Alkaloids of *Catha edulis*. Part 3.† Structures of Cathedulins K1, K2, K6, and K15; New Macrolide-bridged Polyesters of Euonyminol

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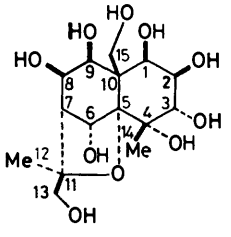
It is shown by mass spectral and ^1H and ^{13}C n.m.r. methods, together with ethanolysis, that the structure of the polyester alkaloid cathedulin K2 ($C_{40}H_{51}NO_{19}$) is compiled from euonyminol (1), one evoninic acid residue (*cf.* 2), five acetic acid residues, and one 2-hydroxyisobutyric acid residue. Some of the ester residues can be positioned on the basis of spectral information. The remainder are assigned as a result of a study of the products formed when cathedulin K2 is treated under controlled conditions with methanolic diethylamine. Four compounds were isolated, $C_{28}H_{37}NO_{13}$ (5), $C_{34}H_{45}NO_{16}$ (6), $C_{36}N_{47}NO_{17}$ (7), and $C_{38}H_{49}NO_{18}$ (8), the structures being assigned spectrally. This leads to the formulation of cathedulin K2 as (4). Using this information, together with further spectral data and information from models, cathedulin K1 ($C_{42}H_{53}NO_{20}$), K6 ($C_{38}H_{49}NO_{18}$), and K15 ($C_{36}H_{47}NO_{17}$) are allocated structures (9), (10), and (11) respectively.

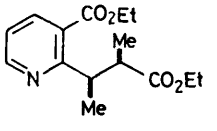
In the preceding papers [1,2] the isolation of a number of weakly-basic new alkaloids from the drug khat, *Catha edulis*, has been described, and the structures of two, sesquiterpenoid poly-ol esters, have been elucidated. We turn in this paper to a group of four alkaloids, closely interrelated, derived from khat of Kenyan origin, and designated cathedulins K1, K2, K6, and K15. The most abundant of these is cathedulin K2 and the major part of the following work was directed to clarification of its structure, which acts as a key to the formulation of the remaining three substances.

RESULTS AND DISCUSSION

Cathedulin K2 could be crystallised, m.p. 181—184 °C, and mass-spectral data indicated the formula $C_{40}H_{51}NO_{19}$. At high gain a low-intensity ion at $M + 42$ (acetate) could be observed and this feature was a characteristic of the mass spectra of these alkaloids and of their partially deacetylated derivatives. The presence of traces of ' homoacetate ' relatives would be a simple explanation and cannot be excluded, but repeated observation of this $M + 42$ ion suggests a degree of thermal disproportionation of the polyester on the spectrometer probe. Preliminary spectroscopic data indicated the presence of various ester linkages, and scission of these by alcoholysis proved informative.



(1)

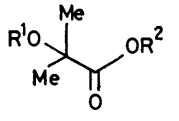


(2)

Ethanolysis yielded euonyminol (1) [identified by comparison of (1), and its octa-acetate, m.p. 192—195 °C, with authentic specimens [3]], along with diethyl evoninate (2), characterised by chromatographic comparison with a sample prepared from the *Euonymus* alkaloid evonine.[3,4] Ethyl acetate was also formed, and quantitative assay by g.l.c. indicated five acetate residues per molecule to be present.

Examination of the ^1H n.m.r. and ^{13}C n.m.r. data at this stage showed signals consistent with an acylated euonyminol core having (*a*) a free 2-hydroxy-group [2-H, δ 4.10; OH 2.94 (br); a small coupling between these protons was observed in deuteriochloroform, disappearing after D_2O exchange]; (*b*) a free tertiary hydroxy-group (OH, 4.53 sharp); (*c*) five acetate units; and (*d*) an evoninate diester bridge spanning C-3 to C-13. Location of the last feature depends on comparison of resonances with other alkaloids containing this evoninate arrangement; [4] in particular, the bridge in this position adopts a conformation requiring $J_{7',8'}$ to be *ca.* zero, and inducing a wide separation, >2 p.p.m., between the C-13 methylene protons [*cf.* 0.94 p.p.m. in the octa-acetate of (1) [4]].

