Alkaloids of *Catha edulis* (Khat). Part 1. Isolation and Characterisation of Eleven New Alkaloids with Sesquiterpene Cores (Cathedulins); Identification of the Quinone–Methide Root Pigments

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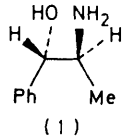
Extraction of fresh and dried specimens of *Catha edulis* (khat) originating from Ethiopia, Kenya, and the Yemen, has led to the isolation of eleven new celastraceous alkaloids having molecular weight of *ca.* 600—*ca.* 1 200 and a sesquiterpene core. They fall into three groups: (*a*) cathedulins E2 and E1, esters of a pentahydroxydihydroagarofuran; (*b*) cathedulins K1(Y1), K2, K6, and K15, esters of euonyminol a nonahydroxyagarofuran, containing one dilactone bridge; and (*c*) cathedulins E3(K11), E4, E5, E6, and K12, more complex esters of euonyminol containing two dilactone bridges.

Apart from norpseudoephedrine (cathine) and the corresponding ketone (cathinone) and a related pyrazine, khat contains steroids and triterpenes including, in the root-bark, a range of triterpenoid quinonemethides characteristic of the Celastraceae.

THE tree *Catha edlus* (Forsk) (Celastraceae) is usually about 3 m high (occasionally 15—20 m), and is widely cultivated in parts of East Africa and the Yemen; it provides a drug known as khat, chat, or quat.[1]

Fresh leaves or tender twigs are usually chewed, though occasionally infusions or smoked material may be employed. The drug acts as a stimulant and suppresses appetite: its use is acceptable to Islam and indeed has religious connections.[1] Being a more profitable crop than coffee it has displaced the latter in some parts. Its use, especially in urban environments, sometimes leads to indolence and disputes, and these socio-economic implications, together with lack of accurate knowledge of the pharmacological effects, has caused concern to the U.N. Commission on Narcotic Drugs. This concern has led to the initiation of work by the U.N. Narcotics Laboratory.[2] Since the Nottingham group had independently taken up investigations in the area, close collaboration was arranged and the present group of papers conveys our joint chemical findings.

Published chemical investigations on khat date from 1887,[3] with regular subsequent re-examinations,[4–6] and a succession of reviews.[7] Much of the early work was confused, and two recent reviews [8,9] provide a valuable guide: the important fact to emerge was that the plant contained (+)-norpseudoephedrine (1).[6] Pharmacological understanding of khat has been greatly hampered by the lack of progress in isolating pure chemical extractives: subjective reports and physiological measurement [8] indicate similarlity of action between the effects of khat and amphetamine (2) but it is far from



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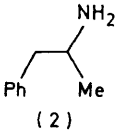


(2)

certain that the activity of khat is solely due to (+)-norpseudoephedrine as once suggested.[8] Krikorian and Getahun [9] consider that the overall response to khat consumption (a user may chew and swallow large amounts per day) is more complex than pure response to (1). It is clear that other alkaloids,[5,10,11] more complicated than (+)-norpseudoephedrine, are present in khat along with a variety of other compounds,[9,12] and structural work on one of these has been reported.[13]

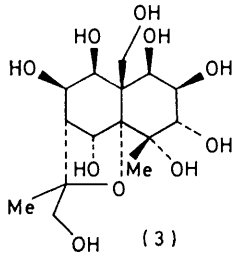
The aim of the present joint work has been to carry out a structural investigation of khat extractives, paying particular attention to the large celastraceous alkaloids which were of a type that had been of recent interest in the Nottingham laboratory.[14] Usage of khat is generally considered to lead to psychological rather than physical dependence, but it is clear that users distinguish a number of types of drug. For this reason we have initially searched for the alkaloids from specimens of three geographical origins (Ethiopia, Kenya, and the Yemen). A total of eleven new weakly-basic alkaloids have been characterised in this work with molecular weights ranging between *ca.* 600 and *ca.* 1 200. Structurally, these compounds fall into three groups and the structural work is reported in the following three parts: [15] preliminary communication of our results has been made.[18] In the present paper we also report on the pigments of the root-bark. Investigations of the phenylalkylamine fraction and the neutral terpenoid substances are described more fully elsewhere.[16,17]

RESULTS AND DISCUSSION

Fresh leaf and young shoot material of khat was collected in Ethiopia, the Yemen (Sana'a market), and Kenya (Nairobi market). Some plant material was extracted either at once, or shortly afterwards, and the remainder freeze-dried and retained for later investigation. Further khat leaves were sun-dried at source as detailed in the Experimental section. Various solvent-extraction procedures were employed, and emphasis was laid on the content of weak bases. In one routine, leaves were treated with ammonia (shown to increase the yield of bases extracted, but without altering the essential composition) and extracted with ether. The

bases were then isolated through dilute acid treatment, and separated by chromatography. Alternatively, ethanol extraction was employed and the diluted extract brought to pH 5.5 before washing with benzene: the neutral products and weak bases were then separated by chromatography.

Although quantitative differences in composition between fresh and dried khat, and between material of different ages were noted, we have not observed any variations in the number and type of the constituent alkaloids. However the alkaloid mixture obtained was dependent on the geographical source of the khat. Plant material from the Yemen gave five alkaloids, cathedulins Y1 (K1, see later), Y7, Y8, Y9, and Y10. With but a limited supply available only cathedulin Y1 could be subjected to a full structural analysis. Cathedulin Y8, however, appears to be identical with E8. Trace amounts of pure cathedulins Y7, Y9, and Y10 were obtained, and mass spectrometry showed them to belong to the same group of sesquiterpene poly-ol esters as the other cathedulins. Kenyan khat provided pure specimens of cathedulins K1, K2, K6, K15, K11, and K12, and cathedulins E2, E3, E4, E5, E6, and E8 were isolated from Ethiopian khat. The only alkaloid common to the last two groups is E3 which is identical to K11. All the cathedulins whose structures have been elucidated have proved to be polyesters or lactones based on one of two terpenoid poly-ols, euonyminol (3), and the 1,2,8,9,-15-pentahydroxydihydroagarofuran (4). Cathedulins E2 and E8 are relatively simple esters of (4); K1(Y1), K2, K6, and K15 form a related group containing one dilactone bridge, while E3, E4, E5, E6, and K12 have more complex structures containing a variety of ester functions and one or two dilactone bridges.



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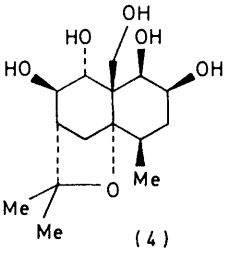

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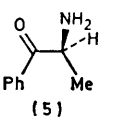
Some alkaloids differ only in the state (free or acetylated) of certain hydroxy-functions. Thus E3, E4; E5, and E6; and K1, K2, K6, and K15 form sub-sets related in this way. It might be suspected that deacetylation could be induced during extraction or chromatography, and that in consequence some of the alkaloids are artefacts. Although this cannot, in all cases, be dismissed, two pieces of evidence suggest that generally, this is not so. First, analytical t.l.c. of fresh material shows essentially the same alkaloid composition as that of the bulk extracts, and, secondly, partial hydrolysis experiments with K2 leads to a set of deacetylated compounds isomeric with, but different from, the natural products K6 and K15. The variations in alkaloid types found in the three khat specimens may be due to different treatment and extraction, but their different origins indicate the importance of further close botanical study of *Catha* species, and a search for chemotypes.

