Tetrahedron Letters No. 10, pp. 1-9, 1960. Pergamon Press Ltd. Printed in
Great Britain.

THE CONSTITUTION OF RING A IN ACONITINE

F. W. Bachelor, R. F. C. Brown and G. Büchi
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts, U. S. A.

(Received 29 March 1960)

IN a collaborative paper we recently proposed structure I for the modified diterpene alkaloid aconitine.[1] The results of a complete X-ray analysis[2] of demethanolaconinone hydriodide trihydrate (II) are in agreement with our views and beyond that provide the absolute[3] and relative configurations of thirteen out of the fifteen asymmetric centers present in aconitine. We now wish to present findings concerning the location of the 1,3-glycol-monomethylether grouping in ring A, for which chemical evidence was lacking,[1] and the configurations of the two remaining asymmetric centers. It was previously argued on chemical grounds that aconitine could not possess a hydroxyl group at C_1 because no carbinolamine ether is formed on oxidation of the alkaloid with chromium trioxide[4] while such

---

[1] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters **2**, 15 (1959).

[2] M. Przybylska and L. Marion, Can. J. Chem. **37**, 1116 (1959).

[3] M. Przybylska and L. Marion, Can. J. Chem. **37**, 1843 (1959).

[4] H. Mayer and L. Marion, Can. J. Chem. **37**, 856 (1959).

products are obtained by oxidation of delcosine[5] and delsoline[6] with potassium permanganate or silver oxide. Such reasoning, unfortunately, is not acceptable because it is based on negative evidence and structures (V)[6] for the carbinolamine ethers which are geometrically impossible.

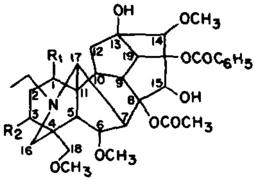
We felt that the location of the hydroxyl function in ring A could be ascertained most conveniently by lactone formation between it and a carboxyl group to be generated at C_4. The recently reported cleavage of the bisnitrone III to the dimer of 4-methyl-4-nitrosopentanoic acid (IV) by sodium periodate[7] suggested that oxidation of the nitrone VII, m.p. 210-212°; λ_{max}^{EtOH} 233 mμ, ε 18620; λ_{210} ε 5000; $\nu_{max}^{CHCl_3}$ 1720 (benzoate), 1605 cm^{-1} (nitrone); $[\alpha]_D^{27}$ +13° (c, 3.09 $CHCl_3$). [Calcd. for $C_{31}H_{41}O_{11}N$: C, 61.66; H, 6.85; N, 2.32; 5 OCH_3, 25.70%. Found: C, 61.41; H, 7.02; N, 2.21; OCH_3, 25.02%] may yield the desired hydroxyacid. The required intermediate VII was available from the pentacyclic nitrone (VI)[1] by treatment with methanolic perchloric acid followed by aerial oxidation of the intermediate hydroxylamine in the presence of cupric ion. In fact, oxidation of VII with hot aqueous periodic acid yielded a crystalline, neutral, blue colored compound (VIII) rather than a carboxylic acid, which had m.p. 233-234° (dec.); $\lambda_{max}^{acetone}$ 670 mμ, ε 23; λ_{max}^{EtOH} 230 mμ, ε 16000; ν_{max}^{Nujol} 1745 (γ-lactone), 1721 (benzoate), 1563 cm^{-1} (nitroso). Calcd. for $C_{30}H_{35}O_{12}N$: C, 59.89; H, 5.87; N, 2.33; 4 OCH_3, 20.61 ; 5 OCH_3, 25.76%. Found: C, 59.66; H, 5.97; N, 2.44; OCH_3, 20.63%. Oxidation of

---

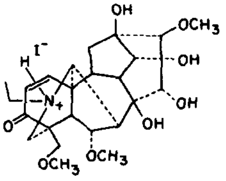
[5] R. Anet, D. W. Clayton and L. Marion, Can. J. Chem. 35, 397 (1957).

