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# STRUCTURE OF GENTIOPICROSIDE

L. Canonica, F. Pelizzoni, P. Manitto and G. Jommi
Istituto di Chimica Industriale della Università
Milano

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VARIOUS structures, none of them completely satisfactory, have been proposed for the gentiopicroside (I) (Korte,[1] Sakurai[2] and Canonica[3]). Continuing our research on this subject, we have now collected a number of new experimental facts, and we wish to propose a new formula, which accounts for all the chemical and physical evidence obtained by us as well as by other authors.

The hexahydroprotogentiogenin (II) contains four oxygen atoms. In all the previous formulations, two of these were assigned to a γ-lactone system; I.R. spectra show instead the presence of a saturated δ-lactone in (II) (1746 $cm^{-1}$ in Nujol; 1730 $cm^{-1}$ in KBr) and of a α-β-unsaturated δ-lactone in the tetraacetylgentiopicroside (IX) and in the two isomeric tetrahydro-derivatives (VII, VIII) (1725, 1704, 1706 $cm^{-1}$ in $CHCl_3$). This discrepancy between the proposed formulae and the spectroscopic evidence has been already

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[1] F. Korte, Chem. Ber. 87, 512 (1954).

[2] F. Korte, Chem. Ber. 87, 780 (1954).

[3] L. Canonica and F. Pelizzoni, Gazz. Chim. Ital. 87, 1251 (1957).

indicated by Korte.[4]

The two remaining oxygen atoms of (II) must be assigned to a 2-hydroxytetrahydropirane system on the following evidence. (II) has reducing properties and by chromic oxidation gives a compound $C_{10}H_{14}O_4$ (III),[5,6] which is a di-δ-lactone as shown by titration and by I.R. spectrum (only one band at 1730 $cm^{-1}$ in Nujol), and does not contain hydroxyls, ketonic groups, double bonds or active hydrogens.

Treatment with methanol in the presence of $H^+$ (II) gives a methylether (IV),[2] identical with that obtained from tetraacetylhexahydrogentiopicroside (V) under the same experimental conditions. The hydrolysis of (V) to give (II), and its trans-etherification to (IV), are accompanied by invertion of the configuration of the hemiacetalic carbon, as shown by the change of the molar rotatory power (ΔM = -690; -719). The entity of this change is in agreement with the values observed in other cases[7] when passing from a β-2-hydroxytetrahydropirane to a α-2-hydroxytetrahydropirane. Elimination of water, either by treatment with TsCl in Py or by heating, (II) gives a compound $C_{10}H_{14}O_3$ (VI).[8] This contains an unconjugated carbonyl as part of a lactone system (I.R. : 1725 $cm^{-1}$; U.V. : nil), does not contain hydroxyls, as shown by the fact the 3330 $cm^{-1}$ band present in (II) is missing here, but contains instead a double bond of type : -O-C=C-(I.R. : 1660 $cm^{-1}$). Treatment with methanol in the presence of acids, (VI) gives

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[4] F. Korte, Fortschritte der Chemie Organischer Naturstoffe Vol. 17, p. 132. Wien (1959).

[5] Y. Asahina, J. Asano, Y. Tanase and Y. Ueno, Chem. Ber. **69**, 771 (1936).

[6] F. Korte, Chem. Ber. **87**, 769 (1954).

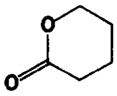
[7] O. Halpern and H. Schmid, Helv. Chim. Acta **41**, 1109 (1958).

[8] Y. Sakurai and K. Yoshino, J.Pharm.Soc.Japan **71**, 795(1951); Chem. Abstr. **46**, 2499 (1952).

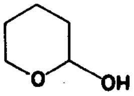
(IV).

(II) also contains a side-chain. This is shown to be an ethyl group because the C-methyl determination according to Kuhn Roth[9] yields propionic acid, which can be separated by V.P.C. The same result is obtained from (VII) and (VIII).

(IX) contains instead a vinyl group and gives formaldehyde on ozonolysis.[5] Therefore (II) contains: a six-membered lactone ring (A), a pirane ring (B) and a side-chain $-C_2H_5$.



(A)



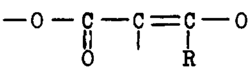
(B)

$-C_2H_5$

The two rings (A) and (B) must share two carbon atoms.

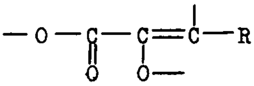
The U.V. spectrum of (VII) has a maximum at 247 mμ (log ε = 3.98). The only possible interpretation of this absorption, is compared with the spectra of α-β-unsaturated lactones and esters,[10] is that an etheral oxygen must be attached to the double bond conjugated with the lactone system. The chromofore in (VII) would then have one of the two structures (C) and (D):

(C)



$$-\mathrm{O}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{|}{\mathrm{C}}=\underset{\substack{|\\ \mathrm{R}}}{\mathrm{C}}-\mathrm{O}$$

(D)



$$-\mathrm{O}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\underset{\substack{|\\ \mathrm{O}-}}{\mathrm{C}}=\overset{|}{\mathrm{C}}-\mathrm{R}$$

where the etheral oxygen is that of the piranic ring and not that of the 2-hydroxyl group, as indicated by the properties of (VI).