In this work, a more limited investigation of constituents other than the weak bases was made. Norpseudoephedrine (cathine) (1) has been detected [19] by t.l.c. and g.l.c. in crude extracts, apparently as only a minor component of the amine bases. The major base in this fraction proved to be a new phenylalkylamine, cathinone [17] (5) (oxalate, m.p. 157—160 °C). This ketone is possibly a precursor of the pyrazine (6), m.p. 122—124 °C, which was also detected.[17] Neutral products from khat leaf include β-sitosterol, β-sitosterol glycoside,[16] friedeline (7),[16] and certain hydroxylated $\Delta^{4\text{-}exo}$ friedeline relatives.[16]



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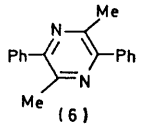

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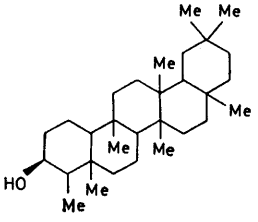

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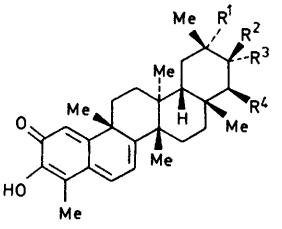

(8); $R^1 = CO_2H, R^2 = R^3 = R^4 = H$
(9); $R^1 = CO_2Me, R^2 = R^3 = R^4 = H$
(10); $R^1CCR^2 = C{=}C, R^3 = R^4 = H$
(11); $R^1 = R^4 = H, R^2 = R^3 = O$
(12); $R^1 = H, R^2, R^3 = O, R^4 = OH$

The roots of Ethiopian khat proved to contain cathedulins E2, E3, E4, E5, and E6, whilst the root-bark was found to be pigmented and to contain various orange-red colouring matters. Triterpenoid quinones have been encountered before in the Celastraceae and those identified in the present work were celastrol (8) [20a] (by t.l.c. only), pristimerin (9),[20a] iguesterin (10),[20b] and 'tingenone',[20c,d] known to be a crystalline mixture of the difficultly separable tingenin-A (11) [20d] and tingenin-B (12).[20c]

EXPERIMENTAL

(1) *Extraction of* Catha edulis (*Forsk*) *collected in Ethiopia.* (*Work carried out in the Nottingham Laboratories*)

General Procedures.—Thin layer chromatograms (t.l.c.) involved alumina G with HF_{254} fluorescor, silica gel G, or silica gel HF_{254}: visualisation was by u.v. irradiation, by spraying with concentrated sulphuric acid, or by spraying with acidified cerium(IV) sulphate followed by charring in heat. Preparative separations (p.l.c.) used 0.8—1.0 mm layers of silica HF_{254} or alumina. Three frequently used t.l.c. and p.l.c. solvent systems are abbreviated as follows: (*i*) E/A, diethyl ether saturated with concentrated aqueous ammonia and used within 2 h: (*ii*) CE 32/A, the organic layer of chloroform–ethyl acetate (3 : 2), equilibrated with

concentrated aqueous ammonia and used the same day; and (*iii*) CM*x*, chloroform containing *x* % methanol. Organic solutions were dried over magnesium sulphate, and evaporated from thin films *in vacuo*. Melting points were measured using a Kofler hot stage apparatus. Optical rotations were measured with an Ericsson 143A automatic polarimeter. Mass spectra were recorded on an A.E.I. MS-902 and a VG 7070 double-focusing spectrometer. ^1H and ^{13}C n.m.r. spectra were normally recorded on a JEOL JNM-PS-100 spectrometer, at 100 and 25.15 MHz respectively, interfaced with a Nicolet 1085 20K computer. Free-induction decays were compiled using 8K data points over 1 000 Hz for ^1H spectra or 6 000 Hz for ^{13}C spectra. All spectra were measured for solutions in deuteriochloroform with tetramethylsilane as internal standard unless stated otherwise.

Extraction of Fresh Leaves.—Fresh leaves of khat were obtained by air freight from Ethiopia, and stored at −28 °C until required. Thawed leaves were then dried in air at ambient temperature for 2 d, and at 50 °C for 24 h, before powdering. The ground leaves (650 g) were extracted (Soxhlet) sequentially with light petroleum (b.p. 60—80 °C) (3 d), diethyl ether (3 d), and methanol (16 h). The ether extract was concentrated to 3 dm^3; on storing at 0 °C for 48 h, no precipitate formed, and the (dark green) solution was extracted with aqueous hydrochloric acid (2M, 4 × 500 cm^3). The aqueous extract was brought to pH 9—10 with saturated aqueous sodium carbonate and exhaustively extracted with chloroform. The organic extracts were washed with brine, dried, and evaporated to provide a green amorphous residue (188 mg). This basic fraction was chromatographed on a column of neutral alumina (100—250 mesh, Grade 1); the total chloroform eluate yielded a yellow foam (172 mg) which was fractionated by p.l.c. [benzene–ethyl acetate–ethanol, (30 : 30 : 1)]. Two major bands were observed, yielding *cathedulin E*2 (65 mg), and an unresolved mixture (initially designated cathedulin E1) (70 mg) of two components. This mixture was separated by p.l.c. (alumina) using benzene–ethyl acetate (2 : 3), when small amounts of pure *cathedulin E*3 and *cathedulin E*4 were obtained. Physical data are presented below. T.l.c. examination of the content of the petrol and methanol extracts revealed none of the components of the basic fraction.

Extraction of Dried Leaves.—Khat leaf, sun-dried in Ethiopia (2.1 kg), was mechanically powdered and extracted during 7 d with diethyl ether in a Soxhlet apparatus. The powdered leaves were dried in air, soaked for 16 h in dilute aqueous ammonia (4 dm^3, 7%), and filtered off. After partial drying in air for 8 h the plant material was re-extracted with ether for a further 7 d. Both extracts were separately concentrated and partitioned with 2M-hydrochloric acid or 2M-aqueous citric acid (reduced tendency to emulsify). The aqueous extracts were adjusted to pH 9—10 by addition of solid sodium carbonate, and were then exhaustively extracted with chloroform. The chloroform layers were washed with brine, dried, and evaporated. In this way the first ether extract yielded a green gum (1.23 g), and the second extract provided a pale green resin (5.40 g). The former was fractionated on a silica column (100 g): after elution with ethyl acetate–n-hexane (1 : 1) (2 dm^3), the eluant was changed to ethyl acetate, when an alkaloid fraction (300 mg) was obtained in the first 500 cm^3 of this solvent. The basic fraction from the second ether extraction was chromatographed on neutral alumina (100—250 mesh, grade 1) with chloroform elution. The total eluate yielded a yellow solid fraction (2.56 g). T.l.c. comparison of the two basic fractions obtained from the ether extracts before and after ammonia treatment showed them to possess similar compositions differing only in the relative intensities of some spots. The fractions were combined to give the total alkaloid fraction (2.86 g; 0.136% of dried leaf).

The neutral fraction of the first ether extract was isolated and its major constituent obtained by p.l.c. using chloroform. Crystallisation from methanol gave β-sitosterol, m.p. 137—138 °C (lit.,[21] m.p. 140 °C) (Found: C, 83.9; H, 11.8. Calc. for $C_{29}H_{50}O$: C, 84.1; H, 12.1%); $[\alpha]_D^{22}$ −35° (*c* 2, chloroform); $\nu_{max.}$ 3 400, 2 940, 1 610, 1 465, and 1 380 cm^{-1}; *m/e* 414 (M^+).

