THE STRUCTURE OF ACONITINE

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THE alkaloid aconitine $C_{34}H_{47}O_{11}N$ is the most important and complicated representative of the class of aconitum alkaloids. The confusing and contradictory chemical studies on aconitine before 1900 have been reviewed by Schulze.[1] Subsequent studies covering the first half of the 20th century, which led only to the clarification of the functional groups, have been reviewed again by Stern.[2]

We now wish to propose the complete structure of aconitine (I) in which the only ambiguity is that a methoxyl and hydroxyl may have to exchange positions. We shall start elaborating the argument by showing that the structure of the C-D ring system of aconitine (II) differs from the recently deduced [3] structure of the C-D ring system of delphinine (III) only by the presence of an additional hydroxyl.

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[1] H. Schulze, Arch. Pharm. **244**, 136, 165 (1906).

[2] E. S. Stern, The Alkaloids, Chemistry and Physiology (Edited by R. H. F. Manske and H. L. Holmes) Vol. IV. Academic Press, New York (1954).

[3a] K. Wiesner, F. Bickelhaupt and Z. Valenta, Tetrahedron **4**, 418 (1958);
[b] K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia In press.

We have first of all established that pyrooxonitine is a ketone. This is supported by the fact that the hydrolysis product of pyrooxonitine, pyrooxonine, already described by Majima [4] shows a carbonyl maximum at 1718 cm^{-1} corresponding to a keto group in a six-membered ring. The infrared examination of pyrooxonitine of course can provide no corroboration of its ketonic character because of the presence of the strong ester peak in the same region. However, the rotatory dispersion curve of pyrooxonitine shows unambiguously its ketonic character by its typical peak at 343 mμ $[\alpha]$ = -1020.

On this finding we based the hypothetical partial structure (II) of aconitine which contains an additional hydroxyl trans to the acetoxy group in the system (III) already established for delphinine.[3] There are now several pieces of evidence which prove this analogy of the partial structures beyond reasonable doubt.

Oxidation of oxonine [5] with chromium trioxide in pyridine gave a mixture of products from which a diketone (m.p. 238°) was obtained by chromatography on florisil in a yield of 5.4%. Calcd. for $C_{25}H_{35}O_{10}N \cdot 1/2\ H_2O$: C, 57.90; H, 7.01; O, 31.45; 4 OCH_3, 23.96%. Found: C, 57.68; H, 7.23: O, 32.18; OCH_3, 23.91%. Infrared (KBr): 3450, 1756, 1721, 1668 cm^{-1}. Ultraviolet: λ_{max}^{EtOH} 295 mμ, log = 1.95, $[\alpha]_D^{24}$ = -155° (ethanol).

We ascribe to this compound the structure IV. It is consequently analogous in the C-D ring system to α-oxodelphonone isomerized with base. The molecular rotation difference corresponding to the conversion of the C-D rings of oxonine to the C-D system of IV may be obtained from the rotations

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[4] R. Majima and H. Suginome, *Ber.* **58B**, 2047 (1925).

[5] R. Majima, H. Suginome and H. Shimanuki, *Ber.* **65**, 595 (1932).

of oxonitine, oxoaconitine, oxonine and IV. The result ($\Delta[\alpha] = -80^{\circ}$) agrees with the rotation change suffered by α-oxodelphonine on oxidation to α-oxodelphonone, followed by isomerization with base ($\Delta[\alpha]_D = -72^{\circ}$). Compound IV takes up 1 mole of lead tetraacetate to give in quantitative yield an amorphous keto acid formulated as V. (For the sake of brevity we shall use only one of the two possible alternatives in ring A.)

The ultraviolet spectrum of V shows a shoulder at 230 mμ and a maximum at 255 mμ. The differential spectrum of V and desmethanol-aconinone [6] is identical with the spectrum of the seco acid from isomerized α-oxodelphonone which has the same characteristic but anomalous chromophore.[3]

We have been able to establish conclusively the analogy of II and III for aconitine and delphinine by a remarkable aromatization reaction. Oxonine takes up in acidic solution exactly 1 mole of periodic acid and the amorphous uncharacterized product VI gives, by heating to 70° in aqueous sodium hydroxide in a stream of oxygen, a phenol of the partial structure (VIII). This compound was isolated by chromatography on silicic acid in a yield of 10%, and remained amorphous. I.R.: 3550, 3420, 1670, 1620, 1585, 1505 cm^{-1}. U.V.: λ_{max}^{EtOH} 238, 283, 315 mμ, log ϵ = 4.25, 3.83, 3.75; (alkaline EtOH): λ_{max} 256, 353 mμ, log ϵ - 4.06, 4.18. These data are in agreement with a model acetophenone of the same substitution.