[6] F. Sparatore, R. Greenhalgh and L. Marion, Tetrahedron 4, 157 (1958).

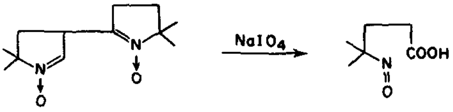
[7] V. M. Clark, B. Sklarz and (Sir) Alexander Todd, J. Chem. Soc. 2123 (1959).



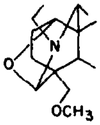
I R$_1$ = OCH$_3$; R$_2$ = OH
or R$_1$ = OH ; R$_2$ = OCH$_3$



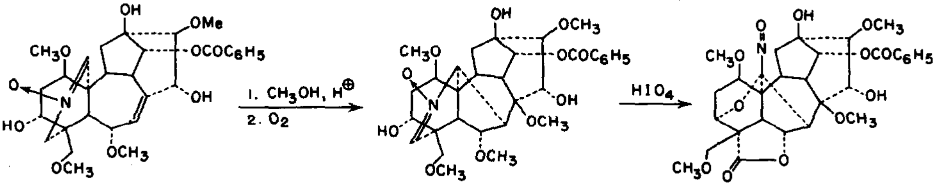
II



III IV



V



VI VII VIII

N-desethylpyroaconitine-Δ^{16}-nitrone[1] (IX) under identical conditions gave an analogous crystalline nitroso derivative (XI), m.p. 237-238° (dec.); $\lambda_{max}^{acetone}$ 685 mμ, ϵ 23; λ_{max}^{EtOH} 232 mμ, ϵ 13000; ν_{max}^{Nujol} 1750 (shifted to 1770 in CHCl$_3$)[8] (γ-lactone), 1720 (benzoate), 1705 (cyclohexanone), 1550 cm^{-1} (nitroso). Calcd. for C$_{29}$H$_{31}$O$_{11}$N: C, 61.15; H, 5.49; N, 2.46; 3 OCH$_3$, 16.35 ; 4 OCH$_3$, 21.80 ; act. H, 0.17%. Found: C, 60.78; H, 5.51; N, 2.34; OCH$_3$, 16.23 ; act. H, 0.12%. It was clear from the spectral data that a

---

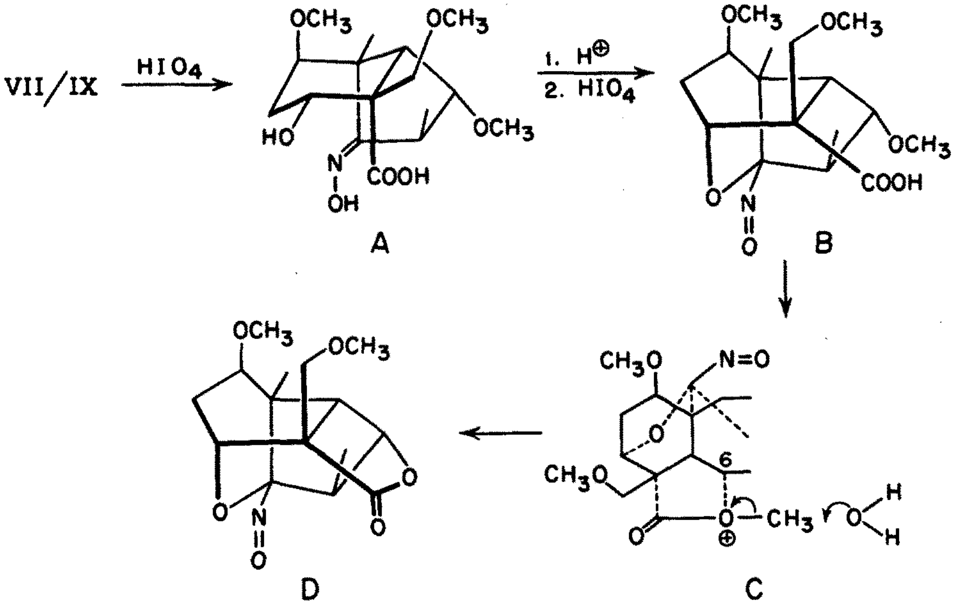
[8] P. Wilder, Jr. and A. Winston, J. Am. Chem. Soc. 77, 5598 (1955). J. A. Berson, J. Am. Chem. Soc. 76, 4974 (1954).