Remaining to be assigned in the n.m.r. spectra were four ^{13}C signals. These were two OR quartets in the range δ 18—25 p.p.m. (2 Me), one OR singlet in the range δ 69—74 p.p.m. (C–O–), and one OR singlet at 168—175 p.p.m. (C=O). Also there were two ^1H resonances to be assigned (each 3 H) in the range δ 1.5—1.7. Only a 2-alkoxyisobutyrate fragment (3) accommodates these data, and in cathedulin K2 it must take the form of a 2-acetoxyisobutyrate. The ^{13}C n.m.r. of 2-acetoxyisobutyric acid itself (3; R^1 = Ac, R^2 = H) has signals at δ 24.3 (2 × Me), 78.0 (C–O), and 177.6 (CO_2H). The ethanolysis products of cathedulin K2 were also shown to contain ethyl 2-hydroxyisobutyrate (g.l.c.) and the free acid (by g.l.c. of its trimethylsilyl derivative). These assays were hampered by two factors; first, the relatively rapid reaction of ethyl 2-



(3)

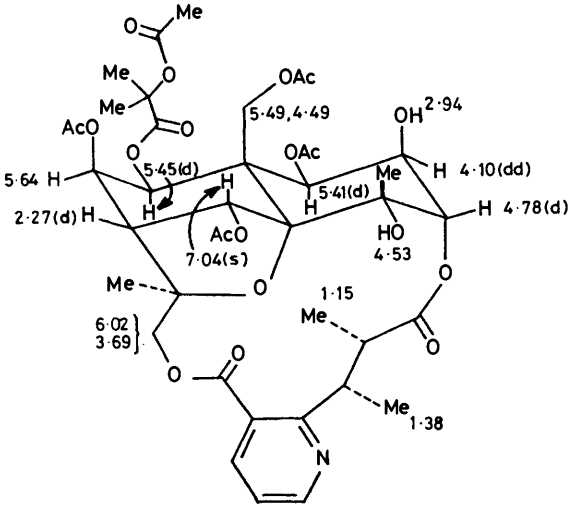
† Part 2 is ref. 2.

hydroxyisobutyrate with ethoxide ion to yield the free acid (presumably by a $B_{AL}2$ process assisted by intramolecular hydrogen-bonding); and secondly, by the high water solubility and steam volatility of the free acid which made micro-detection difficult.

With all the structural elements of cathedulin K2 recognised, the remaining problem was the relative siting of the 2-acetoxyisobutyrate and the acetate functions. This question was tackled through partial alcoholysis studies which, in the event, showed this alkaloid to be completely represented by structure (4). To facilitate discussion, relevant ^{1}H n.m.r. data are displayed on the cipher.

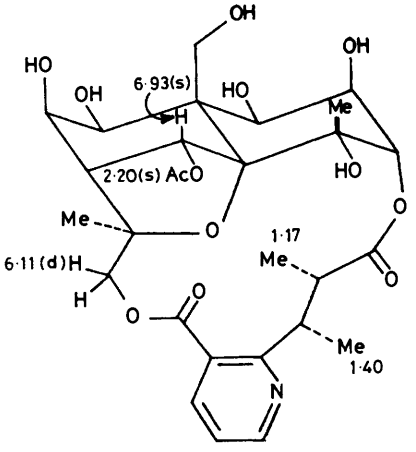
After various trials, a methanol–diethylamine mixture was chosen to effect a large-scale (79 mg alkaloid) partial methanolysis, at room temperature. At least seven products were observed on chromatography. Four of these were characterised, and the structural assignments made for them completed definition of the structure of their progenitor (4).

The most polar product (5), m.p. 185—188 °C, had the formula $C_{28}H_{37}NO_{13}$ from accurate mass measurements; this corresponds to loss of four acetate, and the 2-hydroxyisobutyrate, residues. The remaining acetate was located at C6–OH, H-6 being readily recognised as a sharp singlet ($J_{6,7}$ 0) [3-5] at δ 6.93 (CD_3OD; low solubility precluded measurements in $CDCl_3$ as used for the remaining compounds). The protons at C-1, -2, -8, -9, and -15 all moved upfield to δ <5, and formed an unresolved signal also containing OH resonances. The compound adjacent to (5) on the t.l.c. plate was also crystalline, m.p. 164—168 °C, and was formulated as $C_{34}H_{45}NO_{16}$, *i.e.* it has the sole 2-acetoxyisobutyrate attached to a unit of (5). The position of this additional ester is

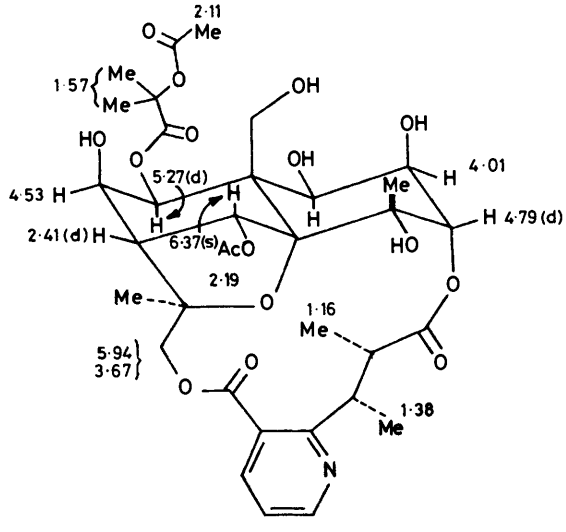


(4)

clear from ^{1}H n.m.r., as shown in (6); C*H*–OCOCMe$_2$OAc appears at δ 5.27 as a doublet J 4.9 Hz. Only 1-H and 9-H can, in these molecules, appear as doublets, with coupling constants of this order, at such chemical shifts (other doublets, 13-H or 15-H, have $J > 10$, and 3-H and 2-H are less deshielded). In both these *Catha edulis* alkaloids, and their relatives, $J_{1,2}$ (cis) falls in the narrow range 3—3.5 Hz, while $J_{8,9}$ is signi-