The total alkaloid extract (2.86 g) was resolved into five parts by p.l.c., using a single elution with E/A. Fraction 1 (highest R_F, 0.6) gave only a yellow gum (70 mg) containing no cathedulins or relatives (^1H n.m.r.) and was not further investigated. Fraction 2 gave a yellow solid (60 mg). Further t.l.c. using CE 32/A and then ethyl acetate–benzene (4 : 1) provided small samples of the minor alkaloids cathedulins E7 (colourless gum) and cathedulin E10 (m.p. 191—194 °C from benzene). Homogeneity of these substances has not been fully established. Fraction 3 provided a yellow gum (90 mg). The major component was purified by further t.l.c. with CE 32/A and then ethyl acetate–benzene (4 : 1) to yield *cathedulin E*8 as a colourless gum (Found: M^+, 595.242 7. $C_{32}H_{37}NO_{10}$ requires *M*, 595.241 7); $\lambda_{max.}$ (MeOH) 227 (ε 14 100), 256 (27 000), 264 (3 000), 270 infl. (2 700), and 283 infl. nm (900); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 730, and 1 593 cm^{-1}; δ 9.38 (1 H, m, 2′-H), 8.78 (1 H, br d, *J* 4.0 Hz, 6′-H), 8.44 (1 H, br d, *J* 8.0 Hz, 4′-H), 8.06 (2 H, m, benzoate *o*-H), 7.3—7.6 (4 H, m, benzoate *m*- and *p*-H, 5′-H), 5.74 (1 H, d, *J* 3.4 Hz, 1-H), 5.67 (1 H, br s, 9-H), 5.59 (1 H, ddd, *J*, 3.4, 3.0, and 3.0 Hz, 2-H), 5.45 (1 H, d, *J* 12.0 Hz, 15-H_a), 4.79 (1 H, d, *J* 12 Hz, 15-H_b), 4.26 (1 H, m, 8-H), 2.71 (1 H, d, *J* 13.0 Hz, 6α-H), 2.55 (1 H, m, 3-H), 2.30—1.70 (4 H, m, 3-, 4-, 6-, and 7-H), 1.97 (3 H, s, OAc), 1.41 (6 H, s, OAc and 12-H_3), 1.38 (3 H, d, *J* 5.1 Hz, 14-H_3), and 1.27 (3 H, s, 13-H_3); *m/e* 595 (2), 580 (0.5), 535 (1), 473 (2), 413 (20), 398 (2), 354 (2), 325 (45), 221 (20), 179 (10), 137 (25), 124 (50), 123 (10), 122 (5), 106 (45), and 105 (100); *m** 481 (595→535), 384 (413→398), 376 (595→473), 360 (473→413), 303 (413→354), 296 (535→398), and 264.9 (473→354).

Fraction 4 afforded *cathedulin E*2, (30 mg), m.p. 149—151 °C (transition at 137—140 °C) from ether–light petroleum, $[\alpha]_D^{31}$ −74° (*c* 0.22, $CHCl_3$) (Found: C, 65.23; H, 5.89; N, 3.94. $C_{38}H_{40}N_2O_{11}$ requires C, 65.14; H, 5.71; N, 4.00%); $\lambda_{max.}$ (MeOH) 225 (ε 22 830), 260infl. (5 600), 264 (6 200), 270infl. (4 900), and 282infl. nm (1 500); $\lambda_{max.}$ (MeOH–H_2SO_4) 227 (17 480), 258infl. (10 440), 262 (11 120), 268infl. (9 250), and 282infl. nm (1 520); $\nu_{max.}$ (KBr) 2 920, 1 730infl., 1 718, 1 595, 1 285, 745, and 718 cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 3 050, 1 730(br), and 1 600 cm^{-1}; *m/e* 640.245 (*M* − 60, $C_{36}H_{36}N_2O_9$ requires 640.242), 412.170 2 ($C_{23}H_{26}NO_6$ requires 412.176 0), 137.095 9 ($C_9H_{13}O$ requires 137.096 6), 124.038 8 ($C_6H_6NO_2$ requires 124.039 8), 123.032 0 ($C_6H_5NO_2$ requires 123.032 0), 106.029 5 (C_6H_4NO requires 106.029 3), and 105.032 2 (C_7H_5O requires 105.033 2); *m** at 558 and 465.5; δ_H($CDCl_3$–D_2O) (220 MHz) 9.32 and 9.23 (both 1 H, d, *J* 2 Hz, 2′- and 2″-H), 8.79 and 8.75 (both 1 H, dd, *J* 2 and 5 Hz, 6′- and 6″-H), 8.42 and 8.28 (both 1 H, ddd, *J* 2, 2, and 8 Hz, 4′- and 4″-H), 8.09 (2 H, m, benzoate *o*-H), 7.3—7.7 (5 H, m, benzoate *m* and *p*-H, 5′- and 5″-H), 6.09 (1 H, s, 9-H), 5.78 (1 H, s,

4-OH), 5.75 (1 H, d, *J* 3.5, 1-H), 5.63 (1 H, ddd, *J* 3.5, 3.0, and 3.0 Hz, 2-H), 5.56 (1 H, m, 8-H), 5.71 (1 H, d, *J* 12 Hz, 15-H_a), 4.71 (1 H, d, *J* 12 Hz; 15-H_b), 2.64 (1 H, d, *J* 13 Hz, 6-H_{eq}), 2.49 (1 H, dd, *J* 3.0 and 3.0 Hz, 7-H), 2.20 (1 H, dd, *J* 3.0 and 13 Hz, 6-H_{ax}), 2.06 (1 H, m, 4-H), 1.98 (3 H, s, 2-OAc), 1.63 (3 H, s, 1-OAc), 1.42 and 1.33 (both 3 H, s, 12-H_3 and 13-H_3), and 1.36 (3 H, d, *J* 8 Hz, 14-H_3); δ_C($CDCl_3$), 169.9 and 169.5 (both s, 2 × *C*OMe), 165.1 (s, 2 × *C*OC_5H_4N), 163.8 (s, *C*OPh), 153.7 (d, C-2′ and C-2″), 151.3 and 151.0 (both d, C-6′ and C-6″), 137.0 (d, C-4′ and C-4″), 133.6 (d, benzoate *p*-C), 130.4 (d, benzoate *o*-C), 129.1 (s, benzoate C-1), 128.4 (d, benzoate *m*-C), 125.1 (s, C-3′ and C-3″), 123.3 (d, C-5′ and C-5″), 87.1 (s, C-5), 81.7 (s, C-11), 76.5, 72.3, 71.2, and 70.5 (all d, C-1, -2, -8, and -9), 65.7 (t, C-15), 50.5 (s, C-10), 48.0 (d, C-7), 39.6 (d, C-4), 32.0 and 31.6 (both t, C-3 and -6), 30.3 (q, C-13), 24.4 (q, C-12), 21.2 and 20.5 (both q, CO*Me*), and 18.2 (q, C-14).

