Alkaloids of Kopsia Species. Part II.[1] The Constitution of Fruticosine and Fruticosamine[2]

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Alkaloids of Kopsia Species. Part II.[1] The Constitution of Fruticosine and Fruticosamine[2]

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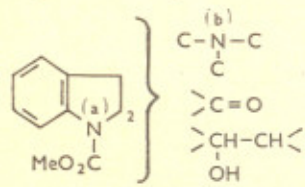
Fruticosine and fruticosamine from *Kopsia fruticosa* (Ker) A.DC. are isomeric heptacyclic alkaloids, $C_{22}H_{24}N_2O_4$, and they differ only in the configuration of the secondary alcohol residue. By combining evidence from chemical, spectroscopic, and mass-spectrometric studies, constitutions are derived for fruticosine and fruticosamine. These are novel alkaloids in being the only representatives of the *Aspidosperma* group which differ from normality in the non-tryptamine portion (C_{9-10} unit) of the molecule.

THE leaves of *Kopsia fruticosa* (Ker) A.DC. contain the isomeric alkaloids fruticosine and fruticosamine.[1,3] Previous work by Battersby and Gregory [1] and by Schmid, Govindachari, and their co-workers [3] showed the molecular formula of the two bases to be $C_{22}H_{24}N_2O_4$ and most of the structural information obtained then can be summarised in partial formula (I). In both



(I)

alkaloids, the ketonic group was shown to be present in a six-membered ring and to be strongly hindered. The present Paper will describe our further studies which lead to the constitutions (II) and (III), respectively, for fruticosine and fruticosamine.*

Partial structure (I) accounts for all the oxygen and nitrogen in the alkaloids and it therefore remains to determine carbon–carbon unsaturation. Under perhydrogenation conditions, fruticosine and fruticosamine both absorbed 3 mol. of hydrogen within experimental error. The two products showed complete loss of the *N*-acylindoline ultraviolet chromophore whereas the N·CO_2Me, ketonic carbonyl, and hydroxyl functions were still present (infrared). Saturation of the benzene ring is thus the only change and this evidence that no olefinic groups are present is supported by n.m.r. The known functions and the molecular formula $C_{22}H_{24}N_2O_4$ now require fruticosine and fruticosamine to be heptacyclic.

The remarkably ready conversion of fruticosamine into fruticosine by mild bases has already been described.[1,3] Further, the demethoxycarbonyl derivatives (IV; R = R′ = H) and (VI; R = R′ = H) are each easily converted into a mixture of the two by mild treatment with acid or base.[1] The interpretation that these conversions simply involve change of configuration at C-3 [see (II) and (III)] by a reverse-aldol process is supported by all the subsequent chemical evidence and particularly by n.m.r. studies (p. 815). Evidence obtained from both alkaloids can therefore be considered together.

The 100 Mc./sec. n.m.r. spectra (Figures 1 and 2) of fruticosine and fruticosamine show no signals in the region corresponding to a proton at C-2 of an acylindoline [5,6] and this is confirmed by the n.m.r. spectrum of *NO*-diacetyldemethoxycarbonylfruticosine [1] (IV; R = R′ = Ac). Position 2 of partial formula (I) is thus fully substituted. The infrared spectrum of fruticosamine shows that its hydroxyl group is intramolecularly hydrogen bonded (broad band at $\nu_{max.}$ 3440 cm.$^{-1}$ in CCl_4) and the spectrum was independent of concentration down to 5×10^{-4}M. Fruticosine lacks this hydrogen bond ($\nu_{max.}$ 3600 cm.$^{-1}$ in CCl_4) and one reflection of this is the ready formation of an *O*-acetyl derivative, whereas the hydroxyl group of fruticosamine resists mild acetylation.[1,3] This hydrogen bonding is also clearly revealed in the n.m.r. spectra of the two alkaloids (see later).

There are three probable sites to which hydrogen bonding of the hydroxyl group could occur in fruticosamine, namely, the N(b)-nitrogen atom, the ketonic carbonyl group or the N·CO_2Me residue. The last is selected, for only on this basis can one striking difference in the n.m.r. spectra of the two alkaloids be explained. In the spectrum of fruticosine (Figure 1) one aromatic proton appears well separated from the rest at low field (τ 2·30) due to the deshielding influence of the amide carbonyl group on the 4′-position as is normal [6] for related alkaloids having the acylindoline residue (I). Fruticosamine (Figure 2) does not show this effect and this can be ascribed to the restraint imposed upon the methoxycarbonyl group by hydrogen bonding. The evidence for hydrogen bonding greatly restricts the possible sites for the hydroxyl group in fruticosamine, and so in fruticosine, and indicates that it must be located at C-3; further evidence will be presented in the sequel.

Fruticosine methiodide [1] undergoes extremely ready Hofmann elimination even initiated by warm sodium hydrogen carbonate solution, and such behaviour

* The illustrated absolute configuration has been arbitrarily set to correspond with that of kopsine (ref. 4), a congener of these alkaloids.

[1] Part I, A. R. Battersby and H. Gregory, *J. Chem. Soc.*, 1963, 22.

[2] A. R. Battersby, J. C. Byrne, H. Gregory, and S. P. Popli, *Chem. Comm.*, 1966, 786.

[3] A. Guggisberg, T. R. Govindachari, K. Nagarajan, and H. Schmid, *Helv. Chim. Acta*, 1963, **46**, 679, and references therein.

[4] A. Guggisberg, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, in the press.

[5] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, *Experientia*, 1960, **16**, 532.