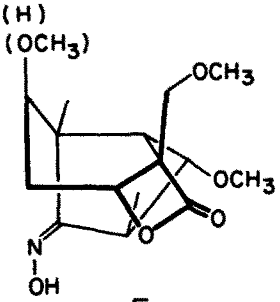
nitroso group and a γ-lactone ring were present in both substances. They furthermore contained one methoxyl group less than their precursors VII and IX and the second transformation also demonstrated that the methoxyl at C_8 was not involved. The formation of the nitroso derivatives can be rationalized by the sequence VII/IX —> A —> B —> C —> D. Non-bonded interactions between the carboxyl group and the oxime function as well as between the substituents at the peri-positions C_4 and C_6 operating in A are absent in D. Internal ether formation, indicated by the presence of nitroso derivatives rather than oximes and by the active hydrogen content of XI, is sterically only feasible if the hydroxyl group in ring A is at C_3 and α-oriented. Analogies for the postulated intermediate C have been provided[9] and the steric relationship of the carboxyl- and methoxyl-substituents in B is such that displacement must have occurred on the methyl group rather than on C_6. This unusually facile lactonization across the peri-positions provides chemical evidence for both location and orientation of the methoxyl function at C_6 and is, incidentally, analogous to the tetrahydrofuran ring formation across the same positions in delphinine.[10]

---

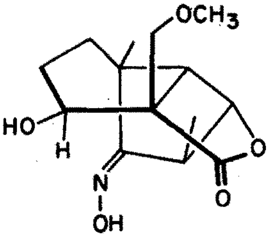
[9] D. S. Noyce and H. I. Weingarten, J. Am. Chem. Soc. **79**, 3093 (1957); **79**, 3098 (1957).

[10] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, Tetrahedron Letters **3**, 12 (1959); K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia **15**, 93 (1959); W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc. **76**, 161 (1954).


VII/IX
HIO4
OCH3
OCH3
HO
OCH3
N
OH
COOH
A
1. H⊕
2. HIO4
OCH3
OCH3
OCH3
COOH
O
N
O
B
CH3O
N=O
O
CH3O
6
O
O
⊕
CH3
O
H
H
C
OCH3
OCH3
O
O
O
N
O
D


