Structures of Cathedulin-2 and Cathedulin-8, New Sesquiterpene Alkaloids from *Catha edulis*

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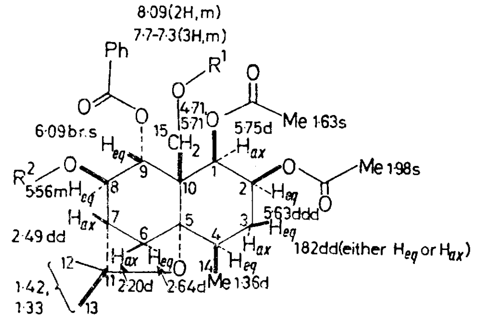
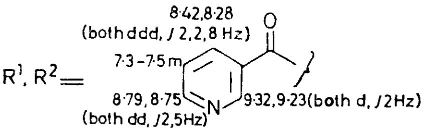
Summary The structures of cathedulin-2 and -8, alkaloids from *C. edulis*, are shown to be (**1**) and (**2**) respectively.

Catha edulis, a drug of importance in areas such as Ethiopia, Somalia, and the Yemen, contains a complex mixture of alkaloids, on which we have reported.[1] Here we describe the full structures of two extractives, cathedulin-2 and cathedulin-8, which are shown to be the esters (**1**) and (**2**) of a new sesquiterpene polyol-ether of the eudesmane type (**3**).





(**1**) $R^1 = R^2$ = nicotinoyl (cathedulin-2)
(**2**) R^1 = nicotinoyl, R^2 = H (cathedulin-8)

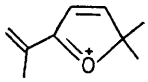
^{1}H N.m.r. data (δ, 220 MHz, $CDCl_3$) for (**1**) are displayed. Coupling constants (in Hz) for (**1**): $*J_{1,2}$, 3·5; $*J_{6eq,7}$, 0; $*J_{2,3eq}$, 3; $*J_{6ax,7}$, 3; $*J_{2,3ax}$, 3; $*J_{7,8}$, 3; $J_{4,14}$, 8; $J_{8,9}$, 0; $*J_{6ax,6eq}$, 13; $J_{15,15}$, 12 (* = spin decoupled).

Cathedulin-2, m.p. 149—151 °C $[\alpha]_D^{31}$ − 74° ($CHCl_3$), $C_{38}H_{40}N_2O_{11}$, contained one benzoyl, two nicotinyl, and two acetyl residues, as shown by mass spectral data [*m/e* 124·039 ($C_6H_6NO_2$), 106·030 (C_6H_4NO), and 105·033 (C_7H_5O)], by ^{1}H n.m.r. data [assignments given in (**1**)], and the isolation of ethyl acetate, ethyl benzoate, and ethyl nicotinate (2:1:2 by g.l.c.) on ethanolysis. The pentaol core (**3**), m.p. 176—179 °C, $C_{15}H_{26}O_6$, was also isolated by ethanolysis. With no *sp*^{2} carbon atoms (^{13}C n.m.r. spectra) and three methyl groups (δ 1·25, d, *J* 8·0 Hz; 1·50, s, 1·21, s), a tricyclic sesquiterpene ether was indicated. Structure (**3**) (see below for stereochemistry) follows from a detailed consideration of the ^{1}H and ^{13}C n.m.r. data shown in (**1**) and (**3**); it presents a new constitutional variant among the polyhydroxylated eudesmanes which the Celastraceae produce. Electron-impact induced fragmentation to the major ion (**4**), characteristic of these ether-terpenoids,[2] was observed.

(**3**) $R^1 = R^2 = R^3 = R^4 = R^5$ = H
(**5**) $R^3 = R^5$ = H, $R^1 = R^2$ = Ac, R^4 = PhCO
(**6**) R^3, R^5 = –CO–, $R^1 = R^2$ = Ac, R^4 = PhCO
(**7**) R^5 = H, $R^1 = R^2$ = Ac, R^4 = PhCO, R^3 = nicotinoyl
(**8**) $R^1 = R^2 = R^3 = R^5$ = H, R^4 = PhCO

^{13}C n.m.r. data($CDCl_3$) for cathedulin-2, $R^1 = R^2$ = Ac, $R^3 = R^5$ = nicotinoyl, R^4 = PhCO, are displayed.

The stereochemistry assigned in (**1**) follows from the spectroscopic evidence. The 2-H is indicated to be in equatorial form by its couplings [see (**1**)] to 1-H and 3-H_2. A *cis*-1H,2H relationship is suggested by $J_{1,2}$ 3·5 Hz; thus, a narrow range of 3·2—3·5 Hz is observed for 1-H_{ax}, 2-H_{eq} couplings in related structures.[3] The observation of NOE's between signals from 14-H_3 and 15-H_2 (16%), and between 14-H_3 and 6-H_{ax} (18%), are possible only when C-14, C-15, and 6-H_{ax} are all axial in a *trans*-fused decalin.[3] With phosgene, the bisdenicotinyl-derivative (**5**) forms a cyclic carbonate (**6**), thus fixing the 8-OH as axial, whilst the near-zero coupling of 8-H_{eq} and 9-H shows the latter to be equatorial too.[2] The positive shielding of the 1-O_2CMe protons by the 9_{ax}-benzoate is parallel to an effect seen in maytoline.[4]



(4)

Allocation of the esterifying acids to their respective sites was aided by selective deacylation studies, followed by observation of the consequence on ring-proton n.m.r. signals. Treatment of (**1**) with methanolic triethylamine at 5 °C gave the 8-denicotinyl compound (**7**), $C_{32}H_{37}NO_{10}$ (8-H, δ 4·26; 9-H, δ 5·67). The same reagent at ambient temperature afforded the bisdenicotinoyl product (**5**), $C_{26}H_{34}O_9$ (15-H_2, δ 4·35 br). On the other hand $NaHCO_3$ in aqueous methanol gave the benzoate (**8**), $C_{22}H_{30}O_7$ (9-H δ 5·54), with the 1-, 2-, and 8-, and 15-protons at higher field). Thus the acetyl groups must engage the C-1 and C-2 hydroxy-groups with nicotinate residues at C-8 and C-15, and the benzoate at C-9.

The second alkaloid isolated from *C. edulis* extracts, cathedulin-8, was readily identified as (**2**) when it was observed to be identical with the 8-denicotinoyl derivative (**7**) (chromatographic and spectroscopic comparison). Cathedulin-8 might be an artefact arising from storage and isolation, but this point is not settled.

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