[6] W. G. Kump, H. Schmid, D. J. Le Count, and A. R. Battersby, *Helv. Chim. Acta*, 1962, **45**, 854.

suggests a β-amino-ketone system in the alkaloid. The n.m.r. spectrum of the methine base (VII), $C_{23}H_{26}N_2O_4$, confirmed this by showing two vinylic protons as singlets (τ 5·84 and 4·32). The wide separation of the signals with one at low field is characteristic of 2-methylenecycloalkanones.[7,8] On the assumption that the six-membered ring containing the ketone is carbocyclic (see later discussion) then the sequence (X) is established. Although one ring has been cleaved in the methine (VII), the carbonyl group is still hindered since it resisted attempted reduction with borohydride.

Analysis of the 100 Mc./sec. n.m.r. spectra of the two alkaloids confirms and extends this sequence. Taking first the spectrum of fruticosine (Figure 1), two signals (1H each) can be seen with chemical shifts in agreement with their being α to the ketonic carbonyl. One at τ 7·58, corresponding to the C-11 proton [see (II)], is a doublet ($J = 5$ c./sec.) which is coupled * to a double doublet at τ 6·46 (1H; $J = 5$ and 11 c./sec.); this last signal arises from H_A at C-10. The 11 c./sec. coupling is a geminal one to H_B at C-10; H_B itself appears as a doublet (1H; $J = 11$ c./sec.) at τ 7·13. The chemical shift for H_B (C-10) is as expected for a proton α to nitrogen whereas H_A is deshielded by its position alongside the aromatic system. Dreiding models show

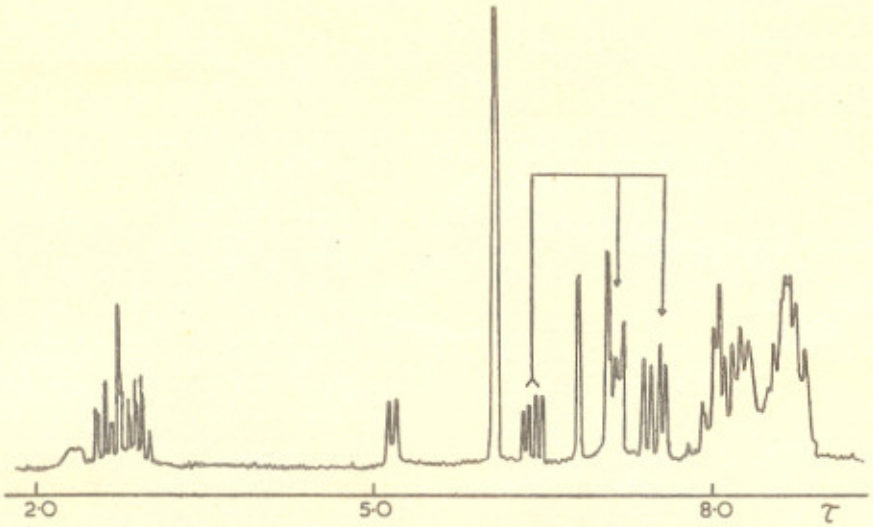


FIGURE 1 100 Mc./sec. n.m.r. spectrum of fruticosine after D_2O exchange ($CDCl_3$)

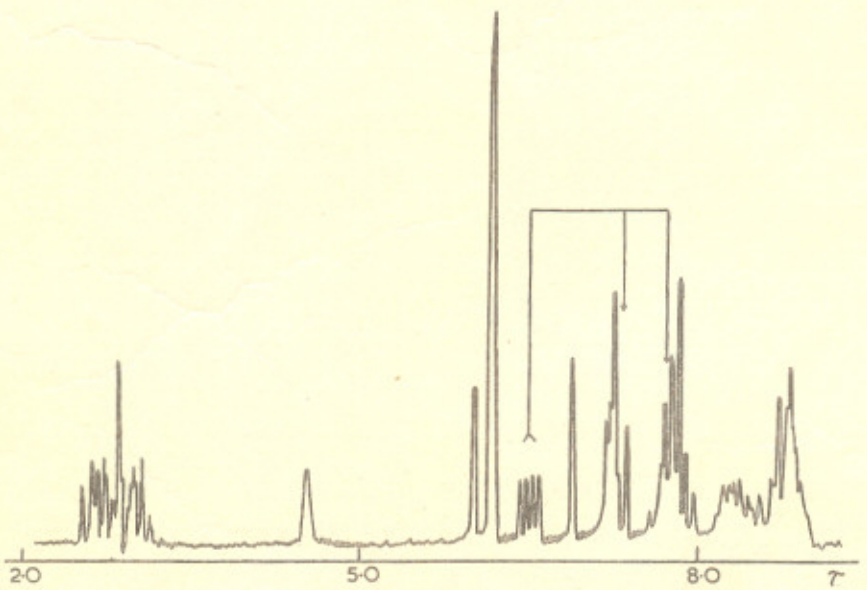


FIGURE 2 100 Mc./sec. n.m.r. spectrum of fruticosamine before D_2O exchange ($CDCl_3$)

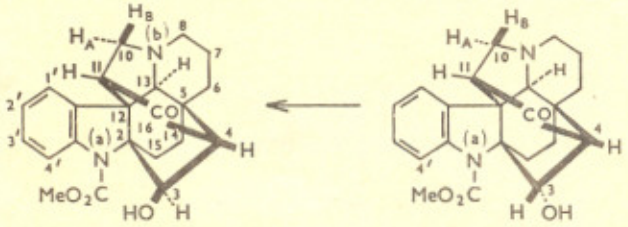
* Couplings thus marked have been confirmed at 100 Mc./sec. by the double resonance technique; unless otherwise stated, the spectra were measured after exchange of the hydroxylic proton with deuterium oxide.