Methylation with diazomethane gave the methyl ether IX, m.p. 139°. This compound, in spite of precisely reproducible melting point and infrared spectrum, gave widely scattered combustion results for carbon. Calcd. for $C_{25}H_{33}O_8N$: H, 7.00; N, 2.95; 5 OCH_3, 32.67%. Found: H, 6.77; N, 2.67; OCH_3, 31.38%. I.R. ($CHCl_3$): 3660, 3400, 1670, 1605, 1505 cm^{-1}.

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[6] A. Lawson, J. Chem. Soc. 80 (1936).

U.V.: λ^{EtOH}_{max} 236.5, 279, 314 mµ, logϵ = 4.52, 4.08, 3.94.

Compound IX was then converted into a highly crystalline and correctly analyzing derivative (X) as follows. It was oxidized with chromium trioxide in acetic acid in quantitative yield to a diketone with no hydroxyl in the infrared. This compound, by vigorous reflux with methanolic HCl, lost the acetoxy group and eliminated the ring A methoxyl. The resulting base was reacetylated to X (m.p. 239°). Calcd. for $C_{24}H_{28}O_7N$: C, 65.21, H, 6.39; 4 OCH_3, 28.09%. Found: C, 65.31, 65.10; H, 6.17, 6.11; OCH_3, 26.00%. I.R.: No hydroxyl, 1685, 1652, 1605, 1505, 1465 cm^{-1}. U.V.: Identical with the sum of the desmethanolaconinone spectrum and the spectrum of IX.

The rationalization of this aromatization reaction involves a simple series of base catalyzed and oxidative steps proceeding from VI to VIII via VII. The loss of the aldehyde carbon in VII occurs at some stage in an oxidative reaction for which analogies can be found in the researches of Danilow.[7]

The proof of the correctness of our formulation is however not derived from mechanistic considerations, but from the fact that we have been able to modify the rigorously established [3] system III of delphinine in such a manner as to make it undergo the same reaction. The starting material was α-oxoisopyrodelphonine which by cleavage with 1 mole of periodic acid gave the crystalline secoaldehyde XI (m.p. 158°). Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; O, 25.03; 4 OCH_3, 27.74%. Found: C, 63.91; H, 7.31; O, 24.95; OCH_3, 27.66%.

Compound XI gave under identical conditions as those used with the aconitine derivative VI the phenol XIII (m.p. 123°) in a yield of

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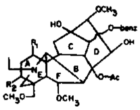
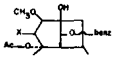
[7] S. Danilow, Ber. **60**, 2390 (1927).

45%, presumably via the intermediate XII. Calcd. for $C_{22}H_{27}O_6N \cdot 1/2\ CH_3OH$: C, 64.73; H, 7.00; O, 24.91; N, 3.36; 3.5 OCH_3, 26.01%. Found: C, 64.93; H, 7.19; O, 24.28; N, 3.25; OCH_3, 25.95%. I.R.: 1697, 1653, 1612, 1582 cm^{-1}. U.V.: λ_{max}^{EtOH} 232, 285 mμ, log ε = 4.32, 4.24; (EtOH-NaOH): λ_{max} 246, 335 mμ, log ε = 4.18, 4.52.

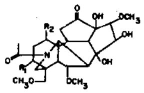
The phenol XIII was methylated with diazomethane and the N-formyl group hydrolyzed. This gave a secondary base (m.p. 144°) formulated according to the structure deduced previously [3b] for delphinine as XIV. Calcd. for $C_{22}H_{29}O_5N$: C, 68.19; H, 7.54; 4 OCH_3, 32.04%. Found: C, 68.34; H, 7.52; OCH_3, 30.97%.



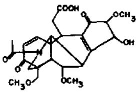
Ia $R_1 = OCH_3$, $R_2 = -OH$
Ib $R_1 = -OH$, $R_2 = -OCH_3$



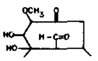
II X = –OH
III X = H



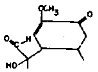
IV $R_1 = OCH_3$, $R_2 = {=}O$
or
$R_1 = {=}O$, $R_2 = OCH_3$



