Tetrahedron 1960, Vol. 9, pp. 284 to 288. Pergamon Press Ltd. Printed in Northern Ireland

THE STRUCTURE AND CHEMISTRY OF HYDROXYLYCOCTONINE

Z. VALENTA and I. G. WRIGHT
Chemistry Department, University of New Brunswick, Fredericton, N.B.

(*Received* 24 *December* 1959)

Abstract—The observed physical properties and some selected reactions define hydroxylycoctonine as IV and its anhydronium salts as III.

THE remarkable X-ray analysis of a derivative of lycoctonine led to structure I for this complex di-terpene alkaloid.[1,2] A majority of the results of the extensive degradation studies of Edwards *et al.*[3] were easily explicable by this structure, which was also recognized as being eminently sound biogenetically.[4,5] The skeleton of structure I clearly differs from a noratisine skeleton only by the additional C_7—C_{17} bond and by the presence of a C_9—C_{10} bond in place of a C_8—C_{10} bond. The elucidation of the structure of delphinine[6] and aconitine[7] (confirmed by an X-ray analysis[8]) established that the carbon skeleton of I is generally present in polyoxygenated di-terpene alkaloids.

However, some experimental results in lycotonine chemistry were not easily explicable on the basis of structure I for lycoctonine. It was found, for example, that lycoctonine, $C_{25}H_{41}O_7N$, is easily oxidized with silver oxide[9] or lead tetra-acetate[10] to hydroxylycoctonine, $C_{25}H_{41}O_8N$. A drastic change in basicity (lycoctonine: pK_a = 8·8; hydroxylycoctonine: pK_a = 5·6 in 50 per cent methanol) indicated that the reaction very likely took place in the environment of the nitrogen atom. Hydroxylycoctonine could be oxidized with potassium permanganate to the lactam hydroxylycoctonam, $C_{25}H_{39}O_9N$, which on vigorous acid treatment yielded ethylamine.[9] These transformations indicated that the additional oxygen function in hydroxylycoctonine is attached to C_{17}. Cookson and Trevett reported that hydroxylycoctonine forms crystalline anhydronium salts (perchlorate, $C_{25}H_{40}O_{10}NCl$ and iodide, $C_{25}H_{40}O_6NI$) which show strong maxima in the infra-red spectrum at 1710 cm^{-1} and 1660 cm^{-1} and can be reconverted into the parent base on treatment with alkali.[10] This result can clearly not be reconciled with the structure II which was considered for hydroxylycoctonine by Edwards *et al.*[3]

In a preliminary communication, we proposed that hydroxylycoctonine must be

[1] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[2] Formula I implies absolute stereochemistry which was established crystallographically. M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1843 (1959).
[3] O. E. Edwards, L. Marion and D. K. R. Stewart, *Canad. J. Chem.* **34**, 1315 (1956).
[4] Z. Valenta and K. Wiesner, *Chem. & Ind.* 354 (1956).
[5] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 3121 (1956).
[6] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron Letters* No. 3, 11 (1959).
[7] 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).
[8] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1116 (1959).
[9] O. E. Edwards and L. Marion, *Canad. J. Chem.* **30**, 627 (1952); **32**, 1146 (1954).
[10] R. C. Cookson and M. E. Trevett, *Chem. & Ind.* 276 (1956).

IV formed by the hydration of III.[11,12] The remarkable formation of III in the oxidation of lycoctonine with lead tetra-acetate or silver oxide can be visualized either as a concerted reaction (as indicated by arrows in formula I) or as a cyclic reaction of the type commonly assumed for lead tetra-acetate and periodate oxidations.[13] Structure IV for hydroxylycoctonine cannot be considered as rigorously proven chemically, but follows logically from its physical and chemical properties. The unusual stability of the intramolecular hydrate has precedents in other cyclic compounds. It was found, for instance, that an oxidation product of delphonine (partial formula VIII) was almost completely hydrated since it showed no peaks in the infra-red carbonyl region.[14,15]

The significantly lower basicity of hydroxylycoctonine must have its explanation in the fact that the hydrated form (IV) is the important species in the base-conjugate acid equilibrium. The low pK_a value is readily reconcilable with the carbinolamine ether grouping present in IV. The spectroscopic results also find a ready explanation in this formulation.

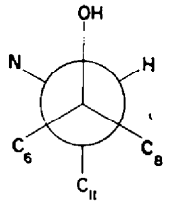
One interesting experimental result of Edwards *et al.*[3] deserves comment at this point. They reported that lycoctonamic acid methyl ester (partial formula Ia) hydrolysed rapidly with base, while the corresponding ester in the hydroxylycoctonine series IVa was almost completely inert under the same conditions. Since the additional C—O grouping of hydroxylycoctonine cannot be in a direct proximity to the carbomethoxyl group, the effect must clearly be a conformational one. As can be seen from the two formulae, the formation of the oxygen ring in IVa displaces the C_6-methoxyl group in the direction of the C_4-carbomethoxyl group, and increases the steric hindrance at the reaction site.

