Tetrahedron Letters No.26, pp. 2189-2192, 1969. Pergamon Press. Printed in Great Britain.

THE STRUCTURE OF LAPPACONINE

N. Mollov, M. Tada and Léo Marion

Department of Chemistry, University of Ottawa,

Ottawa, Canada.

(Received in USA 21 March 1969; received in UK for publication 5 May 1969)

Lappaconitine ($C_{32}H_{44}O_8N_2$) isolated first by Rosendahl (1), is an ester of the alkamine lappaconine ($C_{23}H_{37}O_6N$) with acetylanthranilic acid (2, 3). The only significant attempt described so far to study the structure of the alkamine is that of Mollov. et al. (4) who established that the six oxygens are present in three hydroxyl and three methoxyl groups, and that the molecule also contained an N-ethyl group. From a number of oxidation experiments they concluded that two of the hydroxyl groups were secondary and attached one to a six-membered ring, the other to a five-membered ring, while the third hydroxyl was tertiary. They also assumed that all three hydroxyls are attached to two rings forming a bicyclo-3, 2, 1-octane system.

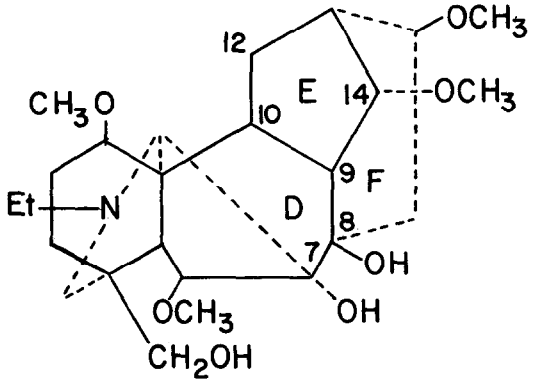
We have ascertained that the n. m. r. spectrum of lappaconine (triplet at δ 1.07, singlets at δ 3.38, 3.28 and 3.26) confirms the presence of an N-ethyl group and three methoxyl groups. Treatment of lappaconine at room temperature for 24 hr with acetic anhydride containing a small quantity of trifluoroacetic acid gives rise to triacetyllappaconine, m. p. 183-185°, thus showing the presence of three hydroxyl groups. Oxidation of lappaconine with potassium permanganate failed in our hands to affect the hydroxyl groups, but merely attacked a CH_2 next to the nitrogen and produced oxolappaconine $C_{23}H_{35}O_7N$, m. p. 175-177°. I. R. ($CHCl_3$) 1640 cm^{-1} Neither did Sarett's complex affect the hydroxyls. The inertness of the three hydroxyl groups towards these reagents suggests that they are probably tertiary.

Oxidation of oxolappaconine with lead tetracetate gave rise to dehydro-seco-oxolappaconine, m. p. 218-220°. Found: C, 63.54; H, 7.39; N, 3.43; m/e 433. Calc. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; N, 3.23; mol. wt. 433. I. R. spectrum: 3530 (OH) 1645 (CO-N), 1660 (double bond) and 1710 cm^{-1} (CO in a five-membered ring conjugated with a double bond). The n. m. r. spectrum contains a triplet centered at δ 1.26 (ET-N), singlets at δ 3.27, 3.50, 3.65 ($3CH_3O$), and a doublet at δ 7.02; J = 3 c. p. s. (double bond with one proton).

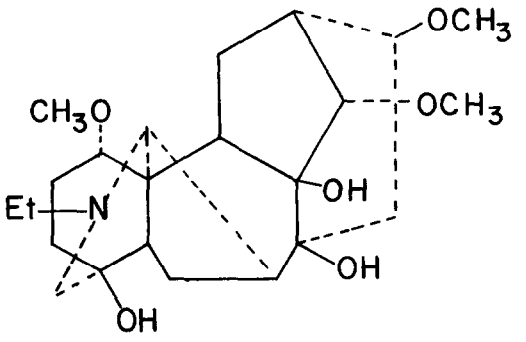
Oxidation of oxolappaconine with periodic acid produced seco-oxolappaconine, decomp. slowly at 243°, m. p. 256-260°. Found: C, 63.33; H, 7.49; N, 3.43; m/e 435. Calc. for $C_{23}H_{33}O_7N$: C, 63.43; H, 7.64, N, 3.22; mol. wt. 455 I. R. ($CHCl_3$), 3480 (OH)

1748 (CO in five-membered ring), 1644 cm^{-1} (CO-N). In the n.m.r. spectrum, triplet at δ 1.16 (ET-N), singlets at δ 3.56, 3.39, 3.22 ($3CH_3O$).

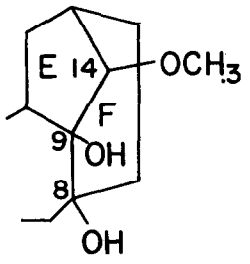
On hydrogenation over palladium-carbon, dehydroseco-oxolappaconine absorbed one mole of hydrogen and was converted to the seco-oxolappaconine obtainable directly by oxidation of oxolappaconine with periodic acid. The displacement of the carbonyl absorption from 1710 cm^{-1} to 1748 cm^{-1} confirms the presence of a double bond α β to the keto group in dehydroseco-oxolappaconine.



