Structures of Cathedulin Alkaloids from *Catha edulis* (Khat) of Kenyan and Ethiopian Origin

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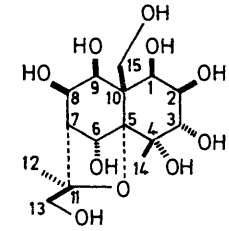
Summary The structures of cathedulins K-1, K-2, K-6, K-12, and K-15, isolated from Kenyan khat, are formulated as (**4**), (**3**), (**5**), (**8**), and (**6**) respectively; cathedulin E-3 (Ethiopian khat) is formulated as (**7**) and E-4, E-5, and E-6 can be treated similarly.

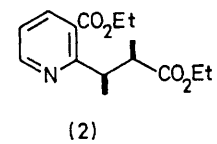
IN earlier reports[1,2] the isolation and structures of a number of alkaloids from *Catha edulis* (khat) of Ethiopian origin was discussed.† Chromatographic examination of khat of Kenyan origin has yielded five weakly basic new alkaloids,[3,4] together with cathedulin K-11 which is identical with cathedulin E-3.[1] The large alkaloid K-12 is connected structurally with E-3, -4, -5, and -6 whilst K-1, -2, -6, and -15 are closely related.

Mass spectral data (electron impact and chemical ionisation) indicate the following formulae: K-1, $C_{42}H_{53}NO_{20}$, m.p. 165—168 °C; K-2, $C_{40}H_{51}NO_{19}$, m.p. 181—184 °C; K-6, $C_{38}H_{49}NO_{18}$, m.p. 176—180 °C; K-15, $C_{36}H_{47}NO_{17}$, m.p. 191—194 °C; K-12, $C_{54}H_{62}N_2O_{23}$, m.p. 268—272 °C.

† These alkaloids were designated (refs. 1 and 2) by the generic term cathedulin followed by a number: this system is expanded by prefacing the number with the letter E to indicate geographic origin of the khat. The new Kenyan series is prefaced by K.



(1)



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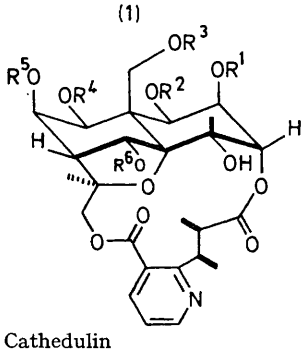

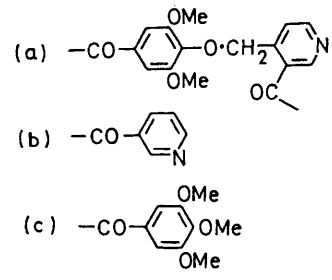

Cathedulin

K-2 (**3**) R^1=H, R^3=Ac; R^2,R^4,R^5,R^6=3×Ac and AcO·CMe_2CO–

K-1 (**4**) R^1=R^3=Ac; R^2,R^4,R^5,R^6=3×Ac and AcO·CMe_2CO–

K-6 (**5**) R^1=R^3=H; R^2,R^4, R^5,R^6=3×Ac and AcO·CMe_2CO–

K-15 (**6**) R^1=R^3=H; R^2,R^4,R^5,R^6=3×Ac and HO·CMe_2CO–

E-3 (**7**) R^1=R^6=Ac; R^2,R^4=Ac and AcO·CMe_2CO–; R^5,R^3=(a)

K-12 (**8**) R^1=R^6=Ac; R^2,R^4=Ac and AcO·CMe_2CO–; R^3=(b); R^5=(c)

E-4 (**9**) R^1=Ac, R^6=H; R^2,R^4=Ac and AcO·CMe_2CO–; R^5,R^3 = (a)

E-5 (**10**) R^1=R^6=Ac; R^2,R^4=PhCO and AcO·CMe_2CO–; R^3 = (b), R^5 = (c)

E-6 (**11**) R^1=Ac, R^6=H; R^2,R^4=PhCO and AcO·CMe_2CO– R^3=(b), R^5=(c)

Cathedulin K-2 is the most abundant alkaloid in this sample of Kenyan khat and on ethanolysis it yields euonyminol (**1**) [identified by comparison of (**1**) and its octa-acetate, m.p. 192—195 °C, with authentic specimens] and diethyl evoninate (**2**). Quantitative ethanolysis indicated five acetate residues (g.l.c.). ^{1}H and ^{13}C n.m.r. data showed signals consistent with an acylated euonyminol core having a free 2-hydroxy-group (2-H, δ 4·10; OH, 2·94br) and a free tertiary hydroxy-group (OH, 4·53 sharp), together with an evoninate diester bridge spanning C-3 to C-13 (shown by comparison of resonances with alkaloids having this feature). Left unassigned are four ^{13}C signals: two OR quartets in the range δ 18—25 p.p.m. (2Me), one OR singlet in the range 69—74 p.p.m. (≡C–O), one OR singlet 168—175 p.p.m. (C=O), and two ^{1}H resonances (each 3H) in the range δ 1·5—1·7. Only an α-oxyisobutyrate unit fits these data and in K-2 it must take the form of an α-acetoxyisobutyrate.

