent $CDCl_3$



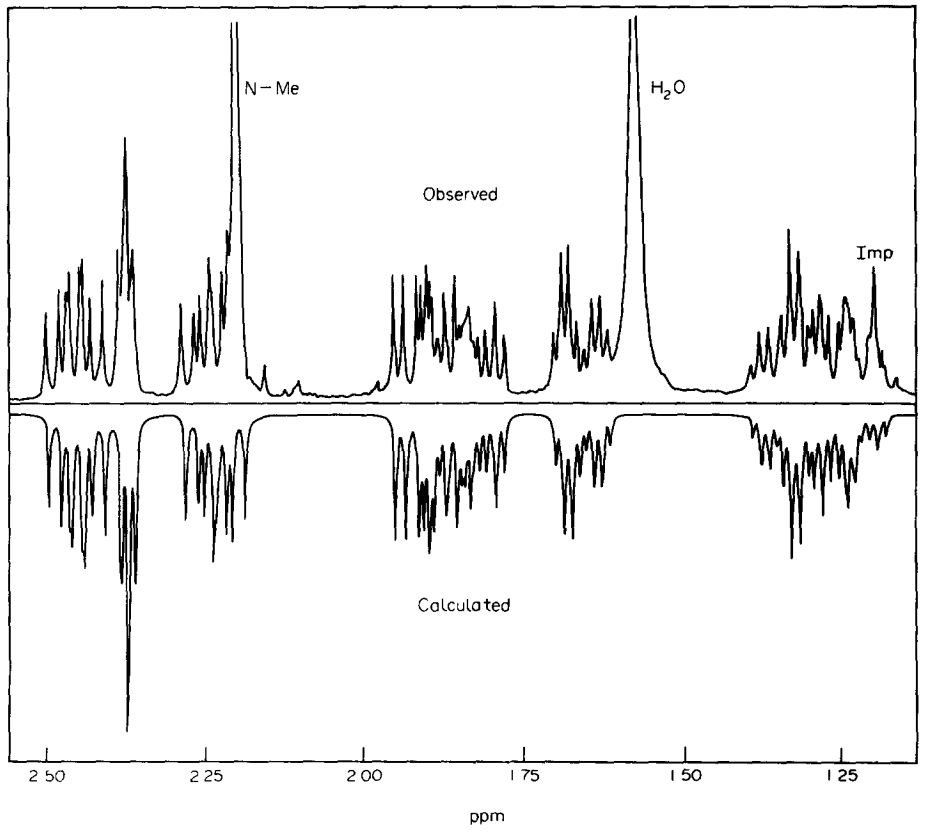


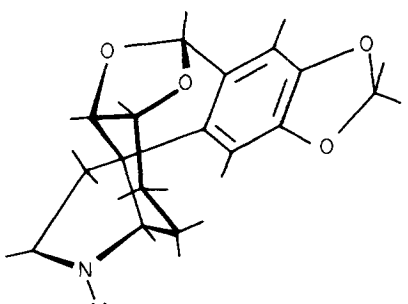
Fig 1 Observed and simulated ^{1}H NMR spectra of augustamine

parison with H-1 and H-1′ is best understood if C-2 is linked to the N-Me-group at δ 2 2, while C-1 should be bonded to a quarternary carbon atom

To avoid difficulties arising from the partial overlapping of the four- and the seven-spin system and to assure and refine the spectral parameters which could be derived by first order analysis, separate spectra simulations of both parts have been performed using the simulation part of the program NMRIT [2] in combination with the plot program KOMBIP [3] The calculated and superimposed spin systems together with the observed spectra are portrayed in Fig 1 The observed and the calculated spectra parts are in excellent agreement

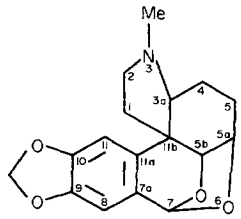
The singlet signal at δ 5 78 is attributed to H-7 in a benzaldehyde acetal moiety which could explain the strong paramagnetic shift, comparable to that of the methylenedioxy proton group at δ 5 85