(H)
(OCH3)
OCH3
OCH3
O
O
N
OH

E


OCH3
HO
H
N
OH
O
O

F

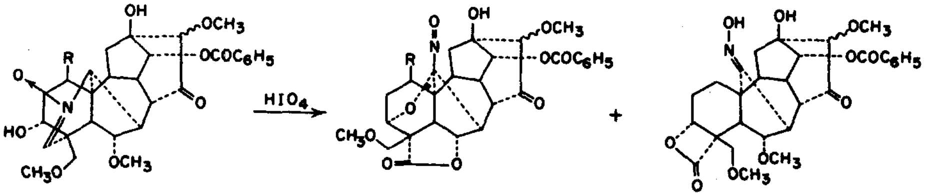
Spectral analysis of the products formed in the two periodic acid oxidations revealed the presence of small quantities of materials which we believe to be β-lactones ($\nu_{max}^{CHCl_3}$ 1825 cm^{-1}) although the products could not be isolated in pure form. We did, however, succeed in the preparation of a pure β-lactone in the 1-desmethoxypyroaconitine series. Reduction of dihydrodemethanolaconitinone[4] with sodium borohydride gave a crystalline product, m.p. 171-174°, $[\alpha]_D^{25}$ +19.5° (c, 0.95 $CHCl_3$). Although the physical constants are in fair agreement (lit.[4] m.p. 171-173°; $[\alpha]_D^{27}$ +24° ($CHCl_3$)) with those previously reported, our product was a mixture of C_3-epimeric alcohols because acetate pyrolysis at 210° yielded crystalline 1-desmethoxypyroaconitine (XIV), m.p. 131-132°; $[\alpha]_D^{25}$ -96° (c, 1.03 $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (benzoate, cyclohexanone). Calcd. for $C_{31}H_{41}O_8N$: C, 67.00; H, 7.44; N, 2.52%. Found: C, 67.11; H, 7.32; N, 2.72% and an amorphous fraction containing 3-epi-1-desmethoxypyroaconitine (XV). Oxidation of XIV with peracetic acid in chloroform gave the amorphous N-oxide m.p. 172-178° (dec.) which, like our other N-oxides,[1] is probably a mixture of the two anticipated diastereomers. It was transformed further to the hydroxylamine by pyrolysis at 185° which in turn was oxidized with potassium ferricyanide in aqueous methanol containing sodium bicarbonate to the crystalline nitrone (X), m.p. 243-244°; $[\alpha]_D^{25}$ -109° (c, 1.05 $CHCl_3$); ν_{max}^{Nujol} 1715 (benzoate, cyclohexanone), 1585 cm^{-1} (nitrone). Calcd. for $C_{29}H_{35}O_9N$: C, 64.31; H, 6.51; N, 2.59%. Found: C, 64.00; H, 6.53; N, 2.76%. An identical sequence of reactions performed on XV gave an isomeric, crystalline nitrone (XVI), m.p. 231-232°, $[\alpha]_D^{25}$ -191° (c, 0.21 $CHCl_3$); ν_{max}^{Nujol} 1708 (benzoate, cyclohexanone), 1600 cm^{-1} (nitrone). Calcd. for $C_{29}H_{35}O_9N$: C, 64.31; H, 6.51; N, 2.59%. Found: C, 63.98; H, 6.61; N, 2.65%. Further, we found that oxidation of X with hot aqueous periodic acid yielded two crystalline products separable by chromatography on acid-washed alumina. The less strongly adsorbed product was the blue nitrosolactone XII, m.p. 179-180° (from acetone-water); ν_{max}^{KBr} 1755 (1775 in $CHCl_3$) (γ-lactone), 1712 (benzoate, cyclohexanone), 1550 cm^{-1} (nitroso). Calcd. for $C_{28}H_{29}O_{10}N \cdot H_2O$: C, 60.32; H, 5.60; N, 2.51; 2 OCH_3, 11.13; 3 OCH_3, 17.22%. Found: C, 60.69; H, 5.61; N, 2.38; OCH_3, 11.27%. A striking property of the second product, m.p. 235-236° (dec. with gas evolution) [Calcd. for $C_{29}H_{33}O_{10}N$: C, 62.69; H, 5.99; N, 2.52; 2 OCH_3, 11.19; 3 OCH_3, 16.76%. Found: C, 62.57; H, 6.16; N, 2.40; OCH_3, 16.24%] was its infrared spectrum which exhibited bands in Nujol and chloroform at 1820 (β-lactone), 1710, 1695 cm^{-1} (benzoate, cyclohexanone, oxime) which we feel is in agreement with structure XIII. Not surprisingly the C=N vibration occurs at a high frequency and as the C=O vibration in cyclic ketones it is greatly affected by ring strain as exemplified by the following measurements in Nujol: cyclohexanoneoxime, 1662;[11] XVIII, 1680; XIX (prepared from bicyclo-[3,2,1]-octan-8-one[12]), 1690 cm^{-1}. These transformations provide further proof for the presence of a 3αOH group in aconitine. As anticipated the oxidation of XVI with periodic acid yielded neither a β-lactone nor a nitroso-γ-lactone but a crystalline oximino-γ-lactone (XVII), m.p. 244-246° (from $CHCl_3$); $[\alpha]_D^{25}$ -150° (c, 0.23 $CHCl_3$); ν_{max}^{Nujol} 1755 (shifted to 1765 in $CHCl_3$)[8] (γ-lactone), 1710-1700 cm^{-1} (benzoate, cyclohexanone, oxime).

