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A NEW PYRROLIZIDINE ALKALOID FROM *SENECIO LATIFOLIUS* DC

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Abstract: The structure of a new pyrrolizidine alkaloid, merenskine N-oxide [1], was determined by spectroscopic methods which included NMR SPI experiments to indicate the mode of esterification.

The hepatotoxic nature of the pyrrolizidine alkaloids from the *Senecio* genus has enjoyed widespread interest and has led to the investigation of the alkaloid content of a vast number of this plant family.[1] In our search for novel pyrrolizidine alkaloids we reinvestigated the alkaloids [2-4] of *Senecio latifolius* DC[5] and isolated a new pyrrolizidine alkaloid N-oxide, merenskine N-oxide [1].[6]

The whole air-dried plants were milled, defatted with ether:petroleum ether (35 - 60°) (1:2) and extracted with commercial ethyl acetate at room temperature while shaken intermittently. The ethyl acetate extracts were combined and chromatographed on Merck Kieselgel 60 using chloroform:methanol:25% aqueous ammonia (85:14:1) yielding amongst other alkaloids merenskine N-oxide [1] as a white solid.

Merenskine N-oxide [1], mp 146°C (dec.; from EtOH), and $[\alpha]^{20}_{D}$ +26,1 ± 1,5° (*c* 0,33; EtOH), analysed for $C_{18}H_{26}ClNO_7\cdot C_2H_5OH$. The IR (KBr) spectrum of [1] suggested an N-oxide (broad band from 2600 to 3700cm^{-1}) and a diester (1760 and 1738cm^{-1}). The m/e at 385 ($M-H_2O$) measures for $C_{18}H_{24}ClNO_6$. The isotopic peak at m/e 387, which is a third of the intensity of the peak at m/e 385, confirms a chlorine atom per molecule of [1]. The ^{1}H NMR spectrum of [1] (500 MHz, MeOH-d_4) indicated a saturated adipic acid derivative forming a 12-membered[7] macrocyclic diester with isatinecine [4].[8] The two methyl doublets (^3J 6,9 Hz) at δ1,071 and δ1,100 respectively, the methyl singlet at δ1,278 and a methylene AB-spinsystem (^2J 11,3 Hz) at δ3,685 and δ3,706 respectively, suggested merenskine N-oxide [1] to be the N-oxide of chlorodeoxysceleratine [5], previously isolated by Gordon-Gray.[4]

Reduction of merenskine N-oxide [1] with reduced Serdoxit,[9] yielded merenskine [2], mp 194,5-195°C (sublimed at 111°C/0,2 Torr), $[\alpha]^{20,4}_{D}$ +32,6 ±1,8° (*c* 0,24; EtOH); analysed for $C_{18}H_{26}ClNO_6$; m/e 387 (M^+; 3,8%) measures for $C_{18}H_{26}ClNO_6$. Other peaks (70 eV; 80°C) characteristic of merenskine [2] are at m/e 343($M-CO_2$; 2,1%); 290($M-CO_2$, H_2O and Cl; 14,2%) and 210 (11,3%). Furthermore, strong peaks indicative of [2] being a diester of retronecine [3], are the three triads[10] at m/e 138(22,5%), 137(5,7%) and 136(27,1%); 121(53,6%), 120(100%) and 119(91,3%); and 95(65,8%), 94(47,7%) and 93(49,4%). The IR (KBr) spectrum of [2] showed a diester (1745 and 1721cm^{-1}). The ^{1}H NMR spectra of [1] and [2] are similar, showing the same necic acid moiety esterified to retronecine [3].[11] The mp and $[\alpha]_D$ of merenskine [2] correspond to those reported for chlorodeoxysceleratine [5] by Gordon-Gray.[4]

Hydrolysis of merenskine [2] with $Ba(OH)_2$ yielded retronecine [3], mp 118,5 - 9°C (acetone; lit.[12] 118 - 9°C), $[\alpha]_D^{20,8}$ +52,8 ±0,8° (*c* 0,38; EtOH) (lit.[13] +50,8°; EtOH), identical to authentic[14] retronecine [3] (mp, mmp, mixed TLC and IR).

During highfield NMR studies on merenskine N-oxide [1], SPI techniques[15] were employed to correctly assign the ^{13}C-signals. The potential usefulness of SPI experiments to determine the mode of esterification[16] of the necic acid to the necine in pyrrolizidine alkaloids is well illustrated with [1] as follows: a three bond connectivity is indicated between an H-9 proton and the lower field carbonyl carbon at δ178,1. A similar three bond connectivity exists between the chloromethyl protons and the higher field carbonyl carbon at δ173,4. These connectivities can be justified only by the mode of esterification as indicated in [1] and not by the reverse mode.