(5)



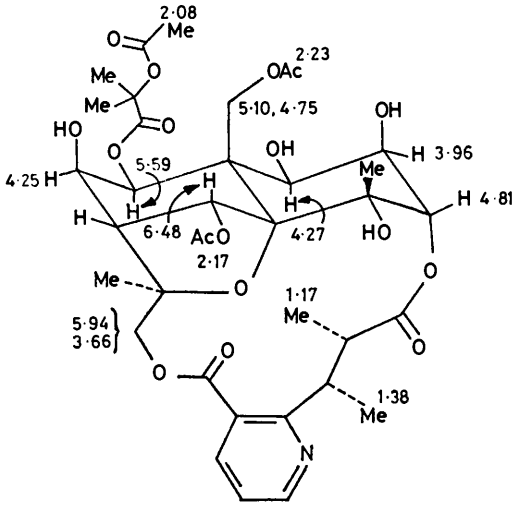
(6)

ficantly greater (*ca.* 5 Hz); [3-5] thus the δ 5.27 resonance is assigned to H-9. In support, irradiation at 2-H (δ 4.01, broad) collapses the 3-H doublet (4.79, J 3 Hz) (1-H is obscured), leaving 9-H unaltered. Irradiation at δ 4.5 (6) reduced the 9-H signal to a singlet. The accumulated evidence thus fixes the constitution of cathedulin K2 as (4).

Two other products from partial methanolysis were recognised as the tetraol (7), $C_{36}H_{47}NO_{17}$, and the triol (8), $C_{38}H_{49}NO_{18}$. In the former, ester functions were placed at C-6 (6-H, 6.48), C-9 (9-H, 5.59), and C-15 (15-H$_2$, 5.10 and 4.75); similar data for the latter, with another deshielded proton (1-H, 5.59), were definitive for its structure.

Of the remaining natural alkaloids, cathedulin K1, m.p. 165—168 °C, has a formula $C_{42}H_{53}NO_{20}$, *i.e.* one

more acetate than K2; this acetate must occupy C-2 (2-H, δ 5.21) and the structure is thus (9). Cathedulin K6, m.p. 176—180 °C, $C_{38}H_{49}NO_{18}$, has one acetate less that K2; a free primary alcohol function can readily be diagnosed as in structure (10) from the resonances of 15-H_a (δ 4.16) and 15-H_b (δ 4.62, $J_{15a,15b}$ 13 Hz). Cathedulin K15 (m.p. 191—194 °C, $C_{36}H_{47}NO_{17}$) has one less



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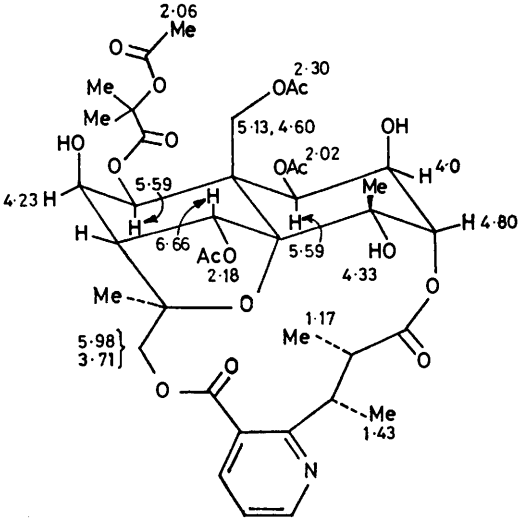

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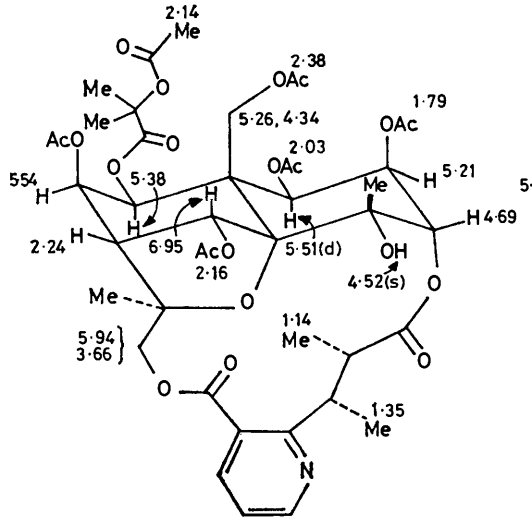