---

[11] A. Palm and H. Werbin, Can. J. Chem. 31, 1004 (1953).

[12] R. Mayer, G. Wenschuk and W. Töpelmann, Chem. Ber. 91, 1616 (1958); A. C. Cope, J. M. Grisar and P. E. Peterson, J. Am. Chem. Soc. in press, to whom we are indebted for a sample.

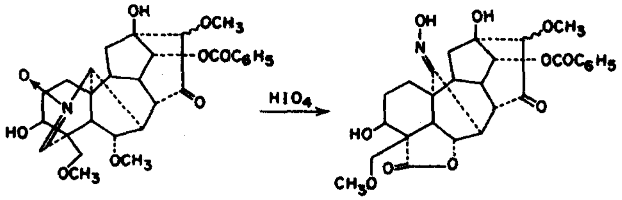
Calcd. for $C_{28}H_{31}O_{10}N\cdot CHCl_3$: C, 52.69; H, 4.88; N, 2.12; Cl, 16.10; 2 OCH_3, 9.39; 3 OCH_3, 14.09%. Found: C, 52.49; 52.47; H, 4.57; 4.67; N, 2.07; 1.96; Cl, 15.68; OCH_3, 9.19%. To secure further evidence for the presence of oxime functions in XIII and XVII, the compounds were heated with benzoyl peroxide and the resulting nitrous acid detected by



IX R = OCH_3
X R = H

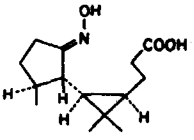
XI R = OCH_3
XII R = H

XIII

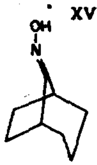


XVI

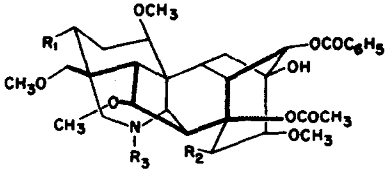
XVII



XVIII



XIX



XX R_1 = OH ; R_2 = OH ; R_3 = C_2H_5
XXI R_1 = H ; R_2 = H ; R_3 = CH_3

the sensitive Griess reagent.[13] Ring A in the oximino-γ-lactone (XVII) again must assume the boat form with equatorially disposed hydroxyl group to allow the formation of a strain free γ-lactone ring (cf. F). We have already pointed out that oxidative cleavage of the two nitrones VII and IX yields only minor quantities of β-lactones while approximately equal amounts of the β-lactone XIII and the γ-lactone XII are formed by oxidation of the desmethoxynitrone X under identical conditions. Consequently, the methoxyl group at C_1 seems to oppose β-lactone formation. If it is assumed that the fused β-lactone ring forces ring A into a pseudo-chair conformation the bulky methoxymethyl substituent at C_4 is quasi-axial and will destabilize a β-lactone by non-bonded interaction with the methoxyl group at C_1 if it is indeed axially oriented (cf. E). This argument is only suggestive and our proposal therefore tentative. Aconitine and delphinine have recently been correlated by Wiesner[14] and the two alkaloids are therefore represented by the complete structures XX and XXI.

We are much indebted to Chas. Pfizer and Co., Inc. for financial support and to the Alfred P. Sloan Foundation for a foreign postdoctoral fellowship to R. F. C. B.

---

[13] F. Feigl, Spot Tests in Organic Chemistry (5th edition), Elsevier, New York, N. Y. (1956), p. 228.

[14] K. Wiesner, D. L. Simmons and L. R. Fowler, Tetrahedron Letters **18**, 1 (1959).