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THE STRUCTURE OF THE OXIDATION PRODUCT OF ACONITINE WITH NITRIC ACID[1)]

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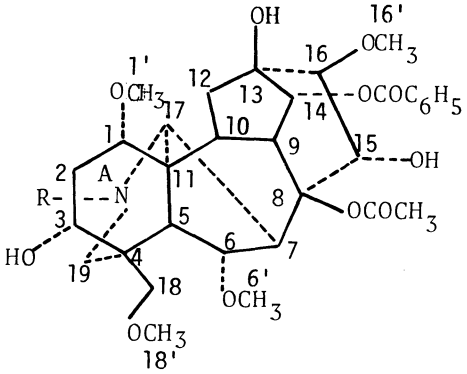
The structure of nitronitrosoaconitinic acid which is an oxidation product of aconitine with nitric acid was confirmed by spectroscopic methods. This compound was found to be a new type of acid having a pKa value comparable to that of carboxylic acids.

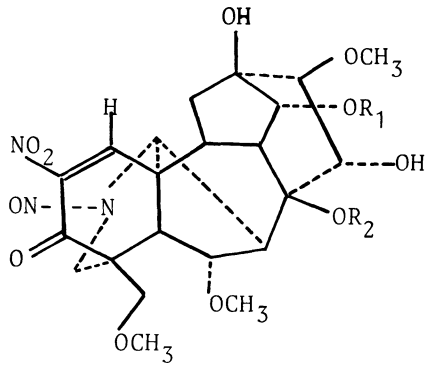
Vigorous oxidation of aconitine (I), mesaconitine (II) and their derivatives with nitric acid yields a nitro-N-nitroso derivative (III),[2,3,4,5,6)] which has been called nitronitrosoaconitinic acid by Suginome.[3)] Two alternative molecular formulae $C_{31}H_{33}O_{13}N_3$[3)] and $C_{31}H_{35}O_{13}N_3$[4)] have been proposed for III on the basis of the elemental analysis. Moreover, one of the present authors[3)] found that although it retained both benzoyl and acetyl groups of aconitine (I), one of the four methoxyl groups and the alkyl group attached to the tertiary nitrogen of I are lost in the transformation. The structure, however, still remains unknown. Compound III has now been subjected to modern structural analysis and in this paper we wish to propose structure III for this compound.

Field desorption mass spectrometry of III recrystallized from aqueous acetone confirmed the molecular formula as $C_{31}H_{35}O_{13}N_3$ [m/e 658 $(M+1)^+$]. The ^1H n.m.r. spectrum ($CDCl_3$, δ) established the presence of an acetoxyl group (1.40, s, 3H), three methoxyl groups (3.18, s, 3.33, s, and 3.82, s, each 3H) and a benzoyloxy group and an olefinic proton (7.26-8.10, m, 6H). The infrared spectrum exhibited bands due to hydroxyl groups at 3400-3700, an α,β-unsaturated carbonyl group at 1700 and 1720, a nitro group at 1373 and 1538 and benzene ring C-H bonds at 720 cm^{-1}. The u.v. spectrum in ethanol showed strong absorptions at 230 (log ε; 4.2) and 343 nm (log ε; 3.4) due to an α,β-unsaturated carbonyl group. The removal of the two acyl groups by an alkaline hydrolysis of III afforded a compound (IV), $C_{22}H_{29}O_{11}N_3$, designated as nitronitrosoaconinic acid,[3)] [m/e 512 $(M+1)^+$; λ_{max}^{EtOH} 230 nm (log ε; 4.1) and 343 (3.1), α,β-unsaturated carbonyl; ν_{max}^{KBr} 3300-3700 (OH), 1700 (C=O), 1370 and 1535 (NO_2); ^1H n.m.r. (D_2O, δ) 3.30, 3.34 and 3.57 (each 3H, three methoxy groups) and 7.63 (1H, olefinic proton)] and indicated generation of an olefinic proton in the transformation of I into III. On acetylation of IV with acetyl chloride all of the four free hydroxyl and N-nitroso groups reacted and an N,O-pentaacetate (V), d.p. 275-279°, was obtained.