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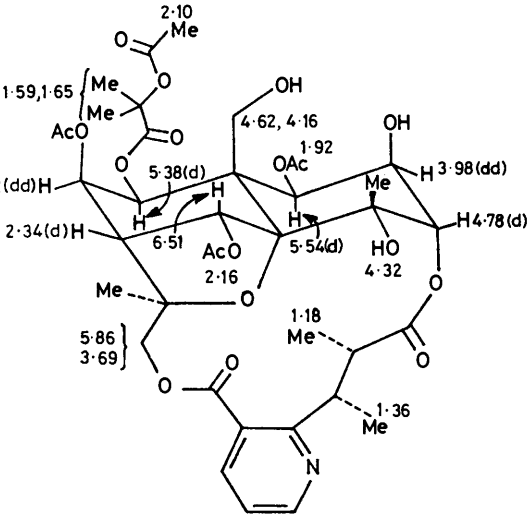
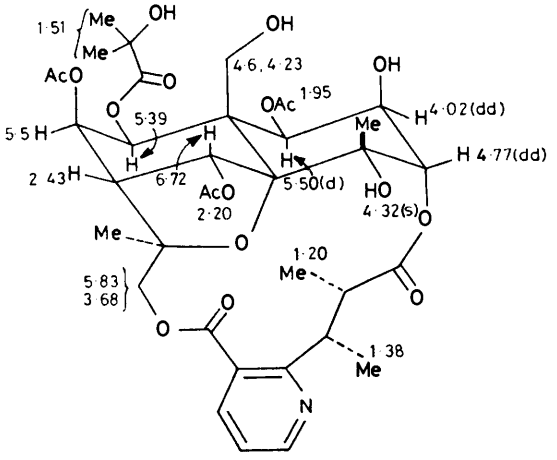


(10)

and (8) all show fragments at *m/e* 129 ($[MeCO_2CMe_2CO]^+$), but such an ion was not observed from K15. Structure (11) is thus allocated to K15.

A general survey of the ^1H n.m.r. data of the compounds discussed here shows that, as expected, the chemical shifts of the protons of the evoninate residue change relatively little, structural variations being confined to the β-face. The four C-methyl groups (C-12, C-14, and alkoxyisobutyrate) resonate within a very narrow range and cannot be assigned with assurance in all cases. The acetate methyl groups also cover a limited shift range, but having in hand the sequence of compounds with from one to six acetates, a consistent pattern in the data appears, allowing reasonable assignments as shown. The α and β equatorial sesquiterpene ring protons (1-H, 2-H, 3-H, 7-H, 8-H, and 9-H) are only modestly responsive to changes at remote sites,

resonating in a maximum range of *ca.* 0.3 p.p.m. The single β-axial proton (6-H) is more variable (δ 6.37—6.95), and its changes are not readily rationalised: this proton is deshielded by the 8-axial oxygen, and further



(11)

deshielding influences may be supplied by the 15-O, and by ester carbonyls, if present, at C-8, C-15, or even C-9; these effects would be dependent on the conformation of the functions. Such conformations, balancing steric repulsions, and hydrogen bonding, where present, are not easily amenable to analysis.

Finally, it is noteworthy that the laboratory deacylation of K2 does not appear to produce K6 or K15 but the isomeric structures (8) and (7): K6 and K15 thus seem not to be artefacts of isolation. It should be pointed out further that there is no direct proof of the location of the 2-alkoxyisobutyrate residues in the alkaloids K6 and K15. However, on biogenetic grounds, its positioning at C-9, as in cathedulin K2, seems very likely, and there are no anomalies in the spectroscopic data to suggest otherwise.

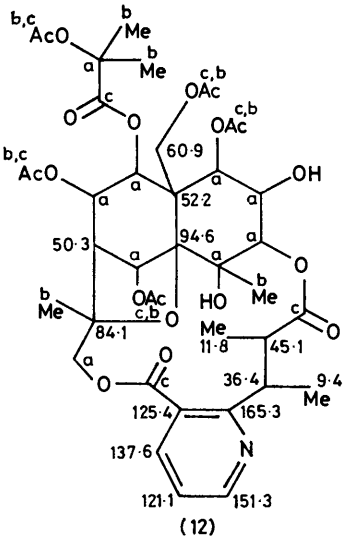
The assignments of ^{13}C resonances for cathedulin K2 are summarised in (12). Multiplicities in the off-resonance decoupled spectra were in agreement with these assignments which were made with the aid of previous studies of sesquiterpenoids,[6,7] and by analysis of two model compounds, dimethyl evoninate (13) and evonine (14), for which relevant data are also given.