Fraction 5 provided a colourless resin (1.80 g) containing (t.l.c.) five components, cathedulin E2 and four new alkaloids. P.l.c. using E/A with six elutions gave; (*i*) cathedulin E2 (99 mg) identical with the above sample; (*ii*) a major band re-processed as described below; (*iii*) a band containing a mixture of cathedulin E5 and E6; and (*iv*) a pure sample of *cathedulin E6*, (81 mg) as a colourless amorphous solid (Found: C, 60.55; H, 5.5; N 2.3%; M^+, 1126.380. $C_{57}H_{62}N_2O_{22}$ requires C, 60.7; H, 5.5; N, 2.5%; M^+, 1 126.383); $\lambda_{max.}$ (EtOH), 217 (46 000), 265 (17 550), and 287infl. nm (6 800); $\nu_{max.}$ ($CHCl_3$) 3 470, 3 000, 1 750, 1 725, 1 595, 1 570, 1 515, and 1 470 cm^{-1}; δ_H($CDCl_3$, 220 MHz), 8.90 (1 H, s, 2″-H), 8.75 (1 H, dd, *J* 2 and 5 Hz, 6′-H), 8.6 (1 H, m, 6″-H), 8.2 (1 H, dd, *J* 2 and 8 Hz, 4′-H), 7.8 (1 H, dd, *J* 2 and 8 Hz, 4″-H), 7.5—7.6 (2 H, d, benzoate *o*-H), 7.45 (2 H, s, 9″- and 13″-H), 7.35 (1 H, m, 5′-H), 7.1—7.2 (3 H, m, benzoate *m* and *p*-H), 6.0 (1 H, d, *J* 13 Hz, 13-H_a), 5.92 (1 H, d, *J* 2.8 Hz, 1-H), 5.78 (1 H, s, 4-OH), 5.72 (1 H, dd, *J* 3 and 3 Hz, 2-H), 5.7 (1 H, s, 6-OH), 5.4—5.5 (2 H, m, 8- and 9-H), 5.25 (1 H, d, *J* 12, 15-H_a), 4.85 (1 H, d, *J* 3.2 Hz, 3-H), 4.83 (1 H, q, *J* 7 Hz, 7′-H), and 4.65 (1 H, d, *J* 12 Hz, 15-H_b), 4.57 (1 H, s, 4-OH), 4.53 (1 H, br s, 6-H), 3.93 (6 H, s, 14″-H_3 and 15″-H_3), 3.90 (3 H, s, 16″-H_3), 3.76 (1 H, d, *J* 13 Hz, 13-H_b), 2.67 (1 H, d, *J* 5 Hz, 7-H), 2.65 (1 H, q, *J* 7 Hz, 8′-H), 2.05 (3 H, s, OAc), 1.85, 1.80, 1.69, and 1.61 (all 3 H, s, 4 × C-Me), 1.29 (3 H, s, 2-OAc), 1.45 and 1.25 (both 3 H, d, *J* 7 Hz, 10′-H_3 and 11′-H_3); δ_C($CDCl_3$) 173.6, 171.3, 170.1, 168.7, 168.7, 165.4, 164.8, and 164.1 (s, 8 × C=O), 165.7 (s, C-2′), 153.0 (d, C-2″), 152.9 (s, C-10″ and C-12″), 151.8 (d, C-6′), 150.4 (d, C-6″), 142.7 (s, C-11″), 138.1 (d, C-4″), 136.3 (d, C-4′), 133.3 (d), 129.1 (d), 128.5 (d), and 128.2 (s) (benzoate *p*, *o*, *m*, and quaternary C), 125.1 (s, C-3′), 124.3 (s, C-3″ and C-8″), 122.7 (d, C-5′), 121.2 (d, C-5″), 107.5 (d, C-9″ and C-13″), 92.5 (s, C-5), 85.6 (s, C-11), 78.8 (s, C-4), 74.9, *ca.* 73.6, 73.5, 72.3, 71.9, 69.2 [all s, C-1, -2, -3, -8, -9, and Me_2C(OR)CO], 71.0 (C-13), 63.3 (t, C-15), 60.8 (d, C-6), 56.2 (q, C-14″, -15″, and -16″), 51.0 (d, C-7), 50.2 (s, C-10), 45.2 (d, C-8′), 36.0 (d, C-7′), 25.2, 24.9 [q, Me_2C(OR)CO], 23.9 (q, C-12), 20.2 and 20.9 (q, 2 × *Me*CO), 18.5 (q, C-14), and 11.7 and 9.5 (q, C-10′ and C-11′).

The major band, (*ii*) above, was re-chromatographed using eight E/A elutions. The separated bands were again chromatographed using CE 32/A, and the process repeated until t.l.c. pure specimens of cathedulin E5 (8.8 mg), cathedulin E4 (145 mg), and cathedulin E3 (27 mg) were finally obtained. *Cathedulin E5* was a colourless amorphous solid (Found: M^+, 1 168. $C_{59}H_{64}N_2O_{23}$ requires *M*, 1 168). *Cathedulin E3* crystallised from ether–light petroleum, m.p. 245.—248 °C, $[\alpha]_D^{20}$ −44.8° (*c* 0.27, $CHCl_3$) (Found: M^+, 1 104.360. $C_{54}H_{60}N_2O_{23}$ requires *M*, 1 104.360); $\lambda_{max.}$ (EtOH) 215 (ε 40 570), 268 (13 010), and 293infl. nm (5 890); $\nu_{max.}$($CHCl_3$) 2 990, 1 750infl., 1 730infl., 1 720, 1 590, and 1 460 cm^{-1}; δ_H($CDCl_3$, 100 MHz), 9.21 (1 H, s, 2″-H), 8.79 (1 H, d, *J* 5 Hz, 6″-H), 8.70 (1 H, dd, *J* 1.8 and 4.8 Hz, 6′-H), 8.09 (1 H, dd, *J* 1.8 and 7.9 Hz, 4′-H), 7.68 (1 H, br d, *J* 5.0 Hz, 5″-H), 7.43 (1 H, d, *J* 1.8 Hz, 9″-H), 7.27 (1 H, dd, *J* 4.8 and 7.9 Hz, 5′-H), 6.96 (1 H, d, *J* 1.8 Hz, 13″-H), 6.42 (1 H, d, *J* 11.1 Hz, 16″-H_a), 6.0 (1 H, s, 6-H), 5.91 (1 H, d, *J* 3.4 Hz, 1-H), 5.88 (1 H, d, *J* 12.0 Hz, 13-H_a), 5.58 (1 H, d, *J* 12.0 Hz, 15-H_a), 5.5—5.65 (1 H, m, 8-H), 5.34 (1 H, br d, *J* 6 Hz, 9-H), 5.08 (1 H, dd, *J* 3 and 3 Hz, 2-H), 4.89 (1 H, d, *J* 11.1 Hz, 16-H_b), 4.61 (d, *J* 2.9 Hz, 3-H), 4.6 (1 H, m, 7′-H), 4.57 (1 H, br s, 4-OH), 4.10 (3 H, s, 15″-H_3), 3.92 (1 H, d, *J* 12.0 Hz, 15-H_b), 3.72 (1 H, d, *J* 12.0 Hz, 13-H_b), 3.10 (3 H, s, 14″-H_3), 2.58 (1 H, q, *J* 7 Hz, 8′-H), 2.3 (1 H, 7-H), 2.25 (3 H, s, COMe), 2.14 (6 H, s, 2 × COMe), 1.84, 1.75, 1.69, and 1.61 (all 3 H, s, 12-H_3, 14-H_3, and Me_2C), 1.38 (3 H, d, *J* 7.1 Hz, 10′-H_3), 1.35 (3 H, s, 2-OCOMe), and 1.19 (3 H, d, *J* 7.1 Hz, 11′-H_3); δ_C($CDCl_3$) 173.6, 171.8, 169.8, 169.8, 169.6, 168.7, 168.2, 164.6, 164.3 (all s, 9 × C=O), 165.3 (s, C-2′), 154.2 and 153.7 (both s, C-10″ and C-12″), 152.9 (d, C-2″), 151.5 (d, C-6′), 150.7 (d, C-6″), 145.3 (s, C-11″), 137.9 (s, C-4″), 137.7 (d, C-4′), 128.9 and 121.1 (both d, C-5′ and C-5″), 126.0, 125.6, and 124.9 (all s, C-3′, C-3″, and C-8″), 106.7 and 105.9 (both d, C-9″, C-13″), 93.7 (s, C-5), 84.6 (s, C-11), 78.4 (C-4), 75.3, 72.6, 72.5, 71.2, 70.7, 70.6, 69.9, 69.7, and 68.4 [C-1, -2, -3, -6, -8, -9, -13, -16″, and Me_2C(OR)CO], 61.8 (m, C-15), 56.3 and 55.1 (both q, C-14″ and -15″), 52.3 (s, C-10), 50.7 (d, C-7), 44.9 (q, C-8′), 36.6 (q, C-7′), 26.8, 25.0, 23.0, and 18.2 (all q, C-12, C-14, (Me_2C), 21.5, 20.9, 20.5, and 20.4 (all q, 4 × *Me*CO), 12.0 (q, C-11′), and 9.8 (q, C-10′).