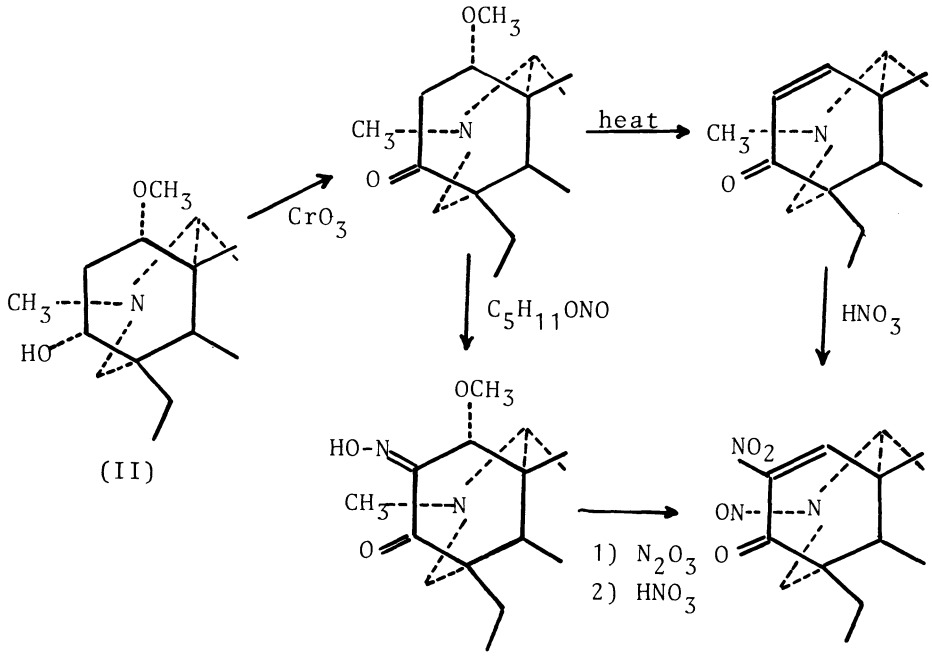
(I) R=CH_2CH_3

(II) R=CH_3



(III) R_1=COC_6H_5, R_2=$COCH_3$

(IV) R_1=R_2=H

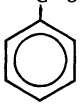


Scheme

The ^{13}C signal assignments[7] of III, IV and V together with those of I reported[8] are shown in the Table. All the assignments were made with the aid of the ^{1}H single-frequency off-resonance decoupling technique and by comparison of their chemical shifts with those of aconitine type diterpenoid alkaloids.[8] Comparison of the signals of III with I and II indicates that only the chemical shifts of C-1, C-2 and C-3 differ significantly from those of the diterpenoid alkaloides, although slight differences for C-4, C-5, C-18 and C-19 are also

Table

Carbon-13 Chemical Shifts of Aconitine (I),[a] Nitronitrosoaconitinic acid (III), Nitronitrosoaconinic acid (IV) and Nitro-N-acetylaconinic acid tetraacetate (V).

Carbon	(I)[a,b]		(III)[b]		(IV)[c]		(V)[b]	
1	83.4	(d)	142.8	(d)	145.8	(d)	144.1	(d)
2	36.0	(t)	148.8	(s)	150.7	(s)	149.1	(s)
3	70.4	(d)	186.7	(s)	189.0	(s)	188.4	(s)
4	43.2	(s)	48.5[d]	(s)	50.4[d]	(s)	49.0[d]	(s)
5	46.6	(d)	51.1	(d)	55.4	(d)	50.3	(d)
6	82.3	(d)	81.1	(d)	82.5	(d)	82.0	(d)
7	44.8[d]	(d)	48.0	(d)	49.2	(d)	47.9	(d)
8	92.0	(s)	89.5	(s)	78.7	(s)	87.9	(s)
9	44.2[d]	(d)	42.1	(d)	48.1	(d)	41.9	(d)
10	40.8	(d)	36.7	(d)	38.6	(d)	37.2	(d)
11	49.8	(s)	50.5[d]	(s)	51.7[d]	(s)	51.7[d]	(s)
12	34.0	(t)	37.3	(t)	39.7	(t)	37.9	(t)
13	74.0	(s)	74.1	(s)	77.6	(s)	79.9	(s)
14	78.9	(d)	78.3[e]	(d)	80.0[e]	(d)	76.1[e]	(d)
15	78.9	(d)	78.5[e]	(d)	81.5[e]	(d)	77.6[e]	(d)
16	90.1	(d)	89.9	(d)	92.9	(d)	88.2	(d)
17	60.7[f]	(d)	62.6	(d)	64.8	(d)	52.5	(d)
18	75.6	(t)	70.5	(t)	72.2	(t)	70.1	(t)
19	48.8	(t)	42.7	(t)	44.0	(t)	46.6	(t)
N-CH_2	46.9	(t)	----		----		----	
CH_3	13.3	(q)	----		----		----	
1'	55.7	(q)	----		----		----	
6'	57.9	(q)	58.3	(q)	58.4	(q)	59.1	(q)
16'	61.0[f]	(q)	61.4	(q)	61.9	(q)	61.6	(q)
18'	58.9	(q)	59.2	(q)	59.5	(q)	59.1	(q)
C=O	172.2	(s)	172.0	(s)	----		C=O 168.2x2	(s)
CH_3	21.3	(q)	21.2	(q)	----		170.1x2	(s)
							170.3	(s)
C=O	165.9	(s)	165.7	(s)	----			
	129.8	(s)	129.2	(s)	----		CH_3 20.9	(q)
	129.6	(d)	129.6	(d)	----		21.2x2	(q)
	128.6	(d)	128.8	(d)	----		21.6	(q)
	133.2	(d)	133.7	(d)	----		22.0	(q)

