Extractives of *Catha edulis* (Khat): Occurrence of Celastraceaeous Alkaloids having Mono- and Bis-macrolide Bridges

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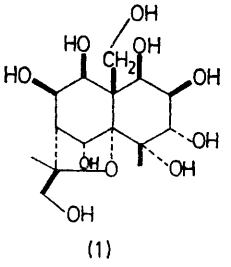
Summary Six purified alkaloids have been isolated from *C. edulis*: four have mol. wts > 1100, two (cathedulin-5 and -6) being mono-macrolide-bridged and two (cathedulin-3 and -4) bis-macrolide-bridged derivatives of euonyminol.

THE leaves of *Catha edulis* Forsk (Celastraceae) (Khat, Chat, or Quat) are used in parts of East Africa and the Yemen as a stimulant acceptable to Islam.[1] Psychological dependence on the drug, and socio-medical aspects have caused concern to the U.N. Commission on Narcotic Drugs.[2]



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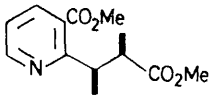

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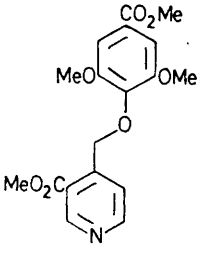

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Earlier investigators have identified (+)-norpseudoephedrine,[3] and other basic extractives have been found:[4] the structure of one of these, cathidine D, has been reported on.[5] The unsatisfactory chemical and pharmacological situation,[1,2,6] coupled with a recent interest in alkaloids of the Celastraceae,[7] has prompted an examination of *C. edulis* constituents.

In our hands, the basic fraction of the ether extract of ammonia-treated dried leaves,†‡ gave, after extensive preparative layer chromatography, nine products (total *ca.* 0·1%), six of which have been purified. Four of these (designated cathedulin-3, -4, -5, and -6) are related and their constitutions are treated here: the two further alkaloids are dealt with in the following communication.[12]

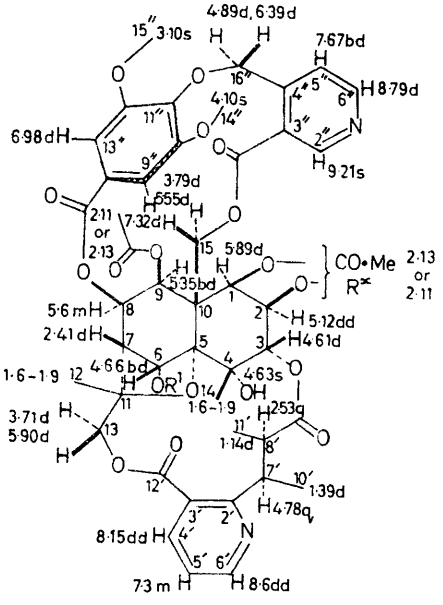
Cathedulins-3, -4, -5, and -6 are amorphous, and present difficult problems in purification: each possesses a mol. wt. > 1100. Current mass-measurement techniques were inadequate to define the molecular formulae when employed in the absence of other evidence, though molecular weights of 1166, 1124, 1230, and 1188 respectively were indicated by electron impact data. After consideration of the chemical evidence, we propose the following formulae: cathedulin-3, $C_{56}H_{66}N_2O_{25}$; cathedulin-4, $C_{54}H_{64}N_2O_{24}$; cathedulin-5, $C_{61}H_{70}N_2O_{25}$; cathedulin-6, $C_{59}H_{68}N_2O_{24}$.

Acetylation of cathedulin-4 (which forms an *N*-oxide, $C_{54}H_{64}N_2O_{25}$) gives cathedulin-3, and acetylation of cathedulin-6 gives cathedulin-5: further, cathedulin-3 can be deacetylated to cathedulin-4 by treatment with diethylamine in methanol at −28 °C. Methanolysis of each of the four alkaloids gave the same sesquiterpene core, euonyminol (**1**),[13] identified as the octa-acetate, m.p. 195—196 °C, by spectral comparison. In addition, cathedulin-3 gave dimethyl

† As indicated by t.l.c., the same alkaloids, in lower yield, were extracted when the treatment with ammonia was omitted.

‡ Extraction of *C. edulis* root bark resulted in the identification of five known methylene-quinone triterpenoids of the celastrol class: celastrol,[8] pristimerin,[8] tingenin A (tingenone),[9,10] tingenin B[9], and iguesterin.[11]

evoninate (**2**),[13] identical with an authentic specimen prepared from evonine, together with dimethyl cathate (**3**), m.p. 163 °C. The structure of the latter ester followed from ^{1}H and ^{13}C n.m.r. data [*cf.* (**4**)]. These results were supported by the isolation of syringyl alcohol, together with evoninyl alcohol [*cf.* (**2**)] when cathedulin-4 was treated with $LiAlH_4$. On the other hand cathedulin-6 gave dimethyl evoninate but no dimethyl cathate on methanolysis: instead, methyl trimethylgallate, methyl nicotinate, methyl benzoate, and dimethyl evoninate were identified (g.l.c.).