Cathedulin E4 was a colourless amorphous solid, $[\alpha]_D^{27}$ −37° (*c* 0.56, $CHCl_3$) (Found: C, 58.6; H, 5.5; N, 2.35%; *M*, 1 062.348. $C_{52}H_{58}N_2O_{22}$ requires C, 58.8; H, 5.5; N, 2.64%; *M*, 1 062.348); $\lambda_{max.}$ (EtOH) 215 (ε 41 000) and 268 nm (12 040); $\nu_{max.}$ ($CHCl_3$) 3 377, 1 756, 1 725, 1 683, 1 594, 1 568, and 1 466 cm^{-1}; δ_H($CDCl_3$, 100 MHz) 9.21 (1 H, s, 2″-H), 8.79 (1 H, d, *J* 4.9 Hz, 6″-H), 8.69 (1 H, dd, *J* 1.8 and 4.9 Hz, 6′-H), 8.15 (1 H, dd, *J* 1.8 and 7.8 Hz, 4′-H), 7.67 (1 H, br d, *J* 5.3 Hz, 5″-H), 7.32 (1 H, d, *J* 1.8 Hz, 9″-H), 7.3 (1 H, m, 5′-H), 6.98 (1 H, d, *J* 1.8 Hz, 13″-H), 6.39 (1 H, d, *J* 11.0 Hz, 16″-H_a), 6.06 (1 H, d, *J* 3.2 Hz, 6-OH), 5.9 (1 H, d, *J* 12.0 Hz, 13-H_a), 5.89 (1 H, d, *J* 3.4 Hz, 1-H), 5.84 (1 H, s, 4-OH), 5.5—5.65 (1 H, m, 8-H), 5.55 (1 H, d, *J* 12.0 Hz, 15-H_a), 5.35 (1 H, d, *J* 5.8 Hz, 9-H), 5.12 (1 H, dd, *J* 3 and 3 Hz, 2-H), 4.89 (1 H, d, *J* 11.0 Hz, 16″-H_b), 4.78 (q, 1 H, *J* 7 Hz, 7′-H), 4.66 (1 H, br d, *J* 3.2 Hz, 6-H), 4.61 (1 H, d, *J* 3.0 Hz, 3-H), 4.10 (3 H, s, 15″-H_3), 3.79 (1 H, d, *J* 12 Hz, 15-H_b), 3.71 (1 H, d, *J* 12 Hz, 13-H_b), 3.10 (3 H, s, 14″-H_3), 2.53 (1 H, q, *J* 7 Hz, 8′-H), 2.41 (1 H, d, *J* 3.7 Hz, 7-H), 2.13, 2.11, and 1.37 (all 3 H, s, COMe), 1.91, 1.83, 1.77, and 1.68 (all 3 H, s, 12-H_3, 14-H_3, and (Me_2C), 1.39 (3 H, d, *J* 7 Hz, 10′-H_3), and 1.14 (3 H, d, *J* 7 Hz, 11′-H_3).

Extraction of Roots.—Dried roots of Ethiopian *C. edulis* were stripped of pigmented bark (see below), ground to a fine powder (2.15 kg), and extracted by Soxhlet with light petroleum (b.p. 40—60 °C) (4 d), diethyl ether (4 d), and methanol (4 d), in sequence. Treatment of the roots with aqueous ammonia as above for dried leaves, and re-extraction with ether for 7 d gave a fourth extract. The two

ether isolates were processed as for the dried leaves above to yield basic fractions, 307 and 660 mg respectively. Repeated p.l.c. of these products as already described resulted in the isolation of cathedulins E2 (29 mg), E3 (87 mg), E4 (93 mg), E5 (3.5 mg), and E6 (22 mg).

Extraction of the Root Bark.—Method (*i*). The bark from the roots (see above) was extracted by Soxhlet using light petroleum (b.p. 40—60 °C). Evaporation of the extract gave a red oil (17.5 g), which was chromatographed on a silica column (220 g, Hopkin and Williams 100—200 mesh); elution commenced with light petroleum and progressed to chloroform, and then to chloroform containing increasing proportions of methanol. An orange-red fraction was obtained with chloroform–methanol (95 : 5), yielding a red residue (3.58 g) on evaporation. This material was again subjected to column chromatography on silica (340 g). The column was pre-washed with ethyl acetate–light petroleum (10 : 90), and eluted with light petroleum–ethyl acetate (80 : 20—0 : 100). Solvent mixture 60 : 40 eluted orange-red products (0.91 g after evaporation). P.l.c. with light petroleum–ethyl acetate (60 : 40) separated three orange-red bands. That of highest R_F was collected and the red solute purified by p.l.c. with ether–benzene (40 : 60). The red fraction was collected, treated with charcoal in methylene chloride–ether, and finally crystallised from ether–light petroleum (b.p. 60—80 °C) to yield a deep red crystalline product (25 mg), m.p. 184—185°, identified as ' tingenone ' by t.l.c. comparison (two solvent systems) with an authentic sample kindly supplied by Professor R. H. Thomson. ' Tingenone ' has been shown to be a mixture, separable with great difficulty, of tingenin A and tingenin B.

The orange-red p.l.c. band of intermediate R_F was re-plated, eluting once with ether–benzene (40 : 60), and twice with ether–benzene (5 : 95). The content of the orange band was extracted into diethyl ether, and, after treatment with charcoal and filtration through silica, the ether solution was concentrated and diluted with light petroleum. Orange needles (9.2 mg) were deposited (two crops), m.p. 216—218 °C. This product was identified as pristimerin, by t.l.c. (two solvents) and i.r. (KBr) comparison with authentic pristimerin, and by m.p. and mixed m.p. 218—220 °C with an authentic sample (m.p. 218—220 °C).