a) Results reported by Pelletier and Djarmati.[8] b) δ, ppm downfield from TMS in $CDCl_3$. c) δ, ppm downfield from TMS in CD_3OD. d) and e) Two values of each compound may be interchanged. f) On the basis of the observation of the spin-lattice relaxation time (T_1) measurements (C-17; 0.2 sec and C-16'; 0.6 sec) the reported assignments of chemical shifts of C-17 (61.0) and C-16' (60.7)[8] should be interchanged. The seperation of closely spaced peaks due to C-17/C-16' into positive and negative signals was observed.

seen. These data suggest that a large structural change took place only in ring A, and more specifically that the α,β-unsaturated carbonyl group was introduced into the A-ring.

The pKa value of III was determined to be about 5 by a spectrophotometric measurement at a wavelength of 332 nm (λ max) in an aqueous solution. This value suggests that the acid strength of III is nearly equal to those of carboxylic acid. In the ^{1}H n.m.r. spectrum a signal due to an olefinic proton at δ 7.63 of IV in D_2O disappeared slowly in the presence of a trace of alkali. Therefore, a system formed by the introduction of a nitro group into the double bond of the α,β-unsaturated carbonyl group is considered to be responsible for the acidity. No study concerning the acidity of such a structure has been reported and further studies are in progress presently in our laboratories. The nitro group could be attached to either the α (C-2) or the β (C-1) position of the α,β-unsaturated carbonyl group. Compound III can be obtained[5] from II *via* chromic acid oxidation to a ketone, nitrosation at the carbon α to the carbonyl and oxidation with nitric acid. This sequence of reactions allows us to confirm that the nitro group is definitely attached to the C-2. On the basis of all the results described above, the structure of nitronitrosoaconitinic acid is formulated as III and a series of reactions from II to afford III are explained as depicted in the Scheme.

References and Notes

1) A part of this study was presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977(Abstr., p. 265) and at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978 (Abstr., p. 339).
2) E. S. Stern, "The Alkaloids", Vol. IV, ed by R. H. F. Manske, Academic Press New York (1954), p. 303.
3) H. Suginome, Ann., 533, 172 (1938).
4) W. A. Jacobs and L. C. Craig, J. Biol. Chem., 136, 323 (1940).
5) R. Majima and K. Tamura, Ann., 545, 1 (1940).
6) W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc., 78, 4048 (1954).
7) Carbon-13 FT n.m.r. spectra were taken at 25.00 MHz using a JEOL-FX-100 spectrometer equipped with a JEC-980-24K computer and 5-mm o.d. tubes. FT-measurement conditions were: spectral width, 5 KHz; pulse width, 5 μs (45°); pulse repetition time, 1.0 sec; number of data points, 8192; numbers of transients, 5000-40000.
8) S. W. Pelletier and Z. Djarmati, J. Am. Chem. Soc., 98 2626 (1976).

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