Since we were in the possession of a relatively large amount of lycoctonine, obtained from the roots of *Inula royleana* DC,[16,17] we decided to study hydroxylycoctonine by additional experiments. Hydroxylycoctonine was reduced with sodium borohydride in methanol to a crystalline compound, $C_{25}H_{43}O_7N$, m.p. 173–175°,

[11] Z. Valenta, *Chem. & Ind.* 633 (1959).

[12] Professor G. Büchi, Massachusetts Institute of Technology, explained independently the formation and properties of hydroxylycoctonine by structures III and IV.

[13] A partial formula of lycoctonine in which the pertinent part of the molecule is drawn in the Newman convention (looking along the C_7–C_{17} axis) shows that a cyclic reaction should certainly be possible. It



appears quite likely that the oxidation with silver oxide is facilitated by the formation of a favourable cyclic complex, since this mild oxidizing agent does not usually split 1,2-aminoalcohols.

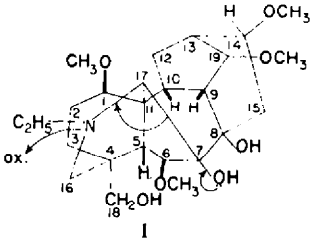
[14] Professor K. Wiesner, personal communication.

[15] The observation of Lyle *et al.* that the salts of 1-methyl-4-piperidone and 1-methyl-3-piperidone crystallize with one molecule of water and do not absorb in the carbonyl region of the infra-red spectrum is significant in this connection. [R. E. Lyle, R. E. Adel and G. G. Lyle, *J. Org. Chem.* **24**, 342 (1959).] The formation of an intramolecular hydrate between the two unsaturated functions of (III) is then simply a consequence of a favourable steric arrangement.

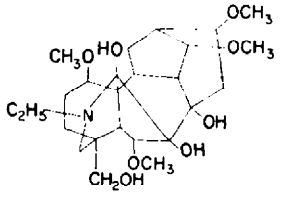
[16] A. Khaleque, S. Papadopoulos, I. G. Wright and Z. Valenta, *Chem. & Ind.* 513 (1959).

[17] O. E. Edwards and M. N. Rodger, *Canad. J. Chem.* **37**, 1187 (1959).

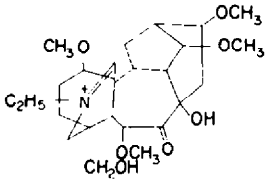
which had no carbonyl peaks in the infra-red spectrum. In consideration of the properties of hydroxylycoctonine this change is best explained as an elimination of water and the reduction of a ketone and a $\diagdown C = \overset{(+)}{N} \diagup$ grouping to the triol (V). The correctness of structure V could be established by an oxidation with periodic acid which gave in a fast reaction and an excellent yield the hemiacetal ketone (VI), $C_{25}H_{41}O_7N$. The absence of a five-membered ring ketone peak in the infra-red spectrum of VI together with the fact that the correctly analyzing oily monoacetate VII (prepared from VI in two steps) did not contain a hydroxyl group establishes the functionality of this compound.



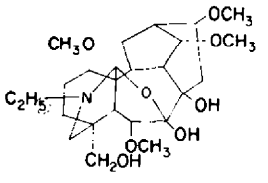
I



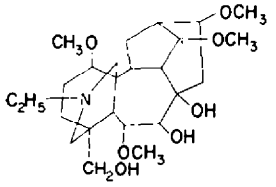
II



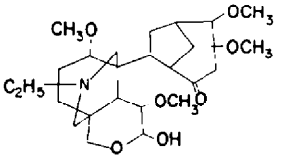
III



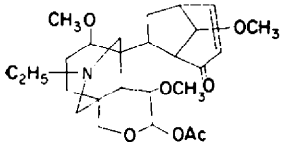
IV



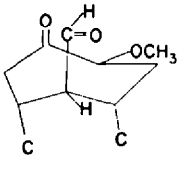
V



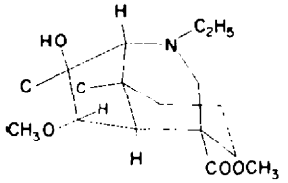
VI



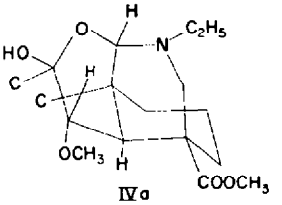
VII



VIII



Ia



IVa

Treatment of VI with silver oxide in methanol yielded a water soluble material which, according to its infra-red spectrum, was clearly an amino acid. It was not further investigated.

At the present time we have no rigorous proof for the configuration of the secondary alcohol group in V. However, it was observed in a preliminary experiment that the diacetate of V slowly loses a molecule of acetic acid on sublimation. Therefore, the hydroxyl group is very likely *trans* to the C_6-methoxyl group. There is no doubt that this methoxyl group has the same configuration in V and III as in I. While equilibration of this group is possible in III due to the α-keto group, a conformational analysis clearly shows the greater stability of the original lycoctonine configuration at C_6.