[7] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 123.

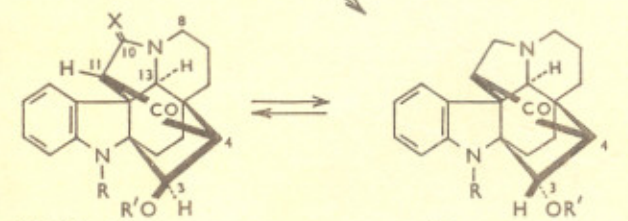
[8] Cf. T. R. Govindachari, B. R. Pai, S. Rajappa, N. Viswanathan, W. G. Kump, K. Nagarajan, and H. Schmid, *Helv. Chim. Acta*, 1962, **45**, 1146.

that the C-11 proton lies at *ca.* 30° and *ca.* 90° to H_A and H_B, respectively. From the Karplus relationship,[9] the expected coupling constants are *ca.* 6 c./sec. for the proton at C-11 to H_A and *ca.* 0 c./sec. for the proton at C-11 to H_B in close agreement with the observed values. The absence of further coupling of the signal due to the C-11 proton is in agreement with there being a quaternary carbon at C-12.

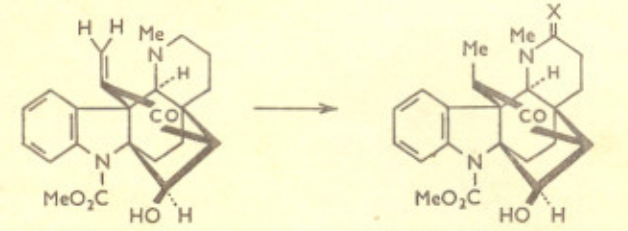
The other signal arising from a proton α to the carbonyl group is the doublet at τ 7·45 (1H; J = 6·5 c./sec.) which is coupled * to the doublet at τ 5·19 (1H; J = 6·5 c./sec.) previously proved [1,3] to arise from the CH of the secondary alcohol residue. It



(II) Fruticosine (III) Fruticosamine



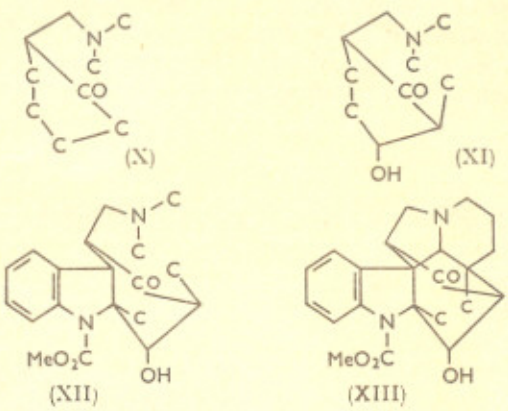
(IV) X = H_2
(V) X = O (VI)



(VII) (VIII) X = H_2
(IX) X = O

follows that the sequence R·CH(OH)·CHR'·CO is present in fruticosine. The dihedral angle between the protons at C-3 and C-4 in structure (II) is *ca.* 35° which accommodates well [9] the observed coupling constant. Further, because the protons at C-3 and C-4 appear in the spectra as doublets, neither R nor R' can carry protons able to cause further splitting of the signal. When the two sequences derived from the n.m.r. studies are combined, partial structure (XI) results.

All the n.m.r. spectra of fruticosine, fruticosamine, and their basic derivatives (see Table) show a sharp singlet (1H) at τ 7·3 ± 0·4 assigned to the proton at C-13 which is flanked by quaternary carbon atoms [see (II) and (III)]. The signal from the hydroxylic proton



(X) (XI) (XII) (XIII)

is variable in position but is generally in the τ 6·8 region; this signal is eliminated by shaking the sample with deuterium oxide.

The n.m.r. spectrum of fruticosamine (Figure 2) shows many of the features displayed by its isomer (Figure 1). Thus, the protons at 10A, 10B, 13, and 11 can be recognised (see Table). There are, however, very significant differences. A broad singlet at τ 4·5 corresponds to the hydroxylic proton, the low-field position being a reflection of hydrogen bonding. In the spectrum of fruticosine, the hydroxylic proton is variable in position but generally near to τ 6·8. Further, the protons at C-3 and C-4 both appear in the spectrum of fruticosamine as singlets at τ 5·98 and 7·75, respectively, and this clear difference from fruticosine allows the C-3 configuration to be rigorously assigned; for fruticosamine (III), the dihedral angle between the protons at C-3 and C-4 is *ca.* 90°.

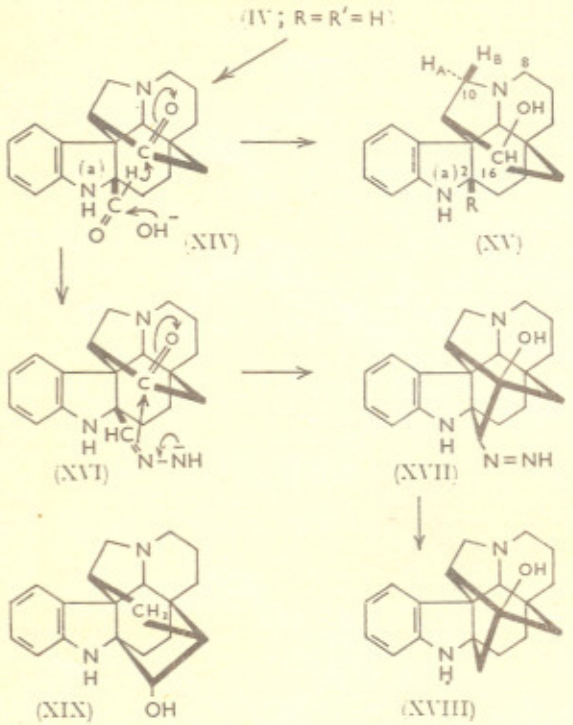
The vast majority of indole alkaloids contain a tryptamine residue and this biogenetic argument can be used here to interlock with the previous evidence for placing the hydroxyl group at C-3; partial structure (XI) can thus be extended to (XII).

