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A NEW PYRROLIZIDINE ALKALOID N-OXIDE AND THE REVISED STRUCTURE OF SCELERATINE

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Abstract: Sceleratine [1] and its N-oxide [2] have been isolated from *Senecio latifolius* DC and their structures determined by spectroscopic and chemical methods and X-ray crystallography.

Recently we isolated the N-oxide of merenskine [3],[1] a new pyrrolizidine alkaloid N-oxide from *Senecio latifolius* DC.[2] We have subsequently isolated sceleratine [1] and its N-oxide [2] from the same source. Sceleratine [1] was first isolated in 1941[3] but its structure was incorrectly assigned.[4] We herein present its correct structure.

Freshly collected plants of *Senecio latifolius* DC yielded, after extraction and extensive chromatography, sceleratine N-oxide [2], mp 152°C (dec.; from EtOH), $[\alpha]_D^{20}$ +48.4 ±0.5° (*c* 1.27; MeOH) and analysed for $C_{18}H_{27}NO_8$. The IR (KBr) spectrum of [2] suggested an N-oxide (broad band from 2900 to 3500 cm^{-1}) and a diester (1717 and 1747 cm^{-1}) . The electron impact mass spectrum (EIMS) (70 eV; 151°C) of [2] showed peaks at m/e 369 (M-0; 0.06%), 170 (6.3%), 142 (34%), 125 (12%), 120 (5.2%), 119 (12%), 117 (11%), 99 (13%), 85 (4.5%), 83 (36%), 81 (11%), 72 (15%), 55 (45%) and 43 (100%) dalton. In the ^{1}H NMR spectrum of [2] (500 MHz; MeOH-d_4) the signals characterizing the necic acid moiety were two methyl doublets at δ1.006 and δ1.089 (^3J 7.0 Hz), a methyl singlet at δ1.272, and a methylene AM-spin system (^2J 10.8 Hz) at δ3.485 and δ3.617.

Reduction of the N-oxide [2] with reduced Serdoxit[5] yielded sceleratine [1][6] with physical properties in fair agreement with those reported for sceleratine,[3] previously assigned structure [4],[4] mp 176.5-177°C (EtOH; lit.[3] 178°C, water), $[\alpha]_D^{20}$ +55.0 ±0.4° (*c* 1.09; EtOH) (lit.[3] $[\alpha]_D^{21}$ +54.0°, *c* 1.02, EtOH), analysed for $C_{18}H_{27}NO_7$ and m/e at 369 dalton (M^+; 4.1%) measured for $C_{18}H_{27}NO_7$. Other MS peaks (70 eV; 99°C) were at 325 (M-CO_2; 1.1%), 236 (13%), 226 (7.8%), 209 (1.9%) and 140 (28%) dalton. Furthermore, strong peaks showing [1] to be a diester of retronecine [5] were the three triads[7] at 138 (17%), 137 (7.4%) and 136 (23%); 121 (42%), 120 (100%) and 119 (77%); and 95 (37%), 94 (49%) and 93 (59%) dalton. The IR (KBr) spectrum of [1] showed an ester(1744 and a shoulder at 1728 cm^{-1}). The ^{1}H NMR spectrum of sceleratine [1] (500 MHz, $CHCl_3$-d) closely resembled that of its N-oxide [2] with respect to the signals of the necic acid moiety. The proton-coupled ^{13}C NMR spectrum

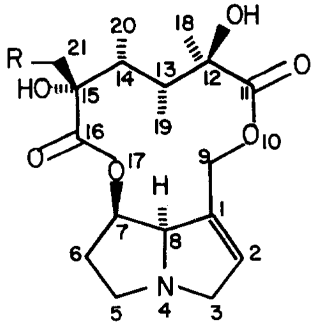
(125 MHz, $CHCl_3$-d) revealed 18 signals, 5 of which were singlets, 5 doublets, 5 triplets and 3 quartets. Two of the singlets represented ester carbonyl carbon atoms (δ175.31 and δ178.00) and another that of an olefinic carbon atom (δ131.13). The remaining two singlet signals indicated oxygenated sp^3 carbon atoms (δ78.65 and δ83.61). Two of the doublets were typically non-oxygenated sp^3 methine carbon atom signals[8] (δ37.58 and δ40.15), complemented by two quartets (δ8.73 and δ9.59). The other quartet (δ25.34) indicated a deshielded methyl group. The only triplet (δ67.20) that could not be assigned to the retronecine moiety was typically the signal of a primary alcohol carbon atom.[8]