While this work was in progress Edwards *et al.* reported additional experiments in the hydroxylycoctonine series[18] which led them to propose independently the structure III for the anhydronium salts. In this new communication, they retained structure II as the representation of hydroxylycoctonine.[19] The two series of experiments establish the correctness of structure III as the expression for the anhydronium salts.

Thus it can be seen that the formation and the properties of hydroxylycoctonine not only can be rationalized on the basis of formula I for lycoctonine, but provide an important chemical information about the relationship of the nitrogen ring and the B-ring in lycoctonine.

EXPERIMENTAL

Triol V. Sodium borohydride (6 g) was added cautiously to a cooled solution of hydroxylycoctonine (2·66 g) in methanol (50 ml). The solution was heated under reflux for 2·5 hr, concentrated, diluted with 100 ml water and extracted with chloroform. The dried extract was purified by a counter-current distribution in nine funnels between chloroform and a citric acid–phosphate buffer (pH 3·6) with chloroform as the moving phase. The material in the first four funnels (1·33 g) was recrystallized repeatedly from aqueous acetone and gave V, m.p. 173–175° (Found: C, 63·71; H, 9·09; O, 23·73; N, 2·91; act. H, 0·631. $C_{25}H_{43}O_7N$ requires: C, 63·94; H, 9·23; O, 23·85; N, 2·98; three act. H, 0·642%. Fractions 6–9 of the distribution contained an oily material which was not further investigated.

Hemiacetal VI. Triol V (252 mg) was treated with a 1% periodic acid solution (50 ml) for 30 min at room temp. The excess of the oxidizing agent was destroyed by adding ethylene glycol (2 ml) and the reaction mixture was evacuated for a few minutes to remove formaldehyde. Basification of the solution with sodium bicarbonate and extraction with chloroform yielded 240 mg of an oily material. Chromatography of this product on acid washed alumina (8 g) and study of the individual fractions by infra-red spectroscopy showed it to be homogeneous. A top chromatographic fraction was dried for analysis as a foam at 70° for 48 hr. (Found: C, 63·91; H, 8·60; O, 24·46; OCH_3, 25·03. $C_{25}H_{41}O_7N$ requires: C, 64·21; H, 8·84; O, 23·95; four OCH_3, 26·55%). I.R. (chloroform) 1707 cm^{-1}. The compound could not be sublimed, since heating to 200° resulted in partial elimination of methanol.

Acetate VII. Hemiacetal VI (100 mg) was treated overnight at room temp with a mixture of conc HCl (10 ml) and ethanol (10 ml). The solution was partially evaporated, treated with 5% aqueous H_2SO_4, washed with chloroform and basified with sodium carbonate. Extraction of the basic aqueous layer with chloroform yielded oily material (96 mg), νI.R. (chloroform) 1675 cm^{-1}. The impure unsaturated ketone was reacted for 12 hr at room temp with a mixture of acetic anhydride (12 ml) and pyridine (12 ml). The solution was evaporated under reduced pressure and the residue was distributed between chloroform and 5% aqueous H_2SO_4. Basification of the aqueous layer with sodium carbonate, extraction with chloroform and evaporation of the solvent yielded an oily product (92 mg) which was chromatographed on acid washed alumina (3 g). Elution with 1% methanol in

[18] O. E. Edwards, M. Los and L. Marion, *Proc. Chem. Soc.* 192 (1959).

[19] Experimental details together with the acceptance of structure IV for hydroxylycoctonine were published by the National Research Council authors after the completion of this manuscript. [O. E. Edwards, M. Los and L. Marion, *Canad. J. Chem.* **37**, 1996 (1959).]

chloroform gave the desired oily acetate VI (43 mg), νI.R. (chloroform) 1735, 1675 cm^{-1}, no OH peak; λ_{max} 226 mμ, which was sublimed for analysis at 180°/0·02 mm. (Found: C, 65·01; H, 7·92; O, 23·73; OCH_3, 19·21; C—CH_3, 4·31; acetyl, 7·85. $C_{26}H_{39}O_7N$ requires: C, 65·38; H, 8·23; O, 23·73; 3(OCH_3), 19·50; 2(C—CH_3), 6·28; acetyl, 8·80%).

Oxidation of VI *with silver oxide.* Hemiacetal VI (22 mg) was shaken for 24 hr with freshly prepared silver oxide in 80% aqueous methanol. Filtration and concentration under reduced pressure, dilution with water and extraction with chloroform yielded an oil (9 mg) which according to its infra-red spectrum was a mixture of VI and the corresponding α,β-unsaturated ketone. Evaporation of the aqueous solution to dryness gave an oily residue (13 mg), νI.R. (chloroform) 3400–3000, 1710, 1603 cm^{-1} (carboxylate).