In summary the seven-proton spin system is contained in a cyclohexane ring B, which is linked with the pyrrolidine ring A, constituting the four-proton system, and with the dioxolane ring C including the H-7 proton The juncture between rings B and A and between B and C has been elucidated by means of the size of coupling constants of the key protons H-3a, H-5b and H-5a H-3a couples with H-4α and H-4β, the coupling constants of which are nearly equal in size (3 6, 3 5 Hz), thus giving evidence of the equatorial position of H-3a and therewith of the *cis*-juncture of cyclohexane- and pyrrolidine-rings B and A The proton H-5a signal appears as a so-called 'quartet', originating from nearly equal size couplings of *ca* 4 Hz with H-5b, H-5α and H-5β This result requires an equatorial position of H-5a as well Consequently ring B and dioxolane ring C are also linked in a *cis*-juncture. This applies also for rings B and D The alkaloid augustamine is, therefore, identified as an all-*cis* tetracyclic system with an annelated methylenedioxy phenyl part Structure **2** represents the relative configuration.



2

The ^{13}C NMR spectra of augustamine gave additional evidence of the proposed structure All signals have been assigned on the grounds of shift values, signal multiplicities, selective heteronuclear decoupling experiments and by comparison with δ-values of other Amaryllidaceae alkaloids The results are summarized in Table 2 Downfield δ 100 there are identified eight signals, seven of them belong to the methylenedioxy phenyl system In the coupled spectrum the two one-bond doublets show no further splitting, thus giving evidence for the 1,2,4,5-substitution pattern of the aromatic ring The triplet signal at δ 100 9 is correlated to the methlenedioxy carbon The signals for C-8 to C-11 (**3**) are in agreement with those of augustine [4], while C-7a is shifted downfield by *ca* 5 ppm because of the double oxygen substitution of the C-7 substitutent C-11a on the contrary is shifted upfield by the same amount in comparison with that of augustine, because of steric interaction with the dioxolane ring



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The eighth signal at δ 100 1 with doublet splitting for C-7 is excellent evidence for the benzaldehyde acetal structure In the case of half aminal element such as in 6-hydroxycrinine alkaloids, the corresponding signal is found between δ 86 and 88 [unpublished results]

Inspecting the shifts of the remaining nine signals upfield of δ 100 the oxiran structure can be ruled out again because of the missing doublet signals around δ 55 [4, 5] Instead they are found for C-5b and C-5a in the range δ 78 5 and 75, where cycloaliphatic methine ether carbons show resonance C-1 and C-2 triplet signals are found at δ 38 and 54 matching with the corresponding signals of C-11 non-hydroxylated crinine alkaloids The only singlet signal in the aliphatic range attributed to C-11b at δ 47 8 as well as the quartet signal for N-Me at δ 39 6 are different from other alkaloids of this type This is also so with the C-4 and C-5 triplet at δ 20.9 and 17 Unexpected is the rather strong downfield shift of the C-3a doublet signal to δ 72 8, probably due to the axial positioned nitrogen-substituent, a configuration also found in crinamine with a corresponding shift value of δ 66.2.

The high resolution mass spectrum of augustamine shows a fragmentation pattern, which has no correspondence to those of any other Amaryllidaceae alkaloids The spectrum exhibits a strong M^+ peak with $[M-H]^+$ as the base peak, which should arise from expulsion of the acetalic H-7 (**1**) The third significant peak is observed at *m/z* 244 and is consistent with $[M-C_3H_5O]^+$ It may originate from the loss of a formyl radical (CHO) and ethylene by cleavage of the labile bonds of rings D and E (**4**)