Careful ethanolysis permitted identification of α-hydroxyisobutyric acid as the free acid (g.l.c., t.l.c.) and as its ethyl ester (g.l.c.) and trimethylsilyl derivative (g.l.c.) using a synthetic specimen for comparison. Analysis is complicated by ready reaction of ethyl α-hydroxyisobutyrate with ethoxide ion ($B_{AL}2$ perhaps) to give the free acid whose water solubility and steam volatility makes micro-detection difficult.

Cathedulin K-2 is thus (**3**) in which only the relative siting of acetate and α-acetoxyisobutyrate remains unclarified.‡ Cathedulin K-1 has one more acetate than K-2 and this occupies C-2 (2-H, δ 5·21): it is thus (**4**). Cathedulin K-6 has one less acetate than K-2 and has a free primary hydroxy-group at C-15 (15-H_a, δ 4·24; 15-H_b, 4·62; J_{AB} 13 Hz), leading to structure (**5**). Cathedulin K-15 has one acetate less than K-6. The sesquiterpene core protons are undisturbed in the ^{1}H n.m.r. spectrum whilst the ·O·CMe_2-CO_2R signals move slightly (δ 1·65 and 1·59 in K-6 to δ 1·51 in K-15): a parallel movement is found in models (δ 1·55 for 3β-cholestanyl α-acetoxyisobutyrate and δ 1·40 for 3β-cholestanyl α-hydroxyisobutyrate). Further evidence that the α-hydroxyisobutyrate residue is present in unacetylated form in K-15 is the absence of a fragment at *m/e* 129 in the mass spectrum. This, assigned to the acetoxyisobutyrate fragment [MeCOO·CMe_2CO]$^+$, is evident in K-1, K-2, and K-6.

The new information allows development of the structures for cathedulins E-3 to E-6, for which incomplete formulations have been assigned.[1] E-3 has now been crystallised, m.p. 245—248 °C, and improved spectral data (^{13}C and ^{1}H n.m.r.) confirm earlier deductions and allow recognition of an α-acetoxyisobutyrate residue. Previously, only three acetates had been recognised (by n.m.r.) in E-3: a fourth, at C-2, and shielded, has now been located at δ 1·37. Quantitative ethanolysis is in agreement with the presence of four acetates, and α-hydroxyisobutyric acid has been chemically identified from E-3. Re-evaluation of the mass-spectral data now allows assignment of the formula $C_{54}H_{60}N_2O_{23}$ (Found: M^+ 1104·360, requires 1104·360) to E-3. All 54 carbons and 60 hydrogens can be observed in the new spectra, leaving no unassigned resonances. Both crystalline and non-crystalline specimens of E-3, however, show a small peak at *m/e* 1166, originally assumed to be probably the molecular ion. It apparently belongs to a contaminating companion alkaloid in which one acetate is replaced by a benzoate. Cathedulin E-3 is thus allocated structure (**7**), the only ambiguity being the placing of the α-acetoxyisobutyrate residue: work on this aspect is in hand.

Cathedulins E-4, E-5, and E-6 present a similar situation and are given molecular formulae $C_{52}H_{58}N_2O_{22}$ (M^+ 1062), $C_{59}H_{64}N_2O_{23}$ (M^+ 1168), and $C_{57}H_{62}N_2O_{22}$ (M^+ 1126) respectively. From our earlier information[1] the formulation of E-4, E-5, and E-6 can be developed analogously to E-3 to give (**9**), (**10**), and (**11**) respectively. Cathedulin K-12 has ^{1}H n.m.r. data very similar to those of E-3, but with the cathate diester bridge signals replaced by those of separate gallate and nicotinate esters. Structure (**8**) accounts for the known information: K-12 may well be the immediate biosynthetic precursor of E-3.

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‡ *Added in proof:* Partial hydrolysis of K-2 (**3**) has yielded, *inter alia*, two compounds having, as defined by ^{1}H n.m.r. and mass spectra, R^1, R^2, R^3, R^5 = H, R^4 = AcO·CMe_2CO–, R^6 = Ac, and R^1, R^2, R^3, R^4, R^5 = H, R^6 = Ac. The α-acetoxyisobutyrate can thus be placed at C-9.

[1] R. L. Baxter, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 463.
[2] R. L. Baxter, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1976, 465.
[3] United Nations Document MNAR/5/1976.
[4] United Nations Document MNAR/2/1977.