Permanganate oxidation of fruticosine yields a neutral product, oxofruticosine, $C_{22}H_{22}N_2O_5$, recognised as a five-membered lactam ($\nu_{max.}$ 1700 cm.$^{-1}$). Spectroscopic evidence showed the acylindoline system and the hydroxyl group to be unchanged whereas the signals corresponding to the C-10 protons were absent from the n.m.r. spectrum of oxofruticosine. This establishes the site of oxidation and in support of structure (V; R = CO_2Me, R' = H) for this lactam, the signal corresponding to the C-11 proton appeared as a singlet 0·6 p.p.m. downfield [10] from its previous position in the spectrum of fruticosine. The singlet arising from the C-13 proton underwent a similar shift of 0·47 p.p.m. All other features of the n.m.r. spectrum of oxofruticosine (see Table) support structure (V; R = CO_2Me, R' = H), and the two C-8 protons, now drawn

* Couplings thus marked have been confirmed at 100 Mc./sec. by the double resonance technique; unless otherwise stated, the spectra were measured after exchange of the hydroxylic proton with deuterium oxide.

[9] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11, and ref. 7, p. 84.
[10] Ref. 7, p. 56.

standing to be gained of the processes leading to the chano-base (XV; R = H). The spectrum of the *NO*-diacetyl derivative of (XV; R = H) displayed two signals in the τ 4·0—6·0 region (1H each) centred at 4·6 and at 5·4. The former was a multiplet which was assigned to the >C*H*·OAc system, and in confirmation it moved 0·9 p.p.m. upfield to *ca.* τ 5·5 in the spectrum of the *N*-monoacetyl derivative. The second signal at τ 5·4 is not present in the n.m.r. spectrum of the chano-base itself (XV; R = H) and can thus be assigned



to a proton at position 2 of the acylindoline system [see (XV; R = H)]. The signal at τ 5·4 is a double doublet with *J ca.* 10 and 6 c./sec. which collapses to a broad singlet by irradiation in the τ 8·3 region. Similar irradiation in the region 8·0—8·5 caused the multiplet at 4·6 to collapse first to a double doublet, *J ca.* 8 and 5 c./sec., and finally to a broad singlet. A Dreiding model of structure (XV; R = H) shows the molecule to be more flexible than that of fruticosine, which is very rigid, so that there is a choice of conformations. However, it is possible in one reasonable conformation of structure (XV; R = H) to accommodate the various observed coupling constants. Further, the demonstrated couplings involving protons yielding signals in the τ 8·0—8·5 region are in accord with structure (XV; R = H). The n.m.r. spectrum of the *NO*-diacetyl chano-base (XV; R = H) also displays a group of signals over the τ 6·6—7·1 region (4H) in which the double doublet arising from the C-10 H_A and the doublet corresponding to C-10 H_B can be seen superimposed upon signals from the C-8 protons.

Formation of the chano-base (XV; R = H) undoubtedly depends upon the close proximity of the aldehydic proton in the " open " form (XIV) of demethoxycarbonylfruticosine to the carbon of the keto-group. Obviously, the keto-aldehyde (XIV) is formed by a reverse-aldol cleavage from demethoxycarbonylfruticosine (IV; R = R′ = H). Attack by hydroxyl anion and hydride transfer as indicated would generate the amino-acid (XV; R = CO_2H). In acid sufficiently strong to protonate N(a), decarboxylation occurs to yield the base (XV; R = H).

A similar type of interaction probably occurs also in the reduction of demethoxycarbonylfruticosine (IV; R = R′ = H) under Wolff–Kishner conditions. The product had the composition $C_{20}H_{24}N_2O$ corresponding to structure (XIX) which would be formed by simple reduction of the ketone (IV; R = R′ = H). However, the product was only slowly converted into its *NO*-diacetyl derivative which showed no signal in the n.m.r. spectrum over the region τ 3·6—6·5. This proves that the system >CH·OAc is not present [cf., *NO*-diacetyl-(XIX)] and further that C-2 of the indoline system is still fully substituted. These findings and all other properties of this product described in the Experimental section are accounted for in structure (XVIII). This is generated by nucleophilic attack from the hydrazone anion (XVI) at the carbonyl carbon as indicated followed by the normal second step of Wolff–Kishner reduction. This type of reaction has interesting synthetic possibilities.

All the substances described in the present Paper have been examined in the mass spectrometer and the *m/e*-values for the parent ions are in agreement with the reported molecular formulæ. The main fragment ions are recorded in the Experimental section. Fruticosine (II) and fruticosamine (III) are relatively stable to electron impact when compared to aspidospermine and its relatives [11] or to the aspidofractine–pleiocarpine group.[12] Further work would be required to allow a full interpretation of the peaks which are observed, but that at *m/e* 352 ($M^+ - 28$) has been shown by accurate mass measurement to involve loss of CO rather than C_2H_4. Elimination of the CH_2·CH_2 bridge does occur, however, from *N*(*b*)-methylfruticosinemethine (VII) and two further structurally valuable fragments appear at *m/e* 110 and 123 corresponding to the ions (XIX) and (XXI), respectively (see annexed Scheme). Fragmentation of the dihydromethine (VIII) occurs with loss of the *C*-methyl group and with the appearance of the $M^+ - 28$ peak; it has not been proved that this is due to loss of C_2H_4. A favoured fragmentation of the lactam (IX) affords a strong peak at *m/e* 124 which corresponds to the ion (XX); this result interlocks with the other mass-spectrometric evidence for the

[11] K. Biemann, M. Friedmann-Spiteller, and G. Spiteller, *Tetrahedron Letters*, 1961, 485.

