THE STRUCTURE OF NEOLINE

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IN connection with the structure determination of the Aconitum napellus
alkaloids napelline,[1] songorine[1] and aconitine,[2] we have decided to
investigate the alkaloid neoline isolated from amorphous aconitine by
Freudenberg and Rogers.[3]

The neoline fraction isolated according to these authors was purified
by countercurrent distribution, followed by crystallization of neoline,
(m.p. 162°). Calc. for $C_{24}H_{39}NO_6$: C, 65.96; H, 9.00; N, 3.21; O, 21.97;
$3OCH_3$, 21.30; $C-CH_3$, 3.43; 3 act. H, 0.69%. Found: C, 65.99; H, 9.03; N,
3.23; O, 21.94; OCH_3, 19.77; $C-CH_3$, 3.38; act. H, 0.61%. pK_a = 6.7.

We now wish to propose the structure I for this alkaloid. This structure
follows from: (a) evidence which shows clearly that the structure of neoline

[1] K. Wiesner, Shô Itô and Z. Valenta, Experientia 14, 167 (1958).

[2] K. Wiesner, M. Götz, D.L. Simmons, L.R. Fowler, F.W. Bachelor,
R.F.C. Brown and G. Büchi, Tetrahedron Letters No. 2, 15 (1959).

[3] W. Freudenberg and E.F. Rogers, J. Amer. Chem. Soc. 59, 2572 (1937).

and delphinine II[4] are based on the same skeletal system, (b) a successful

dehydrogenation of neoline which gave 1-methyl-3-azaphenanthrene (picrate

m.p. 208° identified with a synthetic sample) and a phenanthrene $C_{18}H_{18}$ or

$C_{19}H_{20}$ (trinitrobenzolate, m.p. 184°). These last results, which are

typical of the simple aconite alkaloids,[5] were in turn helpful in the

derivation of the delphinine structure.

Neoline yields with acetic anhydride and pyridine a basic oily

diacetate. Calc. for $C_{28}H_{43}NO_8$: C, 64.55; H, 8.32; 2 acetyls, 16.51.

Found: C, 64.19; H, 8.19; acetyl, 16.13%. With glacial acetic acid and

p-toluene sulphonic acid, a crystalline triacetate (m.p. 161°C) was obtained.

Calc. for $C_{30}H_{45}NO_9$: C, 64.00; H, 8.06; N, 2.49; 3 acetyls, 22.91. Found:

C, 64.10; H, 7.92; N, 2.44; acetyl, 21.36%. I.R.: 1735 cm^{-1} O-acetyl, no

hydroxyl peak.

Oxidation of neoline with chromium trioxide gives 1,19-diketoneoline

(m.p. 175°). Calc. for $C_{24}H_{35}NO_6$: C, 66.57; H, 8.14; N, 3.23. Found: C,

66.59; H, 8.13; N, 2.97%. pK_a = 4.08. I.R.: 1690, 1745 cm^{-1}. Reduction

of diketoneoline with 1 mole of sodium borohydride yields 1-ketoneoline

(m.p. 176°). Calc. for $C_{24}H_{37}NO_6$: C, 66.18; H, 8.56. Found: C, 65.76;

H, 8.54%. pK_a = 5.03. I.R.: 1695 cm^{-1}. This last compound, on

equilibration with sodium methoxide in CH_3-OD followed by exchange of the

two alcoholic protons, incorporates two deuterium atoms. (Calc. 5.41 XSS

D; Found: 5.70 XSS D).

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[4] K. Wiesner, F. Bickelhaupt, D.R. Babin and M. Götz, Tetrahedron
   Letters No. 3, 11 (1959); Tetrahedron In press.

[5] K. Wiesner, J.R. Armstrong, M.F. Bartlett and J.A. Edwards, Chem.
   & Ind. 132 (1954).

The rotary dispersion curve[6] of 1-ketoneoline is typically affected by the charge of the nitrogen in exactly the same manner as with the delphinine derivatives III,[7] and unlike in the case dihydrodesmethanolaconinone.