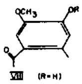
V



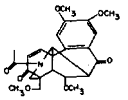
VI



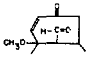
VII



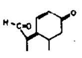
VIII (R = H)
IX $(R = CH_3)$



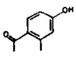
X



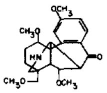
XI



XII



XIII



XIV

The relationship between the nitrogen atom and the acetoxy group became clear from the following transformations. Aconitine N-oxide (XV), m.p. 169° (dec.), was prepared by oxidation of aconitine (Ia) with peracetic acid. The presence of the N-oxide functionality was established by reconversion to aconitine (Ia) by means of zinc dust in acetic acid and rearrangement with aqueous potassium chromate [8] to yield acetaldehyde. This latter finding confirms the presence of an N-ethyl group.[2] Pyrolysis [9] of aconitine N-oxide (XV) at 190° gave a very weakly basic compound (XVI), m.p. 255°, λ^{EtOH}_{max} 232 mμ, ϵ 18400; inflexion 255 mμ, ϵ 104000, λ_{210}, ϵ 10350; I.R. ($CHCl_3$) 3500, 3250 (OH); 1715 (benzoate); 1603 (nitrone, arom. C=C); 860 (trisubst. C=C?); calcd. for $C_{30}H_{39}O_{10}N$: C, 62.80; H, 6.85; N, 2.44; 3 act. H, 0.53; 4 OCH_3, 21.65%. Found: C, 62.83; H, 6.80; N, 2.38; act. H, 0.52; OCH_3, 21.91% which on hydrolysis was converted to an amorphous desbenzoyl compound (XVII), m.p. 192-194°, λ^{EtOH}_{max} 257 mμ, ϵ 8250; λ_{210}, ϵ 6800; I.R. ($CHCl_3$) 1603 cm^{-1} (nitrone). These findings demonstrate the loss of ethylene and acetic acid in the pyrolysis of XV but contrary to the pyrolysis of Ia no ketone function was produced. The spectral data of XVI and XVII are in fair agreement with those of XVIII, λ^{EtOH}_{max} 234 mμ, ϵ 8800; I.R. (neat) 1572 cm^{-1}.[10] Unfortunately no simple monomeric Δ^1-piperideine N-oxides are known.[11] Confirmatory evidence was provided by the N.M.R. spectrum (40 MC) of XVI which exhibited peaks (in $CDCl_3$) at 1018 c.p.s. (H on nitrone) and 1047 c.p.s. (vinyl hydrogen) (relative to 1000 c.p.s. for the aromatic proton of toluene). These critical bands were retained in the spectrum of deuterated XVI. The peak due to the nitrone proton is in good agreement with that of the simple nitrone XIX (1012 c.p.s.).[12] The N.M.R. spectrum furthermore

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[8] O. Diels and E. Fischer, *Ber.* **49**, 1721 (1916); M. S. Fish, N. M. Johnson and E. C. Horning, *J. Amer. Chem. Soc.* **78**, 3668 (1956).

[9] A. C. Cope, N. A. LeBel, H. H. Lee and W. R. Moore, *J. Amer. Chem. Soc.* **79**, 4720 (1957); M. A. T. Rogers, *J. Chem. Soc.* 769 (1955).

[10] R. F. C. Brown, V. M. Clark and A. R. Todd, *Proc. Chem. Soc.* 97 (1957).

[11] J. Thesing and H. Mayer, *Ber.* **89**, 2159 (1956).

[12] R. F. C. Brown, V. M. Clark and A. R. Todd, *J. Chem. Soc.* In press.

confirmed the absence of C-methyl groups in aconitine (Ia).

If it is assumed that the pentacyclic Δ^{17}-nitrone (XVI) originated from the initially produced hexacyclic hydroxylamine [9] the change can be rationalized by concerted fragmentation XX (arrows) and the molecular model of aconitine (Ia) clearly shows that the stringent stereoelectronic requirements [13] are met because N-C_{17}-C_7-C_8-OAc describe a plane. That no rearrangements had occurred in the pyrolysis was ascertained by reconversion of the nitrone (XVI) to aconitine (Ia). Treatment of XVI with zinc dust in hot acetic acid produced a mixture of secondary amines one of which was characterized by a N-nitroso derivative, m.p. 272° (dec.), I.R. (KBr) 3500 (OH); 1715 (acetate, benzoate); 1250 (acetate), calcd. for $C_{32}H_{42}O_{12}N_2$: C, 59.40; H, 6.55; N, 4.33. Found: C, 59.15; H, 6.59; N, 4.15. Ethylation of the mixture of secondary amines with ethyl iodide gave aconitine (Ia) in 28% yield (based on nitrone (XVI)) identified by m.p., mixed m.p., I.R. spectrum and analysis with an authentic sample. The Δ^{17}-nitrone (XVI) has thus undergone acid catalyzed cyclization to a hexacyclic acetoxhydroxylamine which in turn was reduced by zinc to the corresponding secondary amine. The scale model of XVI illustrates the spatial proximity of the C=N and the C=C double bonds and the change is analogous to that proposed for the biogenesis of lycoctonine and delpheline.[14]

The facile cyclization of the nitrone was verified by the following additional transformations. Treatment of the desbenzoylnitrone XVII with perchloric acid in methanol gave a crystalline

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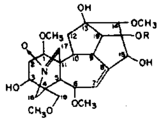
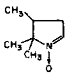
[13] S. Archer, T. R. Lewis and B. Zenitz, J. Amer. Chem. Soc. **80**, 958 (1958); A. T. Bottini, C. A. Grob and E. Schumacher, Chem. & Ind. 757 (1958).