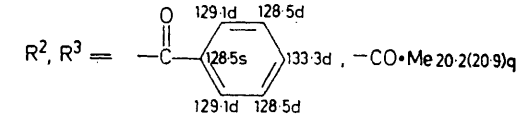


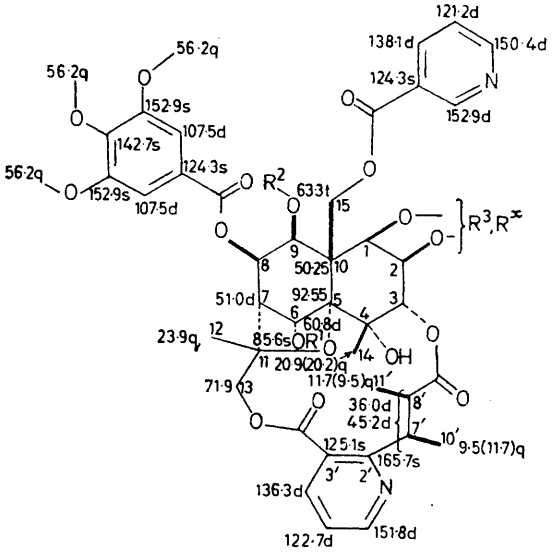
(**4**) R^1 = H (δ 6·06, d) (cathedulin-4)
(**5**) R^1 = Ac (cathedulin-3)
R^x unidentified.

^{1}H N.m.r. data (δ, 220 MHz, $CDCl_3$) for (**4**) are displayed.

Coupling constants (in Hz) for (**4**): $J_{1,2}$, 3·4; $J_{13,13}$, 12·0; $J_{7',10'}$, 7·1; $J_{2,3}$, 3·0; $J_{15,15}$, 12·0; $J_{7',8'}$, 0; $J_{6,7}$, *ca.* 0; $J_{4',5'}$, 7·8; $J_{5'',6''}$, 4·9; $J_{6,6-OH}$, 3·2; $J_{5',6'}$, 4·9; $J_{2'',6''}$, 0; $J_{7,8}$, 3·7; $J_{4',6'}$, 1·8; $J_{9'',13''}$, 1·8; $J_{8,9}$, 5·8; $J_{8',11'}$, 7·1; $J_{16'',16''}$, 11·0.

Consideration of the full ^{1}H and ^{13}C n.m.r. data for the alkaloids now permits the construction of trial constitutions (**4**—**7**) for cathedulin-3 to -6, which at this stage are open to revision and further development. ^{1}H N.m.r. data for cathedulin-4 are shown in (**4**) and ^{13}C n.m.r. data for cathedulin-6 are displayed in (**6**). Each of the four compounds contains an evoninate dilactone bridge, placed to accord with its position in the *Euonymus* alkaloids.[13] The biogenetic parallel is supported by close correspondence of the n.m.r. data for this molecular fragment of the alkaloids, *e.g.*, $J_{7',8'}$ *ca.* 0, indicating the H–C(7′)–C(8′)-H torsion angle to be near 90° when the evoninate section is contained in a C(13)–C(3) bridge (*cf.* *J* 9 Hz in dimethyl evoninate). Selective methanolysis of the C(13)–O–C(12′)–O linkage has been achieved. Cathedulin-3 and cathedulin-4 each incorporate a second dilactone bridge involving the cathate (**3**); this bridge can be opened by hydrogenolysis over a platinum or Raney nickel catalyst to give dihydro-cathedulin-3 [*cf.* (**5**), with C(16″)–O *seco*] in which the AB signal of the 15-H_2 in cathedulin-3 (δ 3·79 and 5·55) collapses. One end of the cathate bridge is thus likely to be attached to C(15)–O: for stereochemical reasons the other terminus is likely to be at C(8)–O_{ax} or C(2)–O_{ax}. The former junction tends to be preferred, since some evidence (see below) points to a different attachment to C(2). The biosynthetic formation of the cathate bridge is of interest, and probably involves formation of the C(16″)–C(4″) bond from the appropriate methoxy and heterocyclic ring carbons. The trimethylgallate and nicotinate residues of cathedulin-5 and cathedulin-6 are placed to correspond to the cathate bridge of (**4**).





(**6**) R^1 = H (cathedulin-6)
(**7**) R^1 = Ac (cathedulin-5)
R^x unidentified.

^{13}C N.m.r. data (p.p.m.) for (**6**) are displayed; certain alternative assignments are possible, but those shown correspond most closely to data for model compounds. C–O ^{13}C resonances: 173·6, 171·3, 170·1, 168·7, 165·4, 164·8, and 164·1; C(1)—C(3), C(4), C(8), and C(9): 78·8—69·2.

All four alkaloids have a free tertiary C(4)–OH; this function is hindered and cannot readily be acylated in any compound of this type. Cathedulin-4 has a free C(6)–OH, acetylated in cathedulin-3: this is indicated by the downfield shift (δ 4·66 → 6·06) of the 6–H. Cathedulin-6 and cathedulin-5 are similarly related. Two acetate groups occupy the C(1) and C(9) equatorial positions and an unidentified residue (*M* 191) is at present located on the remaining oxygen at C(2), though it may become necessary to interchange the C(1) and C(2) substituents. This unidentified residue has proved somewhat elusive in degradation. Mild alcoholysis or hydrolysis (which yields several partly deacylated products not detailed here) suggests that this unit is the first to lose a fragment. The first isolable

product (at $M - 62$ for cathedulin-4) shows a large upfield shift (δ 5·12 → 3·97) for 2-H making C(2)–O– the likely point of attachment. Work on the formulation of this fragment is at present in progress. It occurs also in cathedulin-5 and cathedulin-6, and these two alkaloids have one benzoate residue replacing one of the acetates of cathedulin-3 and cathedulin-4.

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