[12] C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. A. Kump, D. J. Le Count, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, 1963, **46**, 742.

downfield, can be recognised as separate signals which were shown to be coupled.* The coupled * protons at C-3 and C-4 were present unchanged.

Hydrogenation of *N*-methylfruticosinemethine (VII) afforded the dihydromethine (VIII) which showed no signals corresponding to olefinic protons in its n.m.r. spectrum. All features of the spectrum (see Table) are in accord with structure (VIII), in particular, the doublet at τ 9·01 (3H), corresponding to the *C*-methyl group, coupled * to the C-11 proton which appears as a quartet (1H) at τ 6·91. The dihydromethine proved to be a troublesome compound because of its ready conversion by light into a yellow substance not further investigated. When pure fruticosine dihydromethine was oxidised with permanganate, a neutral lactam (IX) was isolated in low yield. This behaved as a single substance under all conditions tested on thin-layer chromatograms but it has resisted crystallisation. However, the lactam, $C_{23}H_{28}N_2O_5$ by accurate mass measurement, was shown to be a six-membered one ($\nu_{max.}$ 1639 cm.$^{-1}$). A full study of the n.m.r. spectrum of this lactam was not possible because of lack of material; nevertheless, the main features of structure (IX) were recognisable. These were the four aromatic protons, the *O*-, *N*-, and *C*-methyl groups, and the protons at C-3 and C-4.

The foregoing evidence proves that the N(b) nitrogen atom is a common member of fused five- and six-membered rings, and partial structure (XIII) is reached. One ring remains to be formed and four hydrogen atoms are available; the only possibility is to join the two remaining atoms [see (XIII)] as in structure (II). Mass-spectrometric evidence will be adduced in further support of the $CH_2{\cdot}CH_2$ bridge. This bridge is in accord with the n.m.r. spectrum of fruticosine. The earlier discussion leaves eight protons still to be assigned which appear as two groups of signals equivalent to four protons each in the ranges τ 7·8—8·5 and 8·5—9·1. These correspond to the protons at C-6, C-7, C-14, and C-15, the only ones in the molecule not subject to some form of deshielding.

Further support for structures (II) and (III) derives from the action of hot strong alkali on fruticosine; the same reaction occurred when these conditions were applied to a mixture of the demethoxycarbonyl bases (IV and VI; R = R′ = H). In each case mainly amphoteric material was obtained which underwent slow decarboxylation in hot acidic ethanol. The product, $C_{19}H_{24}N_2O$, showed no carbonyl groups in the infrared spectrum, but OH and NH groups were apparent. These groups were acetylated to yield the *NO*-diacetyl derivative which by mild hydrolysis afforded the corresponding *N*-monoacetyl derivative. The n.m.r. spectra of these substances allowed an under-

Nuclear magnetic resonance spectra

Compound	Aromatic	3	4	8
(1) Fruticosine (II)	m 2·3 (1H) 4′ m 2·5—3·0 (3H)	d 5·19 (1H)	d 7·45 (1H)	m 7·14 (2H)
(2) Fruticosamine (III)	m 2·4—3·0 (4H)	s 5·90 (1H)	s 7·70 (1H)	m 7·15 (2H)
(3) *O*-Acetylfruticosine (IV; R = CO_2Me, R′ = Ac)	m 2·1 (1H) 4′ m 2·3—3·0 (3H)	d 4·23 (1H)	d 7·28 (1H)	m 7·15 (2H)
(4) *NO*-Diacetyldemethoxycarbonylfruticosine (IV; R = R′ = Ac)	m 2·3—3·0 (4H)	d 4·07 (1H)	d 7·20 (1H)	m 7·15 (2H)
(5) *N*-Methylfruticosinemethine [b] (VII)	m 2·1—3·1 (4H)	d 5·26 (1H)	d 7·30 (1H)	*a*
(6) *N*-Methylfruticosinedihydromethine (VIII)	m 2·1—3·1 (4H)	d 5·23 (1H)	*a*	m 7·13 (2H)
(7) Oxofruticosine (V; R = CO_2Me, R′ = H)	m 2·4 (1H) 4′ m 2·6—3·2 (3H)	d 5·16 (1H)	d 7·28 (1H)	m 7·2 (1H) m 6·0 1(H)
(8) *NO*-Diacetyl chano-base [c] [cf. (XV; R = H)]	m 2·2—3·2 (4H)	—	*a*	m 6·9 (2H)
(9) *N*-Acetyl chano-base [d] [cf. (XV; R = H]	m 2·2—3·2 (4H)	—	*a*	m 6·9 (2H)
(10) *NO*-Diacetyl Wolff–Kishner base [cf. (XVIII)]	m 2·2—3·2 (4H)	*a*	*a*	m 6·9 (2H)