Method (*ii*). *C. edulis* roots (42 g) were extracted with chloroform (1 dm^3) at room temperature for 18 h. The mixture was filtered and the marc re-extracted with warm chloroform (1 dm^3). The combined extracts were evaporated. Analytical t.l.c. on the residue (2.1 g) indicated the presence of celastrol (comparison with an authentic sample), pristimerin, tingenone, and another major pigment of low R_F [using diethyl ether–benzene (40 : 60)]. The latter was isolated by column chromatography on silica (69 g). Elution with ethyl acetate–light petroleum (20 : 80), and evaporation of the appropriate fractions gave the crude pigment (30 mg), further purified by twice repeated p.l.c. (ethyl acetate–cyclohexane 40 : 60, chloroform) to yield iguesterin as a red gum (2.5 mg), identified by the close parallel between its u.v., i.r., ^1H n.m.r., and mass-spectral data with those published.

(2) *Extraction of* Catha edulis (*Forsk*) *collected in Kenya.* (*Isolation and purification work carried out in the Geneva Laboratories*)

General Procedures.—T.l.c. involved silica gel G, and p.l.c. silica gel HF_{254}; the solvent system benzene–ethyl acetate–ethanol (30 : 30 : 2.5) was employed unless otherwise stated. U.v. and i.r. spectra were recorded on Beckman-Acta III and Beckman IR 5A spectrophotometers respectively. ^1H N.m.r. data were either obtained with a Varian HA-100 instrument, or as in section 1. Electron impact mass spectra were collected on Hitachi–Perkin-Elmer RMU6E and LKB 9000 spectrometers. Additional mass spectra and accurate mass measurements were made as in section (1). Chemical-ionisation mass spectra, using isobutane as ionising gas, were recorded on an A.E.I. MS9 instrument.

Extraction of Khat Shoots.—Bundles of khat, young stem and leaf, were purchased at the market in Nairobi, Kenya, and freeze-dried. The powdered material (1.5 kg) was percolated at room temperature with methanol (15 dm^3). The extract was concentrated under reduced pressure (maximum temperature 40 °C) to 1 500 cm^3. An equal volume of water was added, and the turbid solution was carefully extracted with benzene (5 × 3 dm^3). The dried (sodium sulphate) benzene extracts were combined and evaporated to give a green waxy residue. The combined residue (total 51 g) from two such batches was dissolved in benzene (200 cm^3) and chromatographed on a Florisil column (1 500 g, 90 × 7 cm). Elution was begun with benzene: polarity was then increased slowly by the addition of ethyl acetate, and then ethanol, in the following sequence: benzene–ethyl acetate (95 : 5, 90 : 10, 80 : 20, 70 : 30, 60 : 40, 50 : 50); benzene–ethyl acetate–ethanol (50 : 50 : 1.5, 50 : 50 : 2.5, 50 : 50 : 5, 50 : 50 : 10, 50 : 50 : 50, 20 : 40 : 40); and ethyl acetate–ethanol (50 : 50). Fractions (250 cm^3) were collected and monitored by t.l.c. for alkaloid content (Dragendorff's reagent and potassium iodoplatinate reagent); fractions 24—132 gave positive responses. Similar fractions (24—31, 32—34, 35—65, 66—85, 86—99, and 100—132) were combined, and the solvent evaporated off *in vacuo*. Fractions 24—31 gave a residue (3.5 g), which was dissolved in benzene–n-hexane (9 : 1) (80 cm^3) and the solution was extracted with 7% hydrochloric acid (3 × 50 cm^3). The aqueous extract was treated dropwise and with cooling with concentrated aqueous ammonia, to pH 9, and immediately extracted with chloroform (1 × 100 cm^3, 2 × 50 cm^3). The organic solutions were dried and evaporated. The residue (1.3 g) was dissolved in benzene–ethyl acetate, and chromatographed on a 65 × 2 cm column of Kieselgel 60 (Merck) (100 g). Elution was started with benzene–ethyl acetate (50 : 50), and then successively with benzene–ethyl acetate–ethanol (50 : 50 : 0.5, 50 : 50 : 1, 50 : 50 : 1.5, 50 : 50 : 2). Fractions (50 cm^3) were collected and monitored by t.l.c.; those containing a single component were evaporated to yield, first *cathedulin K*1 (for physical and spectroscopic information see cathedulin Y1, later), and then *cathedulin K*2, forming needles from ether–n-hexane, m.p. 181—184 °C, $[\alpha]_D^{20}$ −17.8° (*c* 1.9, $CHCl_3$) (Found: M^+, 849.315. $C_{40}H_{51}NO_{19}$ requires *M*, 849.306), $\lambda_{max.}$ (MeOH) 221 (ε 7 840) and 265 nm (3 680); $\nu_{max.}$ (KBr) 3 400, 3 300, 2 920, 1 750infl., 1 720, 1 700, 1 560, 995, 970, 925, 895, 880, 865, 828, 775, and 745 cm^{-1}; *m/e* 849, 831 (*M* − 18), 807 (*M* − 42), 789 (*M* − 60), and 771 (*M* − 18 − 60); the sample showed a small peak at *m/e* 891; δ_H($CDCl_3$, 100 MHz), 8.75 (1 H, dd, *J* 2 and 5 Hz, 6′-H), 8.13 (1 H, dd, *J* 2 and 8 Hz, 4′-H), 7.32 (1 H, dd, *J* 5 and 8 Hz, 5′-H), 7.04 (1 H, s, 6-H), 6.02 (1 H, d, *J* 12 Hz, 13-H_a), 5.64 (1 H, dd, *J* 4 and 6 Hz, 8-H), 5.49 (1 H, d, *J* 14 Hz, 15-H_a), 5.45 (1 H, d, *J* 6 Hz, 9-H), 5.41 (1 H, d, *J* 3.5 Hz, 1-H), 4.78 (1 H, d, *J* 3 Hz, 3-H), 4.69 (1 H, q, *J* 7 Hz,

7′-H), 4.53 (1 H, s, 4-OH), 4.49 (1 H, d, *J* 14 Hz, 15-H_b), 4.10 (1 H, dd, *J* 3 and 3.5 Hz, 2-H), 3.69 (1 H, d, *J* 12 Hz, 13-H_b), 2.94 (1 H, br s, 2-OH), 2.53 (1 H, q, *J* 7 Hz, 8′-H), 2.27 (1 H, d, *J* 4 Hz, 7-H), 2.42, 2.21, 2.09, 2.05, and 1.95 (all 3 H, s, 5 × COMe), 1.69, 1.64, 1.61, and 1.54 (all 3 H, s, 12-H_3, 14-H_3, and Me_2C), 1.38 (3 H, d, *J* 7 Hz, 10′-H_3), 1.15 (3 H, d, *J* 7 Hz, 11′-H_3); δ_C 174.6, 172.1, 170.9, 170.2, 169.5, 169.3, 169.0, and 168.4 (all s, 8 × OCO), 165.1 (s, C-2′), 151.3 (d, C-6′), 137.6 (d, C-4′), 125.4 (s, C-3′), 121.1 (d, C-5′), 94.6 (s, C-5), 84.1 (s, C-11), 78.5, 78.1, 75.9, 73.9, 71.1, 70.6, 70.0, 69.4, and 69.3 [C-1, -2, -3, -4, -6, -8, -9, and -13, and Me_2C(OR)CO], 60.9 (t, C-15), 52.2 (s, C-10), 50.3 (d, C-7), 45.1 (d, C-8′), 36.4 (d, C-7′), 24.8, 24.2, 22.8, 21.6, 21.3, 21.1, 20.7, 20.5, and 18.4 (all q, 5 × MeCO, C-12, C-14, and Me_2C), 11.8 (q, C-11′), and 9.4 (q, C-10′).