EXPERIMENTAL

For general procedures, see Part 1.[1]

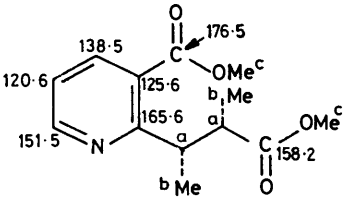
Derivatives and Characteristics of 2-Hydroxy-2-methylpropionic Acid (2-Hydroxyisobutyric Acid).—(a) *Ethyl 2-hydroxy-2-methylpropionate.* The carboxylic acid (3; R^1 = R^2 = H) (5 g) in 3.4% hydrogen chloride in ethanol (13 cm³) over freshly dried sodium sulphate was set aside at ambient temperature for 3 d before heating under reflux for 2 h. The mixture was partitioned between ether and aqueous sodium carbonate. The ether layer was washed, dried, and evaporated to yield the crude ester (1.73 g) which on distillation gave the title ester (3; R^1 = H, R^2 = Et), 1.09 g, b.p. 47—48 °C at 15 mmHg, n_D^{20} 1.408 7 (lit.,[8] b.p. 46 °C at 15 mmHg, n_D^{20} 1.408 0); δ($CDCl_3$) 1.30 (3 H, t, *J* 7.5 Hz), 1.45 (6 H, s), 3.28 (1 H, s, O*H*), and 4.23 (2 H, q, *J* 7.5 Hz). The poor yield is in part due to the water solubility of the ester.

(b) *2-Acetoxy-2-methylpropionic acid.* The acid (3; R^1 = R^2 = H) (2 g) in acetic anhydride (10 cm³) was heated on steam for 2.5 h. The cooled product was diluted with water and shaken periodically during 1 h. Continuous ether extraction (6 h) of the mixture, gave, from the dried



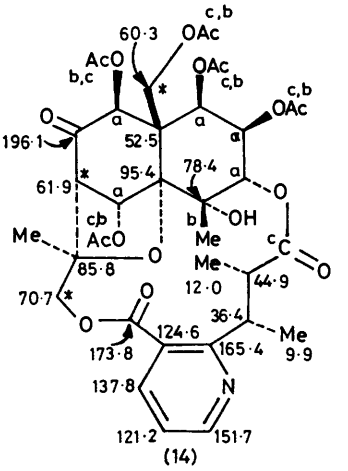
(12)

9 × C_a	69·3 - 78·5
9 × C_b	18·4 - 24·8
8 × C_c	168·4 - 174·6



(13)

2 × C_a	40·2, 40·4
2 × C_b	15·2, 17·9
2 × C_c	51·2, 52·3



(14)

5 × C_a	62 - 75
6 × C_b	19·6 - 20·5
6 × C_c	168 - 169

* ^1H-decoupled

ether layer, a white solid which on recrystallisation from carbon disulphide afforded colourless needles of the title acid (3; R^1 = Ac, R^2 = H), 1.94 g, m.p. 60 °C (lit.,[9] m.p. 61 °C); $\delta_H(CDCl_3)$ 1.60 (6 H, s), 2.07 (3 H, s), and 11.5 (1 H, s,

CO_2H); $\delta_C(CDCl_3)$ 20.9 (q, COMe), 24.3 (q, 2 × Me), 78.0(s), 170.6(s, OCOMe), and 177.6(s, CO_2H).

(c) *Chromatographic behaviour.* Ethyl 2-hydroxyisobutyrate, as prepared above, gave a single peak on g.l.c. on a 5 ft × 0.25 in Carbowax 20M column at 130 °C. Conditions for its detection in alkaloid ethanolysis mixtures are given below. Samples (0.03—1.3 mg) of the free hydroxy-acid were silylated with bis(trimethylsilyl)trifluoroacetamide (20 mm³), containing 1% trimethylchlorosilane, at 60 °C for 5 min: the silyl derivative could be chromatographed (single sharp peak) on a SCOT, 50 ft × 0.02 in, OV 225 column at 119 °C. T.l.c. of the free acid used silica gel G, eluting with 10% butanol in chloroform (containing a trace of formic acid); visualisation was achieved by spraying with Bromocresol Purple, followed by exposure to ammonia vapour, forming a yellow spot on a blue background.

(d) *Behaviour of ethyl 2-hydroxy-2-methylpropionate in ethanolic sodium ethoxide.* The ester (160 mg) was dissolved in freshly-prepared 0.25M-sodium ethoxide in super-dry ethanol and set aside at ambient temperature for 18 h, when the solution was partitioned between ether and water. No ester was detectable by g.l.c. in the ether layer. The acidified aqueous layer was continuously extracted with ether during 18 h. Drying and evaporation of the extracts gave 2-hydroxyisobutyric acid (40 mg, 32%), m.p. 76—79 °C with sublimation, identified by i.r. comparison (KBr) with an authentic specimen. Similar experiments showed that only 16% of the ester remained unchanged after 2.5 h. Complete recovery of ester was observed in control experiments using neutral ethanol solutions.

Ethanolysis of Cathedulin K2.—(a) *Quantitative estimation of acetate units.* Ethyl acetate was detected by g.l.c. using a 5 ft × 0.25 in Carbowax 20M column, with 0.5-mm³ injections of ethanolic solutions. A temperature programme (63 °C, 15° min^{-1} rise to 128 °C) was used to enable ethyl 2-hydroxyisobutyrate to be analysed in the same run. For quantitative estimation, standard curves using fresh solutions of ethyl acetate in ethanol were employed, constructed at the start of, and checked at the end of, each day's analyses. Internal standard (dodecane) was used in addition, and the results calculated from the two methods were averaged.