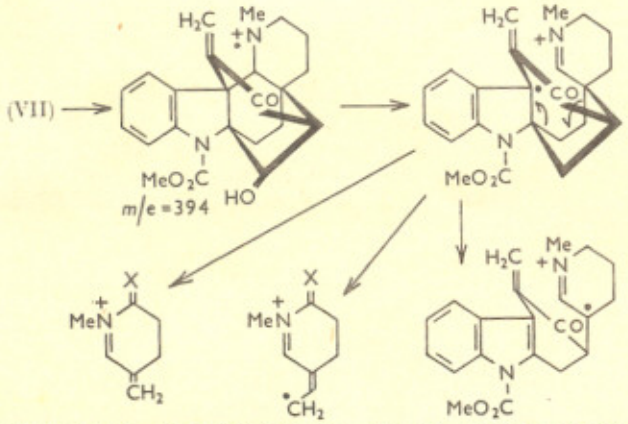
	10A	10B	11	13	OMe [or NMe (marked *)]	OAc	NAc
(1)	q 6·41 (1H)	d 7·13 (1H)	d 7·58 (1H)	s 6·83 (1H)	s 6·12 (3H)	—	—
(2)	q 6·41 (1H)	d 7·19 (1H)	d 7·62 (1H)	s 6·80 (1H)	s 6·10 (3H)	—	—
(3)	q 6·33 (1H)	d 7·12 (1H)	d 7·57 (1H)	s 6·75 (1H)	s 6·20 (3H)	s 8·03 (3H)	—
(4)	q 6·33 (1H)	d 7·08 (1H)	d 7·15 (1H)	s 6·78 (1H)	—	s 8·07 (3H)	s 7·57 (3H)
(5)	—		—	s 7·50 (1H)	s 6·17 (3H) s 7·65 (3H) *	—	—
(6)	d 9·01 (3H)		q 6·91 (1H)	s 7·55 (1H)	s 6·15 (3H) s 7·49 (3H) *	—	—
(7)	—	—	s (6·98 (1H)	s 6·36 (1H)	s 6·15 (3H)	—	—
(8)	q 6·73 (1H)	d 6·9 (1H)	*a*	s 7·44 (1H)	—	s 8·01 (3H)	s 7·70 (3H)
(9)	6·8—7·1 (2H)		*a*	s 7·48 (1H)	—	—	s 7·70 (3H)
(10)	6·5—7·2 (2H)		*a*	*a*	—	s 8·05 (3H)	s 7·65 (3H)

s = Singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

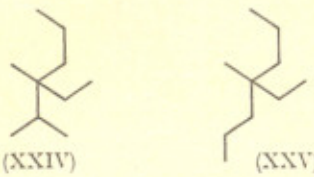
[a] Not resolved. [b] Vinylic protons (s, 1H) at 5·84 and 4·32. [c] C-2 proton q at 5·40; C-16 proton m at 4·60. [d] C-2 and C-16 protons together over 5·3—5·8τ.

* Couplings thus marked have been confirmed at 100 Mc./sec. by the double resonance technique; unless otherwise stated, the spectra were measured after exchange of the hydroxylic proton with deuterium oxide.

piperidine portion of these molecules. The peak at *m/e* 110 also appears in the spectrum of the chano-base



(XV; R = H), but this substance and particularly the Wolff–Kishner product (XVIII) are clearly difficult to break down under mass-spectrometric conditions.



The sum of the foregoing evidence establishes the structures (II) and (III) for fruticosine and fruticosamine.* The non-tryptamine part of these bases, dissected as (XXIV), is a novel one, the normal arrangement being (XXV) for the *Aspidosperma* group. Only the appropriate tracer experiments can determine when the departure from normality occurs and work on this aspect has been undertaken.

EXPERIMENTAL

General Directions.—Melting points were determined on a Kofler block and analysis samples dried at 100° over phosphoric oxide *in vacuo* unless otherwise stated. Solutions were dried over sodium sulphate and evaporated in a rotatory evaporator at <40° (bath). Ultraviolet spectra were determined in 1 : 1 aqueous ethanol and infrared spectra in chloroform, unless otherwise stated. Solutions in $CDCl_3$ were used for n.m.r. spectra which were determined at 60 and 100 Mc./sec. on Varian A. 60 and HA. 100 instruments; double resonance studies were carried out at 100 Mc./sec. Mass spectra were run by direct insertion on the A.E.I. MS. 9 spectrometer.

Fruticosine Mass Spectrum.—Main peaks at *m/e* 380 (100%), 352 (43%), 351 (64%), 348 (21%), 282 (58%), 243 (43%), 230 (43%), 124 (16%), 122 (18%). Strong metastable ion corresponding to 380 ⟶ 352.

Fruticosamine Mass Spectrum.—Main peaks at *m/e* 380 (100%), 352 (56%), 351 (25%), 348 (14%), 282 (25%), 243 (52%), 230 (14%), 122 (25%). Accurate mass of 352 peak is 352·1793 corresponding to $C_{21}H_{24}N_2O_3$ (Calc. 352·1787).

Perhydrogenation of Fruticosine and Fruticosamine.—A solution of fruticosamine (20·8 mg.) in 2N-sulphuric acid (10 ml.) was shaken with hydrogen and prereduced platinum (from 53 mg. of PtO_2) at 23°/765 mm. (uptake 2·95 mol.). After filtration, the solution was extracted with ethyl acetate, then basified and extracted again with this solvent. Evaporation of the second set of extracts gave a residue which crystallised from ethanol to yield the perhydrogenation product, m. p. 275—278°, $\nu_{max.}$ 3670 (OH), 1720 (cyclohexanone), 1685 cm.$^{-1}$ (N·CO_2Me).