[14] R. C. Cookson and M. E. Trevett, J. Chem. Soc. 3121 (1956); Z. Valenta and K. Wiesner, Chem. & Ind. 354 (1956).

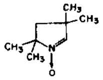
perchlorate (XXI), m.p. 250° (dec.), no U.V., λ_{216}, ϵ135; no nitrone band in the I.R. which exhibited a strongly positive TTC test [15] characteristic of hydroxylamines; calcd. for $C_{24}H_{39}O_{10}N \cdot HClO_4$: C, 47.88; H, 6.70; N, 2.33; 5 OCH_3, 25.78%. Found: C, 48.05; H, 7.02; N, 2.22; OCH_3, 25.90%. Furthermore the reaction of XVII with perchloric acid in ethanol produced a different salt (XXII), m.p. 250° (dec.), λ_{210}^{EtOH}, ϵ138; calcd. for $C_{25}H_{41}O_{10}N \cdot HClO_4$: C, 48.73; H, 6.87; N, 2.27. Found: C, 48.25; H, 6.75; N, 2.30.



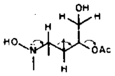
XVI R = BENZOYL
XVII R = H



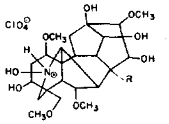
XVIII



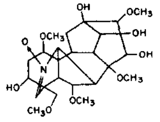
XIX



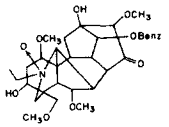
XX



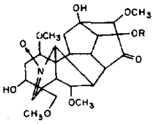
XXI R = -OMe
XXII R = -OEt



XXIII



XXIV



XXV R = BENZOYL
XXVI R = H

Aerial oxidation of the C_{24} hydroxylamine perchlorate (XXI) in aqueous ammonia in the presence of cupric ion gave the crystalline Δ^{16}-nitrone (XXIII), m.p. 183-185°, λ_{max}^{EtOH} 245 mμ, ϵ 7420; λ_{216}, ϵ 2580;

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[15] G. A. Snow, J. Chem. Soc. 2588 (1954).

I.R. ($CHCl_3$) 1613 (nitrone). The relationship of this new nitrone (XXIII) to the hydroxylamine (XXI) was established by reduction of XXIII to XXI with sodium borohydride. Similarly, treatment of the benzoylnitrone (XVI) successively with methanolic perchloric acid, with air, ammonia and cupric ion, and with aqueous sodium hydroxide gave the Δ^{16}-nitrone XXIII.

If our views on the pyrolysis of aconitine N-oxide (XV) to the Δ^{17}-nitrone (XVI) are correct, the pyrolysis of pyroaconitine N-oxide (XXIV) should lead to a <u>hexa</u>cyclic hydroxylamine. This assumption was fully confirmed by experiment. Pyroaconitine N-oxide (XXIV), m.p. 159-164° (dec.) on pyrolysis gave an amorphous hydroxylamine, pos. TTC test, no nitrone bands in the I.R., which was oxidized as above to a crystalline Δ^{16}-nitrone (XXV), m.p. 230-232°, λ_{max}^{EtOH} 234 mμ, ϵ18500, inflexion at 255 mμ, ϵ8800, λ_{210}, ϵ7050, I.R. ($CHCl_3$) 1604 (nitrone), 1725 cm^{-1} (benzoate); calcd. for $C_{30}H_{34}O_{10}N$: C, 63.03; H, 6.53; N, 2.45. Found: C, 62.94; H, 6.60; N, 2.07. Base hydrolysis of XXV gave the Δ^{16}-desbenzoylnitrone (XXVI), m.p. 270-272°, λ_{max}^{EtOH} 249 mμ, ϵ8060, λ_{210}, ϵ2200; I.R. (Nujol) 1625 cm^{-1} (nitrone).

There is no direct evidence for the locations of the primary methoxyl group and the methoxyl in ring F. However, it is clear that there are only three positions (C_5, C_6, C_{18}) vacant for the two groups and the arrangement chosen in I coincides with the situation for which there is experimental evidence in delphinine chemistry [3b] and crystallographic evidence in lycoctonine.

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[16] M. Przybylska and L. Marion, Canad. J. Chem. 34, 185 (1956).

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