Solutions of ethyl acetate (0.5—5.0 mg) in ethanol, and in 0.2M-sodium ethoxide in ethanol (150—400 mm³) were set up in 0.6 cm³. Reactivials at ambient temperature. After 18 h, recovery of the ester from ethanol was complete, but from ethanolic sodium ethoxide recovery was only 50—70%. Careful precautions to exclude water failed to improve the recoveries significantly. The mean recovery of ethyl acetate from 0.2M-sodium ethoxide under the above conditions after 4 h was 88%.

Samples of cathedulin K2 (1—5 mg) in a 0.6 cm³ Reactivial were treated with 0.2M-sodium ethoxide in ethanol (0.4 cm³). Dodecane was added as internal standard. Controls using ethyl acetate in the same ethoxide solution were also set up, and a standard acetate, glucose penta-acetate was treated in the same manner with the same reagents. Aliquots from the ethanolysis of the alkaloid, the glucose penta-acetate, and the control solution, were injected directly onto the g.l.c. column at regular intervals. The results showed that optimum yields of ethyl acetate were achieved in 3—6 h and subsequently decreased with time. The mean results of six runs, analysed from 3—6 h, and corrected for the mean recovery (88%) of ethyl acetate from controls over this period, were 4.6 acetates from glucose penta-acetate (maximum measured 5.1) and 4.9 acetates from cathedulin K2 (maximum measured 5.4).

(b) *Detection of 2-hydroxyisobutyrate residues.*—(*i*) Parallel with the ethyl acetate analyses above, ethanolysis samples of cathedulin K2 were examined (g.l.c.) for ethyl 2-hydroxyisobutyrate. A peak corresponding to this ester was consistently observed in ethanolyses run up to *ca.* 6 h. A control experiment (above) indicated relatively rapid cleavage of the ester, and quantitative estimations were not undertaken. (*ii*) Samples of cathedulin K2 used for estimation of ethyl acetate were acidified (10% aqueous sulphuric acid) and continuously extracted with ether for 18 h. The extract was concentrated and silylated as described above for 2-hydroxyisobutyric acid, and the product analysed by g.l.c. A peak corresponding to the trimethylsilyl derivative of that acid was consistently observed. The maximum quantity of derivative detected in any single run corresponded to *ca.* 0.25 mol equiv.

(c) *Euonyminol and diethyl evoninate.* Samples of cathedulin K2 treated with sodium ethoxide as in (a) above were partitioned between benzene and water. The water layers were further extracted with benzene. The combined organic extracts were dried and evaporated. T.l.c. in two solvent systems, benzene–ethyl acetate–ethanol (8 : 8 : 1) and chloroform–n-hexane (3 : 1), showed a single spot corresponding to dimethyl evoninate (authentic sample prepared from evonine). The aqueous layers were shaken with Amberlite IR 120 (H form) resin for 1 h when the pH was reduced to just below 7. After filtration the solutions were freeze-dried. The residues were warmed with dry pyridine (2 cm³), acetic anhydride (1 cm³) was added, and the solution set aside for 2—5 d at ambient temperature. The mixtures were poured into aqueous sodium carbonate and extracted with chloroform (3×). The combined chloroform extracts were washed (2M-hydrochloric acid, brine), dried, and evaporated. The residual gum was separated by p.l.c., using ethyl acetate–n-hexane (4 : 1). Bands were made visible by spraying with water. The solvent extracts of the major bands from a number of runs were collected (from a total of 24.8 mg alkaloid) and crystallised from ether–n-hexane to yield euonyminol octa-acetate, m.p. 193—196 °C, mixed m.p. 192—195 °C with an authentic sample [3] of m.p. 192—194 °C. The sample had the same R_F on silica gel [ethyl acetate–n-hexane (4 : 1)] as authentic material, and had the same mass spectrum (M^+ 702).

Cholestanyl 2-Acetoxyisobutyrate.—2-Acetoxyisobutyrate (0.16 g, 1.1 mmol) and *ca.* 75% carbonyldi-imidazole (0.25 g, 1.1 mmol) were warmed together in dry benzene (2 cm³); dissolution was accompanied by CO_2 evolution. When reaction was complete, the solution was added to a mixture of cholestanol (0.425 g, 1.1 mmol) and imidazole (0.08 g, 1.2 mmol) in benzene (2 cm³) with a small fragment of sodium metal. The mixture was heated under reflux for 40 min and then set aside overnight. The product was isolated by p.l.c. (chloroform). The band of highest R_F yielded the *title ester* (50 mg, 9%), m.p. 127—129 °C (Found: M^+, 516.418. $C_{33}H_{56}O_4$ requires M, 516.418); $\delta_H(CDCl_3)$ 4.75 (1 H, br, CHOCOR), 2.07 (3 H, s, COMe), 1.55 (6 H, s, CMe_2), 0.92 (6 H, s), 0.85 (6 H, s), and 0.66 (3 H, s) (5 × Me of cholestanyl unit).