Fruticosamine similarly absorbed 2·85 mol. of hydrogen, and the product, m. p. 223—227°, showed $\nu_{max.}$ 3250 (bonded OH), 1730 (cyclohexanone), 1690 cm.$^{-1}$ (N·CO_2Me).

N(b)-*Methylfruticosinemethine* (VII).—The preparation of starting material fruticosine methiodide [1] has been much improved. A solution of fruticosine (0·36 g.) in methyl iodide (10 ml.) was heated under reflux for 8 hr., then cooled and diluted with ethyl acetate (15 ml.), to give pure fruticosine methiodide. Evaporation of the mother-liquors and recrystallisation of the residue from methanol–ethyl acetate gave more methiodide (total 410 mg.). This product (0·4 g.) was dissolved in aqueous 3N-sodium hydrogen carbonate (25 ml.) and the solution was stirred at 65° for 7 hr. The solid which had separated was collected, washed with water, and dried. Extraction of the aqueous solution with ethyl acetate gave more base which was combined with the foregoing solid and crystallised from methanol–ethyl acetate, to afford N-(b)-*methylfruticosinemethine* (280 mg.), m. p. 225—227° (Found: C, 70·4, 69·6; H, 6·8, 6·9; N, 7·1, 7·5. $C_{23}H_{26}N_2O_4$ requires C, 70·0; H, 6·6; N, 7·1%), $\lambda_{max.}$ 245·5, 280, 288 mμ (log ε 4·21, 3·68, 3·64), $\nu_{max.}$ 3560 (OH), 1710 (>CO), 1680 (N·CO_2Me). Mass spectrum: main peaks at *m/e* 394 (100%), 366 (30%), 167 (14%), 137 (18%), 124 (100%), 110 (off scale). The accurate mass of the 366 peak was 366·1531 corresponding to $C_{21}H_{22}N_2O_4$, that is to loss of C_2H_4.

N(b)-*Methylfruticosinedihydromethine* (VIII).—A solution of the methine (340 mg.) in ethanol (30 ml.) was shaken with platinum oxide (180 mg.) at room temperature and pressure. Uptake (1·03 mol.) was complete in 1 hr. The filtered solution was evaporated and the residue in ethanol treated with picric acid. Recrystallisation of the solid from ethanol gave N(b)-*methylfruticosine dihydromethine picrate* (448 mg.), m. p. 218° (decomp.) (Found: C, 56·0; H, 5·1; N, 11·4. $C_{23}H_{28}N_2O_4.C_6H_3N_3O_7$ requires C, 55·7; H, 5·0; N, 11·2%).

This picrate in chloroform was run through a short column of alumina; evaporation of the eluate afforded the *dihydromethine* (305 mg.), m. p. 215—217° (Found: C, 69·4; H, 7·1; N, 7·5. $C_{23}H_{28}N_2O_4$ requires C, 69·7; H, 7·1; N, 7·1%), $\lambda_{max.}$ 248, 281, 290 mμ (log ε 4·2, 3·45, 3·40) (ultraviolet spectrum unchanged in N-hydrochloric acid), $\nu_{max.}$ 3550 (OH), 1715 (>CO), 1675 cm.$^{-1}$ (N·CO_2Me). Main peaks in mass spectrum: *m/e* 396 (84%), 381 (40%), 368 (49%), 310 (15%), 137 (100%), 124 (89%), 110 (off scale).

Oxofruticosine (V; R = CO_2Me, R′ = H).—Potassium permanganate (632 mg.) in stabilised acetone (100 ml.) was added gradually to a boiling solution of fruticosine (310 mg.) in acetone (20 ml.). After the mixture had been heated under reflux for 2 hr., it was cooled, the solid was filtered off, and the filtrate together with the methanolic washings

* The same structures have been independently derived by Professor H. Schmid and his co-workers, private communication from Professor H. Schmid (Zürich).

from the solid was acidified with 2N-hydrochloric acid. The organic solvents were evaporated and the aqueous suspension was separated as usual into neutral, acidic, and basic fractions. The last was mainly fruticosine. Chromatography of the neutral fraction first on neutral alumina with benzene–chloroform (3 : 2) and then on silica gel in benzene–chloroform (3 : 1) gave *oxofruticosine* (62 mg.), m. p. 216—217° (from methanol). This substance was unusual in that it could be obtained from methanol as a form, m. p. 163°, which on drying at 100°/0·1 mm. changed to a form with m. p. 243° (Found: C, 66·4; H, 5·7. $C_{22}H_{22}N_2O_5$ requires C, 67·0; H, 5·6%), $\lambda_{max.}$ (EtOH) 244, 285, 292 mμ (log ε 4·23, 3·38, 3·38), $\nu_{max.}$ 3550 (OH), 1750 (cyclohexanone), 1700 (5-membered lactam), 1683 cm.$^{-1}$ (N·CO_2Me). Main peaks in mass spectrum: *m/e* 394 (100%), 365 (44%), 338 (9%), 322 (22%), 280 (10%).

Oxidation of N(b)-*Methylfruticosinedihydromethine* (VIII).—A boiling solution of the dihydromethine (160 mg.) in stabilised acetone (12 ml.) was treated dropwise during 20 min. with a solution of potassium permanganate (320 mg.) in acetone (54 ml.). The mixture was heated for a further 1·5 hr., then cooled and worked up as for oxofruticosine. The neutral fraction (75 mg.) was chromatographed on alumina, to afford the pure lactam (IX) as a colourless resin (24 mg.). Its composition was determined by accurate mass measurement (Found: 410·1842. Calc. for $C_{23}H_{30}N_2O_5$: 410·1842). Main peaks in mass spectrum: 410 (45%), 382 (4%), 287 (31%), 273 (93%), 138 (26%), 137 (26%), 124 (100%); $\nu_{max.}$ 3500 (OH), 1724 (cyclohexanone), 1675 (N·CO_2Me), 1637 cm.$^{-1}$ (piperidone).