Fractions 35—65 were evaporated, and the residue (6.9 g) was dissolved in benzene–n-hexane (9 : 1) (100 cm^3). The solution was extracted with 7% aqueous hydrochloric acid (3 × 50 cm^3). The extracts were brought to pH 9 (concentrated aqueous ammonia), and extracted with chloroform (3 × 100 cm^3). The dried extract was evaporated and the residue (4.05 g) was dissolved in ether. On standing this solution at 0 °C crystals of *cathedulin K*11 were slowly deposited, m.p. 245—248 °C, $[\alpha]_D^{20}$ −44.4 (*c* 0.96, $CHCl_3$). A detailed t.l.c. and ^1H n.m.r. comparison showed this compound to be identical with cathedulin E3.

Fractions 86—99 were evaporated and the residue (1.5 g) treated as for preceding fractions. The basic component was chromatographed on a 23 × 3 cm column of alumina (150 g) (previously deactivated with ethyl acetate) and eluted with benzene. Step-gradient elution through benzene–ethyl acetate (95 : 5, 90:10, 80 : 20, 70 : 30, 60 : 40, and 50 : 50) was followed by t.l.c. Fractions containing one major component were combined and evaporated, and the residue crystallised from ether to yield *cathedulin K*12, m.p. 268—272 °C (Found: M^+, 1 106. $C_{54}H_{62}N_2O_{23}$ requires *M*, 1 106); $\lambda_{max.}$ (MeOH), 218, 266, and 289infl. nm; $\nu_{max.}$ (KBr) 3 400, 2 920, 1 755infl., 1 745, 1 720, 1 590, 1 565, 975, 875, 848, 765, and 737 cm^{-1}; *m/e* 1 106, 1 088 (*M* − 18), 1 064 (*M* − 42), 1 046 (*M* − 60), 894, 213, 195, 124, 106, and 105; δ_H($CDCl_3$, 100 MHz), 9.26 (1 H, d, *J* 1 Hz, 2″-H), 8.77 (1 H, dd, *J* 1 and 5 Hz, 6″-H), 8.68 (1 H, dd, *J* 2 and 5 Hz, 6′-H), 8.28 (1 H, ddd, *J* 1, 1, and 8 Hz, 4″-H), 8.08 (1 H, dd, *J* 2 and 8 Hz, 4′-H), 7.39 (1 H, dd, *J* 5 and 8 Hz, 5″-H), 7.30 (1 H, dd, *J* 5 and 8 Hz, 5′-H), 7.20 (2 H, s, 9″, 13″-H_2), 5.93 (1 H, d, *J* 12 Hz, 13-H_a), 5.85 (1 H, d, *J* 3 Hz, 1-H), 5.51 (1 H, d, *J* 12 Hz, 15-H_a), 5.7—5.2 (3 H, m, 2-H, 8-H, and 9-H), 5.03 (1 H, d, *J* 12 Hz, 15-H_b), 4.76 (1 H, d, *J* 3 Hz, 3-H), 4.68 (1 H, q, *J* 7 Hz, 7′-H), 4.58 (1 H, s, 4-OH), 3.87 (9 H, s, 3 × OMe), 3.73 (1 H, d, *J* 12 Hz, 13-H_b), 2.63 (1 H, q, *J* 7 Hz, 8′-H), 2.53 (1 H, d, *J* 4 Hz), 2.17 (3 H, s, COMe), 1.97 (3 H, s, COMe), 1.79—1.78 (12 H, br s, 4 × Me), 1.70 and 1.67 (both 3 H, s, Me), 1.40 (3 H, d, *J* 7 Hz, 10′-H_3), and 1.24 (3 H, d, *J* 7 Hz, 11′-H_3).

Fractions 66—85 were evaporated and the residue (5.3 g) was extracted from benzene (100 cm^3) with 7% aqueous hydrochloric acid (4 × 50 cm^3). The extracts were basified to pH 9 (concentrated aqueous ammonia) and washed with chloroform (3 × 100 cm^3). The organic phase, after drying and evaporation, gave a residue (3.1 g) which was combined with the residue of fractions 35—65 after crystallisation of cathedulin K11, and chromatographed on a 65 × 2 cm column of silica gel (100 g). Elution commenced with diethyl ether, stepping to ether–concentrated ammonia (100 : 0.25), ether–methanol–concentrated ammonia [97.5 : 2.5 : 0.25(A), 95 : 5 : 0.25], and 50-cm^3 fractions were collected. Those from solvent system (A) crystallised from ether to give another sample of cathedulin K11 (1.25 g). The other fractions were re-chromatographed on a similar column and elution was carried out with ether, ether–methanol–concentrated ammonia [95 : 0.25 : 0.5(B), 95 : 0.25 : 1, 95 : 0.25 : 2, and 95 : 0.25 : 3]. Solvent (B) gave fractions which after evaporation and crystallisation afforded *cathedulin K*6, m.p. 176—180 °C (Found: M^+, 807.296. $C_{38}H_{49}NO_{18}$ requires *M*, 807.295); $\lambda_{max.}$ (MeOH) 221 and 265 nm; $\nu_{max.}$ ($CHCl_3$) 3 500, 2 930, 1 760infl., 1 750infl., 1 725, and 1 590 cm^{-1}; *m/e* 807, 789 (*M* − 18), 765 (*M* − 42), 747 (*M* − 60), and 729 (the sample also showed a small peak at *m/e* 849); δ_H($CDCl_3$, 100 MHz), 8.67 (1 H, dd, *J* 2 and 5 Hz, 6′-H), 8.03 (1 H, dd, *J* 2 and 8 Hz, 4′-H), 7.23 (1 H, dd, *J* 5 and 8 Hz, 5′-H), 6.51 (1 H, s, 6-H), 5.86 (1 H, d, *J* 11 Hz, 13-H_a), 5.54 (1 H, d, *J* 3 Hz,1-H), *ca.* 5.5 (1 H, m, 8-H), 5.38 (1 H, d, *J* 6 Hz, 9-H), 4.78 (1 H, d, *J* 3 Hz, 3-H), 4.62 (1 H, d, *J* 13 Hz, 15-H_a), 4.62 (1 H, d, *J* 13 Hz, 15-H_b), 4.6 (1 H, q, *J* 7 Hz, 7′-H), 4.24 (1 H, s, OH), 4.16 (1 H, d, *J* 13 Hz, 15-H_b), 3.98 (1 H, br dd, 2-H), 3.69 (1 H, d, *J* 11 Hz, 13-H_b), 2.55 (1 H, q, *J* 7 Hz, 8′-H), 2.34 (1 H, d, *J* 4 Hz, 7-H), 2.16 (3 H, s), 2.10 (6 H, s), 1.92 (3 H, s) (4 × COMe), *ca.* 1.8 (br, OH), 1.70 (3 H, s), 1.65 (3 H, s), 1.63 (3 H, s), 1.59 (3 H, s) (4 × Me), 1.36 (3 H, d, *J* 7 Hz, 10′-H_3), and 1.18 (3 H, d, *J* 7 Hz, 11′-H_3).