1-Ketoneoline shows in chloroform a negative maximum at 323 mμ (α = -243°) and in glacial acetic acid a positive maximum at 317 mμ (α = +1450°). Compound III shows maxima at 325 mμ (α = -300°) and 326 mμ (α = +1455°) in the same two solvents respectively.

The rotary dispersion curve of the C_{19} keto group in 1,19-diketoneoline is superimposable on the curve of α-axodelphonone[8] (λ_{max} 320 mμ; α = +1600). It may be obtained by subtraction of the dispersion curve of 1-ketoneoline from the curve of 1,19-diketoneoline.

Oxidation of neoline diacetate with potassium permanganate gave a mixture of amides which on mild hydrolysis with alcoholic sodium hydroxide yielded 20% of a secondary base des-(N)-ethylneoline (m.p. 205°). Calc. for $C_{22}H_{35}NO_6$: C, 64.60; H, 8.63. Found: C, 64.84; H, 8.75; (N)CH_3, 0.0%. This compound resulted by hydrolysis of the N-acetyl product with participation of the C_1 hydroxyl. Desethylneoline may be converted into neoline by acetylation and reduction of the amorphous acetylation product with lithium aluminium hydride. Methylation of desethylneoline with methyl iodide in methanol in the presence of anhydrous sodium carbonate gave N-methylneoline (m.p. 210°). Calc. for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31; (N)CH_3, 3.55. Found: C, 65.27; H, 8.80; N, 3.43; (N)CH_3, 3.50%.

[6] C.Djerassi, R.Riniker and B.Riniker, J.Amer.Chem.Soc. 78, 6362 (1956).

[7] Unpublished derivative prepared by D.R. Babin, Univ. of New Brunswick.

[8] K.Wiesner, F.Bickelhaupt and Z.Valenta, Tetrahedron 4, 418 (1958).
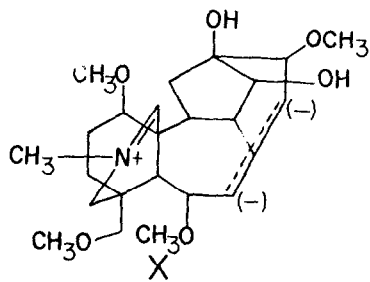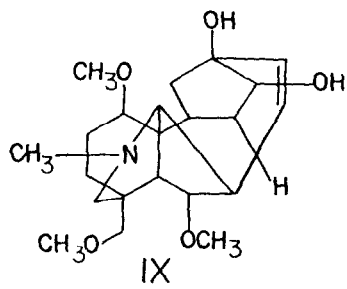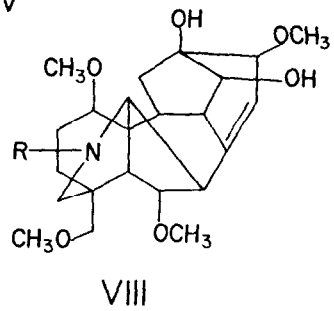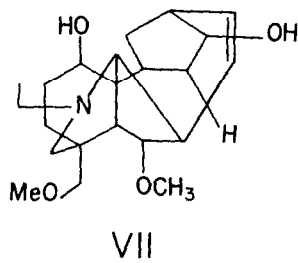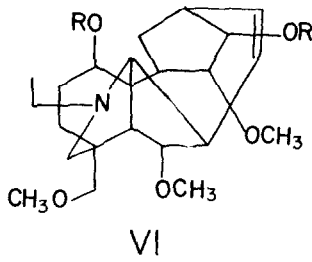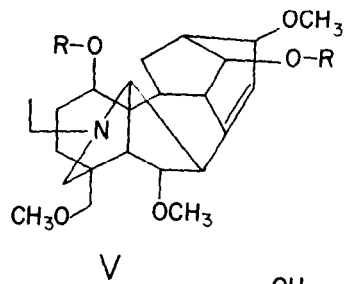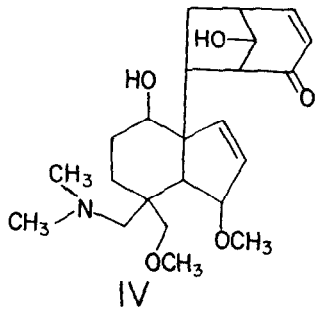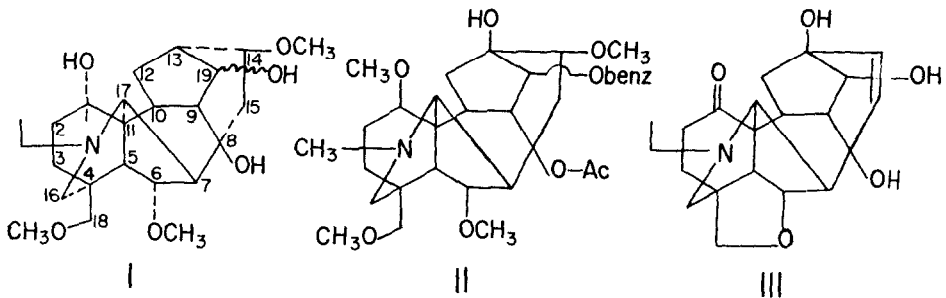
N-methylneoline was quaternized with methyl iodide in nitromethane and the amorphous quaternary salt subjected to an alkaline degradation. By extensive countercurrent distribution a small yield of a crystalline base (m.p. 241°) was isolated from the degradation mixture. Calc. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.46; 2OCH$_3$, 15.33. Found: C, 67.78; H, 8.51; N, 3.52; OCH$_3$, 13.84%. I.R.: 1677, 1608 cm^{-1}. U.V.: λ_{max} 232 mμ, log ε = 3.9. This degradation is completely analogous to a similar reaction of delphonine methiodide[4] and the product is formulated as IV.