Cholestanyl 2-Hydroxyisobutyrate.—2-Hydroxyisobutyric acid (0.13 g, 1.25 mmol) was treated with carbonyl diimidazole (1.25 mmol) in benzene (3 cm³) as above, and used

in a similar way to esterify cholestanol (1.25 mmol) in benzene (3 cm³) containing imidazole (1.25 mmol) and sodium. Isolation of the products by p.l.c. [chloroform–methanol (200 : 1)] gave a gummy solid (0.09 g) which was separated into two components by further p.l.c.: that of higher R_F proved to be the required *title ester* (10 mg) (Found: M^+, 474.401. $C_{31}H_{54}O_3$ requires M, 474.407); $\delta_H(CDCl_3)$ 4.77 (1 H, br, C*H*OCOR), 3.15 (1 H, s, O*H*), 1.43 (6 H, s, C*Me*$_2$), 0.93 (6 H, s), 0.86 (6 H, s), and 0.66 (3 H, s) (5 × Me of cholestanyl unit).

Partial Methanolysis of Cathedulin K2.—A number of trial experiments were carried out using small quantities (<0.5 mg) of alkaloid with various base–solvent and acid–solvent mixtures, monitoring the reaction with small (5 × 5 cm) high-resolution t.l.c. plates. Diethylamine–methanol (room temperature) was chosen for larger-scale experiments since it gave rise to a manageable number of products with varying polarities (relating to the number of free hydroxy-groups in the product). After several further trials to establish that the desired type of hydroxy-ester was formed, the following experiment was carried out. Cathedulin K2 (79 mg) in dry methanol (15 cm³) containing diethylamine (0.75 cm³) was set aside at 23 °C for 50 min. The solvent was then evaporated off and the residue was separated by p.l.c. on four 20 × 20 × 0.05 cm HF_{254} silica plates using chloroform–methanol (19 : 1). At least eight bands could be distinguished; the main ones were extracted (chloroform–methanol–ether) and, on evaporation, the following fractions (all colourless solids) were obtained; 5D1 (16.2 mg, R_F 0.02); 5D3 (4.9 mg, R_F 0.12); 5D4 (2.4 mg, R_F 0.15); 5D5 (5.6 mg, R_F 0.21); 5D6 (1.8 mg, R_F 0.24); and 5D7 (17.8 mg, R_F 0.27). The last fraction was unchanged cathedulin K2. Fraction 5D1 crystallised from methanol–ether to yield the *hexaol* (5) m.p. 185—188 °C (Found: M^+, 595.223. $C_{28}H_{37}NO_{13}$ requires M, 595.226). The sample was barely soluble in chloroform, and n.m.r. data were collected in CD_3OD; $\delta(CD_3OD)$ 8.82 (1 H, 6′-H), 8.31 (1 H, 4′-H), 7.53 (1 H, 5′-H), 6.93 (1 H, d, 6-H), 6.11 (1 H, d, J 12 Hz, 13-H$_a$), 5.0—47. (m, 1-, 2-, 3-, 7-, 8-, 9-, 13b-, and 15-H, and hydroxy-protons), 2.41 (1 H, d, J 4 Hz, 7-H), 2.20 (3 H, s, COMe), 1.68 and 1.57 (both 3 H, s, 12-H$_3$ and 14-H$_3$), 1.40 and 1.17 (both 3 H, d, J Hz, 10′-H$_3$ and 11′-H$_3$); *m/e* * 595 (12), 577 (100), 560 (16), 535 (56), 518 (40), 505 (16), 504 (16), 500 (16), 428 (28), 458 (16), 446 (24), 316 (16), 308 (16), 306 (24), 299 (24), 288 (40), 281 (200), and 280 (1 120); smaller fragments, here and below, are not listed Fraction 5D3, m.p. 164—168 °C, appeared from mass spectrometry to be a mixture and was accordingly re-chromatographed using chloroform–methanol (19 : 1), double elution. The upper band provided the *pentaol* (6) (1.5 mg) (Found: M^+, 723.270. $C_{34}H_{45}NO_{16}$ requires M, 723.274); $\delta(CDCl_3)$ 8.68 (1 H, dd, J 2 and 5 Hz, 6′-H), 8.02 (1 H, dd, J 2 and 8 Hz, 4′-H), 7.28 (1 H, m, 5′-H), 6.37 (1 H, s, 6-H), 5.94 (1 H, d, J 11 Hz, 13-H$_a$), 5.27 (1 H, d, J 4.9 Hz, 9-H), 4.79 (1 H, d, J 3 Hz, 3-H), 4.53 (1 H, obscured, 8-H), 4.01 (1 H, br, 2-H), 3.74 (1 H, s, O*H*), 3.67 (1 H, d, J 11 Hz, 13-H$_b$), 2.41 (1 H, d, J *ca.* 2 Hz, 7-H), *ca.* 2.4 (1 H, d, J 7 Hz, 8′-H), 2.19 and 2.11 (both 3 H, s, COMe), 1.66 and *ca.* 1.57 (both 3 H, s, 12-H$_3$ and 14-H$_3$), 1.57 (6 H, s, CMe$_2$), 1.38 and 1.16 (both 3 H, d, J 7 Hz, 10′-H$_3$ and 11′-H$_3$); decoupling experiments with irradiation at (*a*) 4.53, (*b*) 4.01, and (*c*) 3.67, collapsed (*a*) the doublet at 5.27 to a singlet, (*b*) the doublet at 4.79 to a singlet (5.27 unaffected), and (*c*) the doublet at 5.94 to a singlet: *m/e* 723 (81), 705 (100), 698 (24), 697 (12), 681 (21), 675 (9), 664 (12), 663 (12), 647 (12), 646 (63), 644 (9), 643 (12), 642 (15), 638 (15), 618 (15), 616 (24), 586 (12), 578 (15), 577 (18), 576 (12), 574 (18), 560 (36), 559 (15), 558 (12), 542 (24), 531 (12), 530 (24), 518 (12), 506 (18), 500 (60), 489 (18), 488 (117), 446 (39), 378 (57), 312 (51), 280 (420), and 129. Fraction 5D4 on evaporation gave white crystals, m.p. 140—146 °C (2.4 mg) of the *tetraol* (7) (Found: M^+, 765.278. $C_{36}H_{47}NO_{17}$ requires M, 765.284); $\delta_H(CDCl_3$–$D_2O)$ 8.67 (1 H, dd, 6′-H), 8.02 (1 H, dd, 4′-H), 7.26 (1 H, m, 5′-H), 6.48 (1 H, s, 6-H), 5.94 (1 H, d, 13-H$_a$), 5.59 (1 H, 9-H), 5.1 (1 H, d, 15-H$_a$), 4.81 (1 H, 3-H), 4.75 (1 H, d, 15-H$_b$), 4.27 (1 H, 1-H), 4.25 (1 H, 8-H), 3.96 (1 H, 2-H), 3.66 (1 H, d, 13-H$_b$), 2.23, 2.17, and 2.08 (all 3 H, s, 3 × COMe), 1.64 (3 H), 1.62 (3 H), and 1.56 (6 H) (all s, 4 × CMe), and 1.38 and 1.17 (both 3 H, d, CH*Me*); *m/e* 765 (100), 749 (10), 748 (16), 724 (5), 723 (6), 707 (5), 706 (11), 705 (6), 704 (6), 689 (5), 688 (15), 687 (5), 680 (15), 676 (5), 662 (6), 646 (5), 644 (5), 634 (13), 628 (6), 620 (8), 619 (6), 616 (19), 602 (10), 560 (11), 542 (10), 500 (8), 488 (8), 470 (5), 368 (8), 322 (5), 313 (6), 308 (10), 280 (26), and 129.