In order to verify the validity of the experimental findings and also to determine the absolute configuration of merenskine N-oxide [1], single crystal X-ray crystallography was carried out on [1].

Crystals of merenskine N-oxide [1] are orthorhombic, space group $P2_12_12_1$ with z = 4, a = 17,752 (9), b = 13,142 (8) and c = 9,991 (6) Å, D_c = 1,23 g cm^{-3} and $\mu(MoK_\alpha)$ = 1,65 cm^{-1}. A total of 2006 reflections were measured in the ω - 2θ mode with $3 \leq \theta \leq 23°$ on a Philips PW1100 four circle diffractometer, of which 672 were regarded as unobserved ($I < 2\,\sigma\,I$). The structure was solved by direct methods using the program MULTAN 80,[17] and refined by blocked-matrix least-squares techniques using the program SHELX.[18] All the non-hydrogen atoms were refined anisotropically. The positions of the three 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 σ_F^{-2} weights, was reached at R(w) = 0,056. The solvent molecule (EtOH) in the asymmetric unit takes part in intermolecular hydrogen bonding with the oxygen atom of the N-oxide group: 0(27) - 0(28) = 2,626 Å. The non-planar five membered ring is in an envelope conformation $_{c(6)}E(\phi = 254°, Q = 0{,}45$ Å),[19] and the angle between the least squares plane of the two five membered rings is 105°.

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

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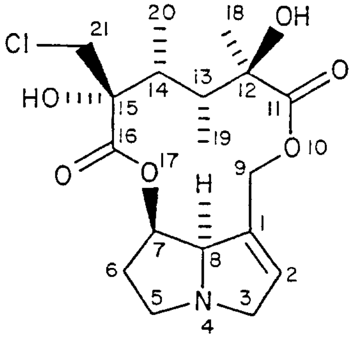
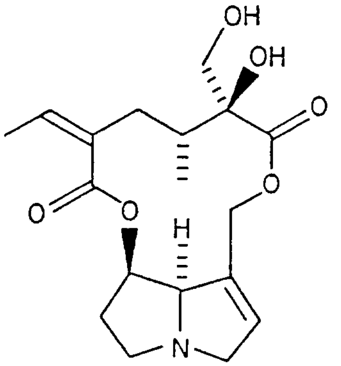
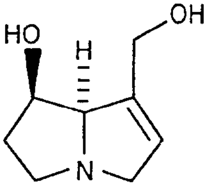


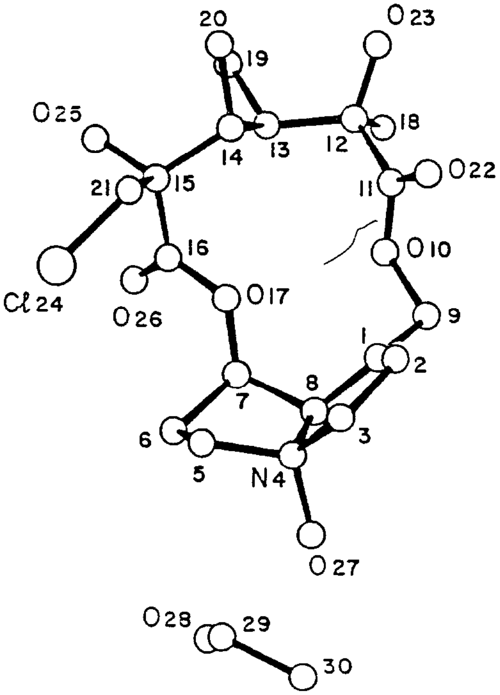
Merenskine N-oxide (1)
(N-oxide of (2))
Merenskine (2)

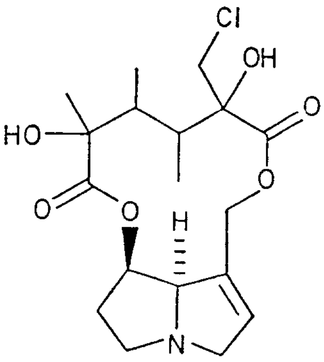


Retrorsine (6)
Isatidine (7) ((6) N-oxide)



Retronecine (3)
Isatinecine (4) ((3) N-oxide)





Chlorodeoxysceleratine (5)

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7. $\Delta\delta$ of the H-9 protons is 1,049 ppm and is thus indicative of a 12-membered pyrrolizidine alkaloid macrocycle (See ref. 11).
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