Neoline triacetate was pyrolysed at 200° and the product pyroneoline diacetate (V, R = Ac) recrystallized from methanol (m.p. 183°). Calc. for $C_{28}H_{41}NO_7$: C, 66.70; H, 8.14; N, 2.78; 2 acetyls, 17.10; 3OCH$_3$, 18.46. Found: C, 66.31; H, 8.05; N, 2.62; acetyl, 17.20; OCH$_3$, 18.78%. I.R.: 1735 cm^{-1} O-acetyl, 1640 cm^{-1} double bond. The N.M.R. spectrum of V (R = Ac) (toluene scale, 40 Mc) shows a doublet at 1032, 1036 c.p.s. with an area 1H due to the C_{15} hydrogen split by the C_{14} hydrogen.

Warming with methanolic perchloric acid converted pyroneoline diacetate into isopyroneoline diacetate VI (R = Ac) characterized as the perchlorate (m.p. 253°). Calc. for $C_{28}H_{41}NO_7 \cdot HClO_4$: C, 55.67; H, 6.96; N, 2.32; Cl, 5.88. Found: C, 55.63; H, 6.75; N, 2.32; Cl, 5.89%. When CD$_3$OH was used for the above reaction, the resulting VI (R = AC) was shown to contain one deuterated methoxyl. Calc. for $C_{27}H_{38}NO_6(OCD_3) \cdot HClO_4$: 7.15 XSS D. Found: 7.01 XSS D.

Compounds V and VI (R = Ac) may be hydrolysed by alkali to V and VI (R = H) (m.p. 172° and 151° respectively). Calc. for $C_{24}H_{37}NO_5$: C, 68.70; H, 8.83. Found V: C, 68.99; H, 9.05; VI: C, 68.79; H, 8.80%. Both compounds V and VI (R = H) may be hydrogenated to yield nonidentical

dihydroderivatives (m.p. 149° and 180° respectively). Calc. for $C_{24}H_{39}NO_5$:
C, 68.40; H, 9.26; Found: dihydro V: C, 68.33; H, 9.47; Dihydro VI: C,
68.24; H, 9.48%.