Hydrolysis of sceleratine [1] with aqueous 0.1 M $Ba(OH)_2$ yielded retronecine [5], mp 116 - 116.5°C (acetone; lit.[1] 118.5 - 119°C, acetone) and $[\alpha]_D^{21.0}$ +55.5 ±0.9° (*c* 0.34; EtOH) (lit.[1] $[\alpha]_D^{20.8}$ +52.8 ±0.8°, *c* 0.38; EtOH), identical to authentic retronecine [5] (mp, mmp and mixed TLC) and sceleranecic bislactone [6],[9] mp 152.5 - 153°C (EtOH/H_2O; lit.[3] 156°C, H_2O) and $[\alpha]_D^{19.7}$ -6.1 ±1.3° (*c* 0.41; EtOH) (lit.[3] $[\alpha]_D^{24}$ -9.3°, *c* 1.08, H_2O). The IR (KBr) of [6] indicated a bislactone (1758 and a shoulder at 1782 cm^{-1}). The EIMS (70 eV; 67°C) of [6] showed peaks at m/e 170 (M-CO_2; 5.2%), 142 (170-C_2H_4; 28%), 125 (12%), 99 (15%), 97 (17%), 85 (20%), 83 (39%), 71 (31%), 69 (44%), 57 (63%), 55 (69%) and 43 (100%). The FDMS of [6] showed peaks at 184 (M-CH_2O; 8.7%), 169 (9.4%), 155 (41%), 141 (16%), 127 (100%) and 113 (31%). The ^1H and ^{13}C NMR spectra (80 and 20 MHz respectively, $CHCl_3$-d) were compatable with structure [6]; δ_H1.19 d (^3J 7.3 Hz, 6H), δ_H1.58 s (3H), δ_H1.46 - 2.10 m (2H), δ_H2.61 t (^3J 6.6 Hz, 1H, CH_2**OH**) and δ_H3.67 - 4.19 m (2H); and δ_C13.29 and 13.45 (2xCH**C**H_3), δ_C16.40 (CCH_3), δ_C38.59 and 42.46 (2xCH), δ_C59.60 (**C**H_2OH), δ_C81.73 and 82.08 (2x**C**CO_2) and δ_C168.48 and 169.54 (2x**C**O_2). Sceleranecic bislactone [6] was identical to authentic material[4] (mp, mmp, mixed TLC and IR).

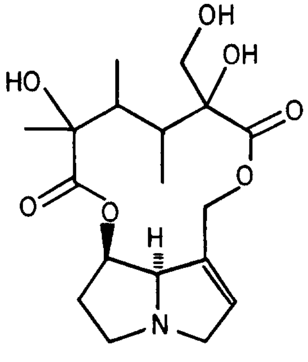
The NMR technique of selective population inversion (SPI)[10] was also applied to sceleratine [1] to determine the mode of attachment of the necic acid to retronecine [5]. An H-9 proton and the H-18 methyl protons were shown to be connected through three bonds to the lower field carbonyl carbon atom at δ178.00. An H-21 proton, in turn, is connected through three bonds to the higher field carbonyl carbon atom at δ175.31.

Single-crystal X-ray crystallography was then executed on sceleratine [1] to determine the stereochemistry of the four chiral centres in the necic acid moiety relative to the necine moiety.

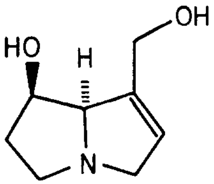
Crystals of sceleratine [1] are orthorhombic, space group $P2_12_12_1$, with z = 4, a = 10.547 (4), b = 14.406 (4) and c = 16.506 (5) Å, D_C = 1.22 gcm^{-3} and $\mu(MoK_\alpha)$ = 0.9 cm^{-1}. A total of 2521 reflections were measured in the mode with $3 \leq \Theta \leq 25°$ on an Enraf Nonius CAD-4 diffractometer, of which 820 were regarded as unobserved ($I < 2\sigma I$). The structure was solved by direct methods and refined by blocked matrix least squares techniques using SHELX.[11] All the non-hydrogen atoms were refined anisotropically. There are two ethanol molecules in the asymmetric unit, and the C-C bond of one had to be constrained during



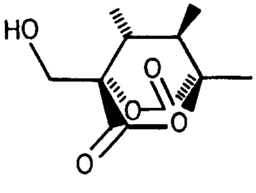
Sceleratine (1), R=OH
Sceleratine N-oxide (2) ((1) N-oxide)
Merenskine (3), R=Cl



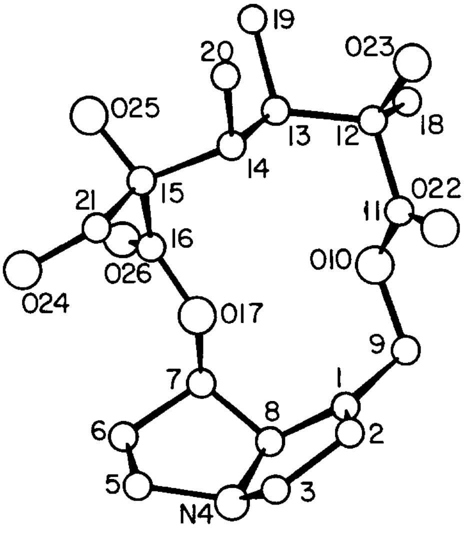
(4)



Retronecine (5)



Sceleranecic bislactone (6)



the refinement. The position of all the hydroxyl hydrogen atoms were obtained from a difference Fourier synthesis, but the remaining hydrogen atoms were included in calculated positions. Convergence, using all the data and $\sigma^{-2}(F)$ weights, was reached at R(w) = 0.056. The saturated five-membered ring is in a flattened envelope $_{C(6)}E(\phi = 263°, Q = 0.06\ \text{Å})$[12] conformation. The angle between the least squares planes of the two five-membered rings is 136 (2)°.

Tables of structure factors, fractional atomic coordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre.

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