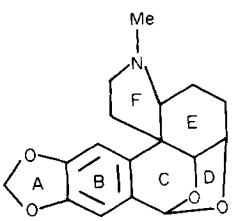

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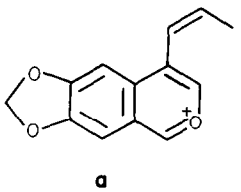
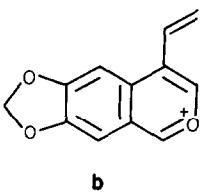
Table 2 20 MHz ^{13}C NMR spectrum of augustamine*

Carbon	δ(ppm) multiplicity	Carbon	δ(ppm) multiplicity
C-9, 10	147 64 *s*	C-5a	74 98 *d*
C-9, 10	145 18 *s*	C-3a	72 75 *d*
C-11a	133 58 *s*	C-2	54 32 *t*
C-7a	131 38 *s*	C-11b	47 80 *s*
C-8	106 94 *d*	Me-N	39 61 *q*
C-11	104 56 *d*	C-1	38 32 *t*
O-CH_2-O	100 87 *t*	C-4	20 89 *t*
C-7	100 11 *d*	C-5	17 02 *t*
C-5b	78 53 *d*		

*Solvent $CDCl_3$

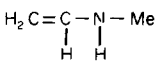


a

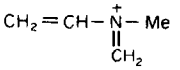


b

a $C_{13}H_{11}O_3$
m/z 215 (25)



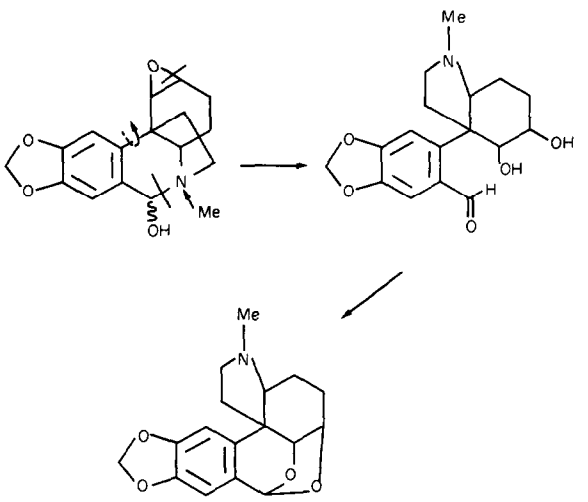
b $C_{12}H_9O_3$
m/z 201 (21)



c C_3H_7N
m/z 57 (4)

d C_4H_8N
m/z 70 (24)

Scheme 2 Mass spectral fragmentation of augustamine



Scheme 3 Possible biogenetic relationship of augustamine to other 6-hydroxy alkaloids of the crinine series

The next peaks of lower relative abundance were noticed at *m/z* 215 with a composition $C_{13}H_{11}O_3$ (**a**) (Scheme 2) and *m/z* 201 with a composition $C_{12}H_9O_3$ (**b**) under removal of C_4H_8NO and $C_5H_{10}NO$, respectively Again the formyl radical is eliminated in addition to either species **c** or **d** This indicates opening of the pyrrolidine ring F in addition to that of D and E Fragment ions **a** and **b** are likely to have substituted benzopyranyl structures

Augustamine is biogenetically linked to the 6-hydroxy alkaloids in the crinine series (Scheme 3), which on hydrolysis of the half aminal function, *N*-methylation and rotation around the C-11a–C-11b axis could form the cyclic benzaldehyde acetal structure The vicinal diol moiety could originate from oxiran ring opening

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REFERENCES

1 Ali, A A , Kating, H , Frahm, A. W , El-Moghazi, A M and Ramadan, M A (1981) *Phytochemistry* **20**, 1121
2 Swalen, J D and Reilly, C A (1964) *QCPE* **11**, 33
3 Aksnes, D W (1972) *QCPE* **11**, 205
4 Frahm, A W , Ali, A A and Kating, H (1981) *Phytochemistry* **20**, 1735
5 Zetta, L , Gatti, G and Fuganti, C (1973) *J Chem Soc Perkin Trans* 2, 1980