The Constitutions of Fruticosine and Fruticosamine

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EARLIER work[1,2] established the partial structure (I) for fruticosine and fruticosamine, both $C_{22}H_{24}N_2O_4$, the heptacyclic bases from *Kopsia fruticosa*.[1,2] Mild bases (ammonia, sodium carbonate) convert fruticosamine into fruticosine and it will be shown that this change involves inversion of configuration at the secondary alcohol residue; evidence derived from both substances can therefore be considered together. Only the essential data required to establish structure (II) for fruticosine and (III) for fruticosamine are outlined here. Further chemical, spectroscopic, and mass-spectrometric results, all in agreement with structures (II) and (III), will be described in our full Paper.

The n.m.r. spectrum of fruticosine has no signals in the region corresponding to a proton at position-2 of an acylindoline[3] showing C-2 to be fully substituted. Because the hydroxyl group of fruticosamine is hydrogen-bonded intramolecularly to the methoxycarbonyl group (infrared, n.m.r.), it is placed at C-3; other possibilities are eliminated by later evidence. The proton at C-3 is coupled* only with that at C-4, both signals being doublets (J = 6·5 c./sec.) centred at τ 5·19 and 7·45, respectively, (1 H each). The chemical shift of the C-4 proton corresponds to attachment of the carbonyl group at position-4 and so follows the sequence –CH(OH)·CHR·CO–. Structure (II) accommodates the observed J-value for the system C-3(H)–C-4(H),

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

the dihedral angle between these two protons[5] being *ca.* 35°.

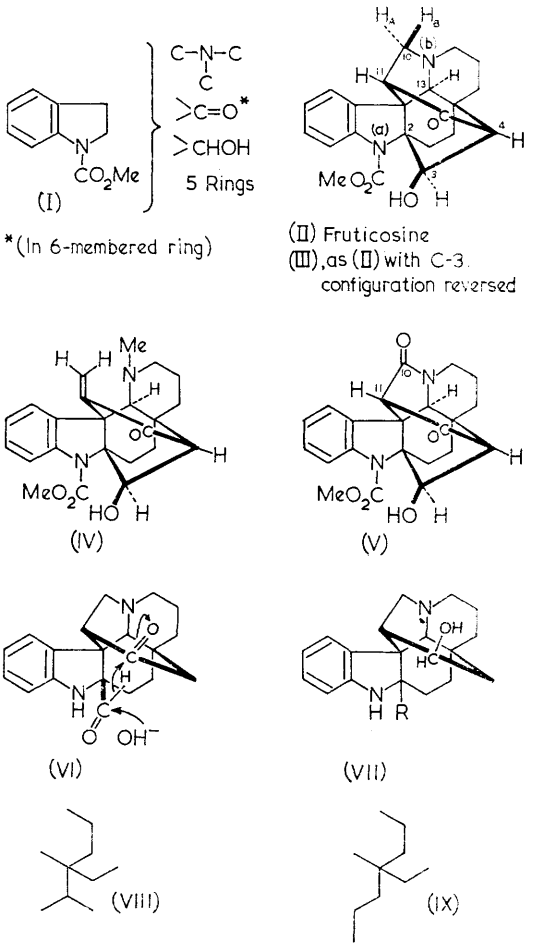
The relationship of N_b to the ketonic function is established by the extremely ready Hofmann elimination which fruticosine methiodide undergoes with sodium carbonate solution[4] (β-aminoketone). The n.m.r. spectrum of the resultant methine, $C_{23}H_{26}N_2O_4$ (IV), shows two vinylic protons as singlets (τ 5·84 and 4·23), the low-field position of one of these being characteristic of 2-methylenecyclohexanones.[6] This evidence establishes the sequence –CO·CHR·CH_2·N< and further support is adduced later. Hydrogenation of (IV) affords the dihydromethine (as IV, double bond reduced) which is oxidised by permanganate to a six-membered lactam (M^+, 410; 1639 cm.$^{-1}$). Similarly, oxidation of fruticosine yields oxofruticosine (V), $C_{22}H_{22}N_2O_5$, (M^+, 394) recognised as a five-membered lactam by infrared (1700 cm.$^{-1}$) and n.m.r. (later). The nitrogen atom N_b is thus a common member of fused 5-, and 6-rings.

All the foregoing deductions are strongly supported by n.m.r. studies. For fruticosine, H_A (C-10) appears as a double doublet τ 6·46 (J = 11 and 5 c./sec.) coupled† both to H_B (C-10), which appears as a doublet (J = 11 c./sec.) at τ 7·13, and to the C-11 proton seen as a doublet (J = 5 c./sec.) at τ 7·58. The observed J-values are in good agreement with those expected from the Karplus relationship[5] on the basis of structure (II) since the dihedral angle between H_A and the C-11 proton is *ca.* 30°, whilst H_B is set at *ca.* 90° to the proton at C-11. A sharp singlet at τ 6·83 corresponds to the proton at C-13 which is flanked by quaternary carbon atoms.

The n.m.r. spectrum of fruticosamine (III) is closely similar to that of fruticosine save that (a) the hydroxylic proton appears at τ 4·5 (hydrogen bonding; *cf.*, position at τ 7·1 in fruticosine) and (b) the protons at C-3 and C-4 appear as singlets in agreement with the dihedral angle between them of *ca.* 85° in structure (III).

The n.m.r. spectrum of oxofruticosine (V) establishes that lactam formation involves C-10 since the signals corresponding to 10A and 10B are absent whilst the proton at C-11 now appears as a singlet at τ 6·98. The singlet due to C-13(H) undergoes a similar downfield shift to τ 6·36.

The foregoing evidence leads to constitution (II) for fruticosine and (III) for fruticosamine.[7]† Further support derives from the conversion of fruticosine by hot alkali into an amino-acid which decarboxylates in acid to yield a carbonyl-free base, $C_{19}H_{24}N_2O$ (M^+, 296). These changes can be understood on the basis of structure (II) by considering hydride transfer to occur as illustrated on the "open" form of demethoxycarbonylfruticosine



(VI; reverse aldol). Decarboxylation of the product (VII; R=CO_2H) then affords (VII; R=H) which as its *NO*-diacetyl derivative shows a double doublet at τ 5·4 arising from the proton at C-2 of the acylindoline system. The >CH·OAc system can be recognised as a multiplet at τ 4·6 and as expected for a secondary alcohol, the corresponding signal appears *ca.* 1·0 p.p.m. upfield in the spectrum of the *N*-monoacetyl derivative.

Fruticosine and fruticosamine are novel alkaloids in being the only representatives of the Aspidosperma group to possess the C_{9-10} unit in

† The illustrated absolute configuration has been arbitrarily set the same as in kopsine, (ref. 8), a congener of these alkaloids.

the form (VIII); normally this unit appears as (IX). The point at which the branch from the normal biosynthetic pathway occurs will be studied by tracer methods.

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[7] The same structures have been independently derived by Prof. H. Schmid and his co-workers; private communication from Prof. H. Schmid.
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