Of the two alternative structures (C) and (D), the latter is excluded

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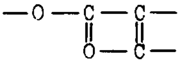
[9] C.F. Garbers, H. Schmid and P. Karrer, Helv. Chim. Acta 37, 1336 (1954).

[10] F.E. Bader, Helv. Chim. Acta 36, 215 (1953); F. Korte, J. Falbe and A. Zschocke, Tetrahedron 6, 201 (1959).

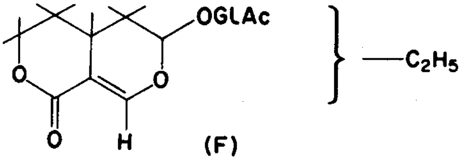
by the fact that the compound (VIII), which is formed together (VII) in the hydrogenation of (IX) and on further hydrogenation gives the same hexahydroderivate (V), still contains one conjugated double bond ($\lambda_{max}$ = 230 mμ ; log ε = 3.90). This can only be part of a chromophore (E), incompatible with (D).

(E)



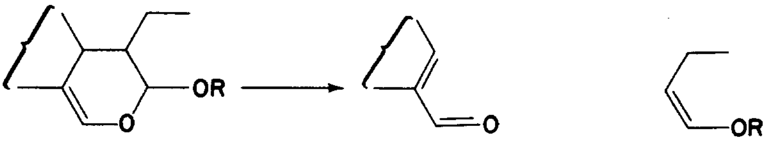
Finally, obtaining formic acid by mild hydrolysis of (X)[8] shows that in the cromophore (C) the substituent R is a hydrogen atom.

These results agree in pointing out for (VII) the partial structure (F):



(F)

The ethyl group is quite probably linked to the 3-position. In fact the pyrolysis of (XI) gives with good yields butyrric aldehyde,[5] which can be assumed to be formed by the breaking up of the pirane ring, through a retro-Diels - Alder.



On the basis of the above consideration, we propose for (I), (VII), (VIII), (II) and correlated compounds the structures of Fig. 1.

These formulations and in particular the method of linking rings (A)

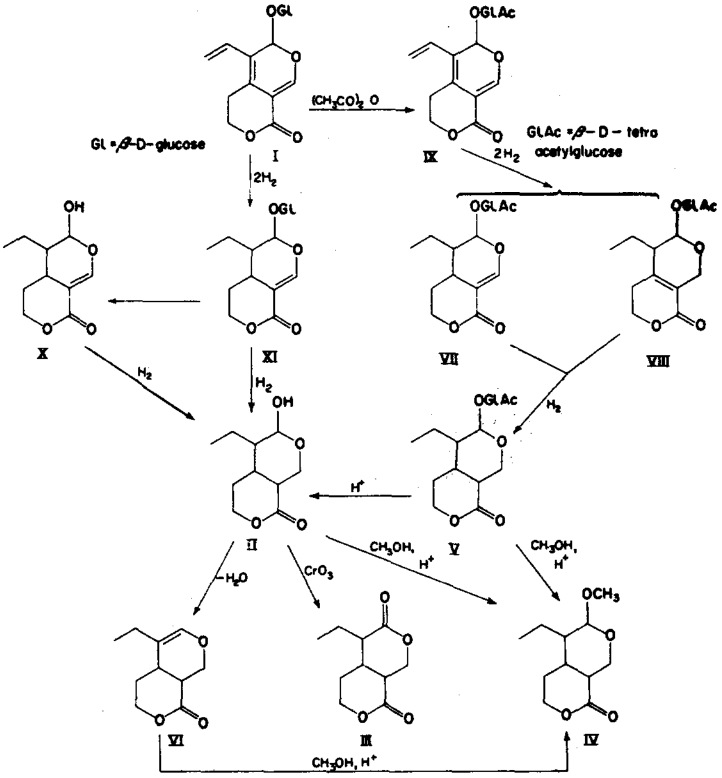


FIG. 1.

and (B) find a complete and independent proof in the NMR spectra.[11]

The NMR evidence confirms the presence of an ethyl group in (IV), (VII) and (VIII) [ centred triplet at 54.5 and 61 cycles/sec from the TMS reference, for the $CH_3$- of (IV) and (VII), and of (VIII) respectively].

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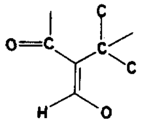
[11] We are greatly indebted to Dr. A. Melera for the measurement of the NMR spectra. Measurements were carried out on a Varian 4302, 60 megacycles spectrophotomer with electronic integrator, in the Research Laboratory of the Varian A.G., Zurich. Samples were dissolved in $CDCl_3$ and TMS was used as internal reference.

The ethyl group is not present in (IX).

The electronic integration shows that (IV) contains five protons on carbon atoms linked to an etheral oxygen, while (III) contains only four such protons. (VII) contains one olefinic proton (centred doublet at 45[illegible] cycles/sec with J ~ 2 cycles/sec) which can be attributed to a system such as (G):



(G)

This system is present also in (IX).

The structure with three double bonds attributed to (I) accounts for the absorption maximum at 273 mμ ($\log \varepsilon = 3.84$) and for its hydrogenation to (VII) and (VIII).

Also besides the proposed structure has evident biogenetic relationships with another substance extracted from gentianaceae : the alkaloid gentianin.[12]

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[12] T.R. Govindachari, K. Nagara and S. Rajappa, J. Chem. Soc. 551 (1957).