The Chano-base (XV; R = H).—A solution of fruticosine (350 mg.) in ethanol (20 ml.) was mixed with aqueous 5N-sodium hydroxide (20 ml.) and heated under reflux for 12 hr. Evaporation of the ethanol and extraction of the aqueous solution thrice with ethyl acetate afforded demethoxycarbonylfruticosine (30 mg.). The aqueous solution was evaporated to dryness and the residue extracted with hot ethanol until the extracts gave no colour test with ceric sulphate.[13] The residue left by evaporation of the alcoholic extracts was heated under reflux with N-hydrochloric acid for 5 hr., the cooled solution was basified and extracted with ethyl acetate. These extracts afforded a solid which was recrystallised from methanol to give the *chano-base* (110 mg.), m. p. 284—287° (Found: C, 77·1; H, 8·2; N, 9·7. $C_{19}H_{24}N_2O$ requires C, 77·0; H, 8·2; N, 9·5%), $\lambda_{max.}$ 204, 240, 289 mμ (log ε 4·52, 3·80, 3·40), $\nu_{max.}$ (Nujol) 3320, 3140 cm.$^{-1}$ (OH and NH). There was limited specific fragmentation in the mass spectrometer, the major peaks being at *m/e* 296 (100%), 110 (60%).

NO-*Diacetyl Derivative of the Chano-base* (XV; R = H).—Acetic anhydride (2 ml.) was added to a solution of the chano-base (110 mg.) in pyridine (5 ml.) and after being left at room temperature for 24 hr., the mixture was poured on to ice. An excess of hydrochloric acid was added and the solution was extracted with ethyl acetate before being basified and re-extracted with ethyl acetate. Evaporation of the second set of extracts gave a residue which crystallised from methanol–di-isopropyl ether to yield the NO-*diacetyl derivative* (100 mg.), m. p. 228—229° (Found: C, 72·4; H, 7·4; N, 7·6. $C_{23}H_{28}N_2O_3$ requires C, 72·6; H, 7·4; N, 7·4%), $\lambda_{max.}$ 253, 280, 288 mμ (log ε 4·15, 3·68, 3·57), $\nu_{max.}$ 1722 (OAc), 1650 cm.$^{-1}$ (NAc). Main peaks in mass spectrum: *m/e* 380 (100%), 337 (22%), 321 (31%), 277 (33%).

N-*Acetyl Chano-base*.—0·5N-Sodium hydroxide (1·2 ml.) was added to a solution of the foregoing diacetyl derivative (97 mg.) in methanol (16 ml.), and this was kept at 20° for 3 hr., diluted with water and extracted thrice with ethyl acetate. The extracts yielded a solid which crystallised from methanol–di-isopropyl ether to afford the N-*acetyl chano-base* (54 mg.), m. p. 201° (Found: C, 74·4; H, 7·8; N, 8·3. $C_{21}H_{26}N_2O_2$ requires C, 74·5; H, 7·7; N, 8·3%), $\lambda_{max.}$ 253, 282 mμ (log ε 4·24, 3·70), $\nu_{max.}$ 3600 (OH), 1643 cm.$^{-1}$ (NAc). Main peaks in mass spectrum: *m/e* 338 (100%), 295 (15%), 277 (19%), 130 (50%).

Wolff–Kishner Reduction.—Demethoxycarbonylfruticosine (109 mg.) was added to a solution of potassium hydroxide (0·6 g.) and anhydrous hydrazine (1·2 ml.) in dry ethanediol (2·5 ml.) at 60° with protection against moisture. The solution was heated at 155°(bath) for 5 hr., cooled, diluted with water (15 ml.), and extracted thrice with ethyl acetate. Evaporation of the dried extracts, which had been washed with water, gave a solid (101 mg.) which crystallised from methanol to give the *base* (XVIII), m. p. 193° (82 mg.) (Found: C, 77·8; H, 7·9; N, 9·1. $C_{20}N_{24}N_2O$ requires C, 77·9; H, 7·8; N, 9·1%), $\lambda_{max.}$ 244, 296 mμ (log ε 3·79, 3·38), $\nu_{max.}$ 3590, 3392 cm.$^{-1}$ (OH and NH).

This product was converted into its NO-*diacetyl derivative* as earlier for the chano-base save that even after 7 days unchanged starting material remained. The total basic material was fractionated on neutral alumina in benzene–chloroform (9 : 1) and the pure product (71 mg.) crystallised from methanol (44 mg.), m. p. 172—173° (Found: C, 73·7; H, 7·3; N, 7·0. $C_{24}H_{26}N_2O_3$ requires C, 73·4; H, 7·2; N, 7·1%), $\lambda_{max.}$ 256, 282, 290 mμ (log ε 4·13, 3·63, 3·59), $\nu_{max.}$ 1727 (OAc), 1635 cm.$^{-1}$ (NAc).

The mass spectrum of the Wolff–Kishner product showed a strong parent peak at *m/e* 308 and no fragment ions greater than 5% of the parent ion. Mainly the expected breakdown of the OAc and >NAc functions was observed in the spectrum of the *NO*-diacetyl derivative; *m/e* 392 (100%), 350 (12%), 349 (14%), 332 (26%), 289 (55%), 112 (18%), 96 (55%).

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[13] H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1950, **33**, 512.