Fraction 5D5 provided the *triol* (8), m.p. 164—168 °C from methanol (Found: M^+, 807.291. $C_{38}H_{49}NO_{18}$ requires M, 807.295); $\delta(CDCl_3)$ 8.68 (1 H, dd, J 2 and 5 Hz, 6′-H), 8.02 (1 H, dd, J 2 and 8 Hz, 4′-H), 7.26 (1 H, m, 4′-H), 6.66 (1 H, s, 6-H), 5.98 (1 H, d, J 12 Hz, 13-H$_a$), 5.6 (2 H, br s, 1-H and 9-H), 5.13 (1 H, d, J 13 Hz, 15-H$_a$), 4.80 (1 H, d, J 2 Hz, 3-H), 4.60 (1 H, d, J 13 Hz, 15-H$_b$), 4.33 (1 H, s, OH), 4.23 (1 H, m, 8-H), 4.0 (1 H, br, 2-H), 3.71 (1 H, d, J 12 Hz, 13-H$_b$), 2.30, 2.18, 2.06, and 2.02 (all 3 H, s, COMe), 1.66, 1.62, 1.60, and 1.54 (all 3 H, s, CMe), 1.43 and 1.17 (both 3 H, d, C*H*Me); double irradiation at δ 3.71 collapsed the 5.98 doublet; *m/e* 807 (100), 791 (8), 790 (13), 765 (23), 749 (8), 748 (18), 747 (8), 730 (10), 704 (13), 698 (13), 696 (8), 676 (8), 662 (13), 661 (8), 658 (8), 644 (10), 634 (8), 616 (15), 602 (18), 594 (8), 542 (10), 530 (15), 488 (8), 456 (5), 280 (5), and 129.

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* In the mass spectra of alcohols (5), (6), (7), and (8), a prominent high-mass peak is taken as reference (100), but is not a true base peak; fragments with *m/e* <280 are not systematically listed. In each compound small residues of products with an additional acetate could just be observed (peaks >M^+).

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