Fractions 100—132 provided, on evaporation, a residue (3.5 g) which was dissolved in benzene (50 cm^3) and the basic part (3 g) extracted as above when it was combined with the residue from fractions 86—99 after removal of cathedulin K12. Part (2 g) of this mixture was chromatographed over silica gel using ether–methanol–concentrated ammonia [95 : 1 : 0.25, 95 : 2 : 0.5, 95 : 3 : 0.5(C), 95 : 4 : 0.5, 95 : 5 : 0.5, 95 : 10 : 0.5, and 95 : 20 : 0.5].

Fractions (5 cm^3) were collected, and those eluted by solvent (C) yielded, after evaporation and crystallisation, *cathedulin K*15, m.p. 191—194 °C from ether–n-hexane (Found: M^+, 765.286. $C_{36}H_{47}NO_{17}$ requires *M*, 765.285); $\lambda_{max.}$ (MeOH) 221 (ε 8 400) and 264 nm (3 850); $\nu_{max.}$ ($CHCl_3$) 3 500, 2 920, 1 765infl., 1 750infl., 1 730, and 1 595 cm^{-1}; *m/e* 765, 747, 723, 705, and 687 (higher peaks at *m/e* 807 and 849 were noted); δ_H($CDCl_3$, 100 MHz), 8.68 (1 H, d, *J* 4.9 Hz, 6′-H), 8.04 (1 H, d, *J* 7.2 Hz, 4′-H), 7.26 (1 H, obscured, 5′-H), 6.72 (1 H, s, 6-H), 5.83 (1 H, d, *J* 11 Hz, 13-H_a), *ca.* 5.5 (1 H, m, 8-H), 5.50 (1 H, d, *J* 3.7 Hz, 1-H), 5.39 (1 H, d, *J* 5.6 Hz, 9-H), 4.77 (1 H, d, *J ca.* 2 Hz, 3-H), *ca.* 4.6 (1 H, d, *J* 13.7 Hz, 15-H_a), *ca.* 4.6 (1 H, 7′-H), 4.32 (1 H, s, 4-OH), 4.23 (1 H, d, *J* 13.7 Hz, 15-H_b), 4.02 (1 H, dd, *J* 2, 4 Hz, 2-H), 3.68 (1 H, d, *J* 11 Hz, 13-H_b), *ca.* 3.3 (2 × O*H*), 2.57 (1 H, q, *J* 7 Hz, 8′-H), 2.43 (1 H, d, *J* 4.4 Hz, 7-H), 2.20, 2.06, and 1.95 (all 3 H, s, 3 × COMe), 1.71, 1.64 (each 3 H, s, 12-H_3 and 14-H_3), 1.51 (6 H, s, CMe_2), 1.38 (3 H, d, *J* 7 Hz, 10′-H_3), and 1.20 (3 H, d, *J* 7 Hz, 11′-H_3).

(3) *Extraction of* Catha edulis (*Forsk*) *collected in the Yemen.* (*Isolation carried out in the Geneva Laboratories*)

General procedures followed those given in (2) above.

Extraction.—Fresh khat shoots (harvested early on the day of sale) were purchased in Sana'a market. Extraction was carried out in the University of Sana'a on the same day. Further samples were extracted shortly afterwards in Cairo (Laboratory of Drug Analysis and Control, Ministry of Public Health), and in the U.N. Laboratory, Geneva.

The following method was employed. Cut leaves (1.5 kg) with sodium hydrogencarbonate (30 g) were refluxed in ethanol (6 dm^3) for 1 h. The mixture was filtered, and the filtrate concentrated to 3 dm^3, diluted with water (3 dm^3), and acidified with 10% hydrochloric acid to pH 5.5. The aqueous solution was then extracted with benzene (5 × 3 dm^3). The combined, dried, benzene extracts were evaporated and the green waxy residue (5.9 g) was dissolved in chloroform (50 cm^3). This solution was chromatographed on a 30 × 5 cm column of silica gel (200 g). Elution was started with benzene, progressed to benzene–ethyl acetate mixtures (9 : 1, 8 : 2, 7 : 3, 6 : 4, 5 : 5), and then to benzene–ethyl acetate–ethanol (5 : 5 : 0.125, 5 : 5 : 0.25, 5 : 5 : 0.5, 5 : 5 : 1.25), followed by a final wash with chloroform–methanol (9 : 1). Fractions 16—41 (100-cm^3 fractions) contained weakly basic alkaloids. On the basis of t.l.c. monitoring, fractions were combined to yield seven new fractions, each with several components. These new fractions were separated by p.l.c. on alumina F_{254} [benzene–ethyl acetate–ethanol (30 : 30 : 0.5)], and the corresponding bands combined. The separated components were then re-purified by p.l.c. on silica using the same solvent system. Twelve components were obtained in small quantity. Sufficient material was obtained of five samples to allow mass spectra to be measured. Cathedulin Y7 had M^+ 958 and fragment ions $M - 42$, $M - 60$, and 43; $M - 105$, 77, and 105; $M - 124$, 78, 106, and 124; $M - 212$ and 195; $M - 206$, 151, 160, 178, and 206, deriving from acetate, benzoate, nicotinoate, gallate, and evoninate esters respectively. Cathedulins Y9 and Y10 had M^+ 900 and 980 respectively, and the same fragment ions as listed for Y7.

Cathedulin Y1 (identical with K1, above) (Found: M^+, 891.310. $C_{42}H_{53}NO_{20}$ requires M, 891.316); $\lambda_{max.}$ (MeOH) 221 (ε 8 180) and 265 nm (3 760); $\nu_{max.}$ (KBr) 3 520, 2 920, 1 760infl., 1 750, 1 580, 985, 940, 910, 840, 795, and 780 cm^{-1}; *m/e* 891, 876, 863, 849, 831, and 789; δ_H($CDCl_3$, 100 Mz), 8.64 (1 H, dd, *J* 2 and 5 Hz, 6′-H), 8.03 (1 H, dd, *J* 2 and 8 Hz, 4′-H), 7.22 (1 H, dd, *J* 5 and 8 Hz, 5′-H), 6.95 (1 H, s, 6-H), 5.94 (1 H, d, *J* 11 Hz, 13-H_a), *ca.* 5.54 (1 H, m, 8-H), *ca.* 5.51 (1 H, d, *J* 4 Hz, 1-H), 5.3 (1 H, d, *J* 5 Hz, 9-H), 5.26 (1 H, d, *J* 13 Hz, 15-H_a), 5.21 (1 H, m, 2-H), 4.69 (1 H, d, *J* 3 Hz, 3-H), 4.60 (1 H, obscured, 7′-H), 4.52 (1 H, s, 4-OH), 4.34 (1 H, d, *J* 13 Hz, 15-H_b), 3.66 (1 H, d, *J* 11 Hz, 13-H_b), 2.52 (1 H, q, *J* 7 Hz, 8′-H), 2.24 (1 H, d, *J* 4 Hz, 7-H), 2.38, 2.16, 2.14, 2.03, 1.97, and 1.79 (all 3 H, s, 6 × COMe), 1.65, 1.59, 1.55, and 1.45, (all 3 H, s, 4 × Me), 1.35 (3 H, d, *J* 7 Hz, 10′-H_3), and 1.14 (3 H, d, *J* 7 Hz, 11′-H_3); *m/e* 891, 849 ($M - 42$), 831 ($M - 60$), 685 ($M - 206$), 206, 178, 160, 151, and 43. Cathedulin Y8 had *m/e* 595 (M^+), 553 ($M - 42$), 535 ($M - 60$), 490 ($M - 105$), 471 ($M - 124$), 124, 106, 105, 78, 77, and 43.

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