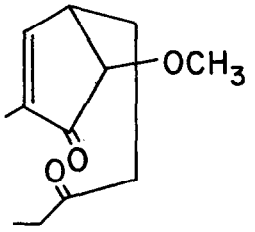
I



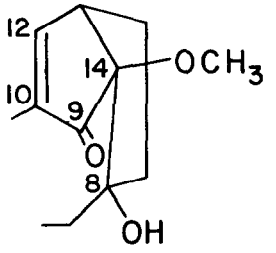
V



II



III



IV

The behavior of lappaconine towards lead tetraacetate and periodic acid indicates the presence in the base of a vicinal glycol. This glycol is also amenable to scission by the action of other oxidizing agents. For instance, dehydroseco-oxolappaconine can be obtained by shaking a solution of lappaconine in methylene chloride with potassium dichromate and 30% sulfuric acid for 48 hr at room temperature. If, however, lappaconine is shaken with potassium dichromate and 5% sulfuric acid for 2 hr at room temperature the main product

is seco-lappaconine $C_{23}H_{35}O_6N$, m.p. 212-214° (decomp.), although if the reaction is carried out at 40° the product is dehydroseco-lappaconine, $C_{23}H_{33}O_6N$, m.p. 180-181°.

As a working hypothesis it has been assumed that lappaconine like all the other known highly oxygenated diterpenoid alkaloids possesses the same C-N ring system as first determined for lycoctonine I (5, 6). Because of its different behavior on oxidation with lead tetraacetate and periodic acid, it is obvious that the vicinal glycol present in lappaconine cannot occupy the same position (C-7, C-8) as in lycoctonine. The only other way of placing a ditertiary vicinal glycol in a ring structure such as I so that on scission it will give rise to an $\alpha\beta$-unsaturated cyclopentenone without violating Bredt's rule is at C-8, C-9. On scission a C-8, C-9 glycol II would give rise to a cyclopentenone and a carbonyl present in a ten-membered ring III. The latter which arises from the hydroxyl at C-8 is not detectable in the infrared spectrum of the product, and must be masked. The most likely explanation is that it undergoes an aldol condensation with a hydrogen at C-14, a position activated by the α carbonyl (IV). The double bond in dehydroseco-oxolappaconine which is $\alpha\beta$ to the carbonyl arising from the hydroxyl at C-9 can be located only between C-10 and C-12 (IV).

When dehydroseco-oxolappaconine dissolved in a solution of hydrogen chloride in methanol is kept for 30 min. at room temperature, it is converted into nor-dehydroseco-oxolappaconine, m.p. 345°. Found: C, 62.81; H, 6.85; N, 3.49; m/e 419. Calc. for $C_{22}H_{29}O_7N$: C, 62.99; H, 6.97; N, 3.34; mol.wt. 419.5. I.R. ($CHCl_3$): 1640, 1705 cm^{-1}. N.m.r.: triplet centered at δ 1.17 (N-ET), singlets at δ 3.26 and 3.44 (2 OCH_3). Hence the CH_3 of a methoxyl group has been hydrolyzed under these mild conditions. A similar result is obtained by the action of acetic anhydride containing trifluoracetic acid on dehydroseco-oxolappaconine which produces monoacetyl-nor-dehydroseco-oxolappaconine, m.p. 256-258° (decomp.), containing two methoxyl groups only. The methoxyl which is so readily hydrolyzed must be located at C-14, a position which in the seco-derivative is activated by the vicinity of a carbonyl.

At this stage an X-ray crystallographic analysis undertaken by Dr. G. Birnbaum (see preceding paper) was completed. It confirmed that lappaconine V has the same C-N skeleton as lycoctonine although the A ring has the boat form as in delcosine (7) instead of the chair form. It also confirmed the location of the vicinal glycol at C-8, C-9 and of the methoxyl group at C-14, as well as revealing the positions occupied by the remaining three substituents.

Acknowledgment. We express our gratitude to the National Research Council of Canada for their support of this research, and acknowledge the assistance of Dr. J.P. Boca in the early stages of the work.

REFERENCES

1. H. V. Rosendahl. Thesis, Karolinska Institutet, Stockholm, Sweden, 1894; Arb. Pharmakol. Inst. Dorpat 11, 1(1895).

2. H. Schulze and F. Ulfert, Arch. Pharm. 260, 230 (1922).

3. G. Weidemann, Arch. exptl Pathol. Pharmakol. 95, 166 (1922).

4. M. Khaimova, N. Mollov, P. Cerneva, A. Antonova, and V. Ivanova. Tetrahedron Letters, No. 38, 2711 (1964).

5. M. Przybylska and L. Marion, Can. J. Chem. 34, 185 (1956).

6. O. E. Edwards, L. Marion and D. K. R. Stewart, Can. J. Chem. 34, 1315 (1956).

7. L. Marion, Pure and Applied Chem. 6, 621 (1963).