Acetylation of des(N)ethylneoline with acetic anhydride-p-toluene
sulphonic acid gave N-acetylneoline triacetate (m.p. 205°). Calc. for
$C_{30}H_{43}NO_{10}$: C, 62.40; H, 7.45. Found: C, 62.36; H, 7.43%. Pyrolysis of
this last compound yielded (N(acetyl-pyroneoline diacetate (V, R = Ac;
N-acetyl instead of N-ethyl) as a foam which failed to crystallize.
Reduction of this last compound with lithium aluminium hydride gave a
crystalline compound (m.p. 191°) represented by VII. Calc. for $C_{23}H_{35}NO_4$:
C, 70.90; H, 9.00; $2OCH_3$, 15.95. Found: C, 70.80; H, 8.88; OCH_3, 15.85%.
The N.M.R. spectrum of VII showed a poorly resolved multiplet with an area
2H centered around 1020 c.p.s. The identical compound VII may be obtained
by lithium aluminium hydride reduction of V (R = H or Ac).

An analogous behaviour on reduction is displayed by corresponding
delphinine derivatives. Pyrodelphonine VIII (R = CH_3) and α-oxopyrodelphonine
VIII (R = $C \lessgtr \begin{smallmatrix} O \\ H \end{smallmatrix}$) give on lithium aluminium hydride reduction the identical
oily product (I.R. and N.M.R. spectrum) IX. Calc. for $C_{23}H_{35}O_5N$: C, 68.20;
H, 8.71; $3OCH_3$, 22.99. Found: C, 67.74; H. 8.46; OCH_3, 21.89%. No U.V.
spectrum. N.M.R. shows poorly resolved multiplet with an area 2H centered
around 1028 c.p.s.

Finally, we wish to report the unexpected spectroscopic properties of
compounds V (R = H or Ac). These compounds show an ultraviolet spectrum (V
(R = H) λ_{max} 236 mμ, log ε = 3.85; V (R = Ac) λ_{max} 243 mμ, log ε = 3.75),
which disappears on acidification and reappears on neutralization. Compound
V (N-acetyl instead of N-ethyl) and VI do not show any ultraviolet absorption.

The same spectroscopic anomally occurs in the delphinine series.
Pyrodelphonine VIII $(R = CH_3)$ shows a similar spectrum $(\lambda_{max}$ 245 mμ, log
ε = 3.8) which disappears on salt formation and is absent in α-oxopyrodel-
phonine (VIII, $R = C\!\!<^O_H$). The N.M.R. spectra of VIII $(R = CH_3)$ and VIII
$(R = C\!\!<^O_H)$ are completely analogous. Compound VIII $(R = CH_3)$ shows a
doublet with an area 1H at 1030-1034 c.p.s. Compound VIII $(R = C\!\!<^O_H)$ shows
the same doublet at 1019-1023 c.p.s. The greater shielding of the C_{15}
proton in the basic compound provides us with a possible explanation of the
unexpected spectroscopic behaviour.

The double bond in V or VIII is highly strained. This strain might
cause that compound VIII should be represented, to a small extent, by the
limiting structure X. The model of X shows that there is an overlap of
orbitals between the 7-8 or 8-15 double bond and the $N-C_{17}$ double bond. If
such a mesomerism is possible it could well give rise to ultraviolet
absorption. Alternative explanations involving an equilibrium between VIII
and a highly absorbing isomeric species with two conjugated double bonds
have been considered, but they seem to be ruled out. In any case, the
parallel spectroscopic behaviour of VIII and V is an additional powerful
argument for the analogy of the neoline and delphinine structure.

The placement of the C_{18} and C_6 methoxyls in formula I is based on the
possibility to obtain certain derivatives of neoline with an internal ether
of the type shown in formula III. (The corresponding experiments will be
described in a complete publication.)

The configuration of the C_1 hydroxyl has been already commented on.
The configuration of the C_{14} mehtoxyl follows from the ease of the allylic
rearrangements in compound V. The configuration of the C_6 mehtoxyl must be

exo with respect to the 1,2,3-bicyclooctane system of ring B to account for the easy displacement with ether formation. The absolute configuration of I follows from the coincidence of various rotatory dispersion curves in the neoline and delphinine series (vide supra).

Delphinine has been correlated[9] directly with aconitine, and recently the absolute configuration of aconitine has been established in a brilliant X-ray analysis by Maria Przybylska.[10]

[9] K. Wiesner, D.L. Simmons and L.R. Fowler, Tetrahedron Letters No. 18, 1 (1959).

[10] M. Przybylska and L. Marion, Canad. J. Chem. 37, 1843 (1959).