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THE STRUCTURE OF SWERTIAMARIN

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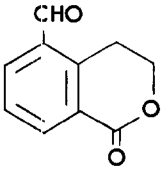
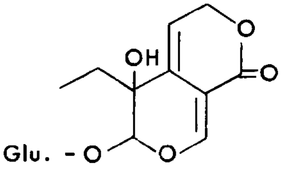
SWERTIAMARIN (I), a bitter principle of Swertia Japonica Makino, affords erythrocentaurin (II) and glucose by the enzymatic hydrolysis with emulsin as follows:[1,2,3]

$$\underset{\text{I}}{C_{16}H_{22}O_{10}} + H_2O \longrightarrow \underset{\text{II}}{C_{10}H_8O_3} + C_6H_{12}O_6 + 2H_2O$$

We have proposed formula II for erythrocentaurin[3] and recently confirmed its structure by synthesis.[4] Although formula IA has also been proposed for swertiamarin in our previous report,[5] we now wish to propose structure IB for this substance on the basis of subsequent, experimental evidence.



II



IA

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[1] **T. Kariyone et al. J.Pharm.Soc.Japan 47, 133 (1927); 49, 702 (1929).**

[2] **T. Kubota and Y. Tomita, Chem. & Ind. 1958, 229.**

[3] **T. Kubota and Y. Tomita, ibid. 1958, 230.**

[4] **T. Kubota and Y. Tomita, Tetrahedron Letters to be submitted.**

[5] **Y. Tomita and T. Kubota, 'Abstracts of Papers of the 2nd Symposium on Natural Products, Japan', p. 17 (1958).**

1) Swertiamarin acetate (III), $C_{24}H_{30}O_{14}$, m.p. 190-191°, rapidly decolorized aqueous permanganate solution, slowly consumed bromine in acetic acid solution, gave a negative color reaction with tetranitromethane, and showed a red color with triphenyltetrazolium chloride. Infrared spectrum showed the presence of hydroxyl group (2.85 μ) resisting to acetylation, conjugated double bond (6.18 μ), α,β-unsaturated-δ-lactone (5.89 μ), and trisubstituted double bond (11.9 μ). Ultraviolet spectrum showed two absorption maxima at 206 mμ (logε 3.2) and 234 mμ (logε 4.0).

2) When swertiamarin acetate (III) was hydrogenated in the presence of platinum catalyst in acetic acid, dihydroswertiamarin acetate (IV), $C_{24}H_{32}O_{14}$, m.p. 175-176°, with a single maximum at 233.5 mμ (logε 4.0), was easily formed. Dihydroswertiamarin acetate showed infrared bands at 2.85, 5.89, 6.18, and 11.9 μ. On further hydrogenation IV slowly absorbed one mole of hydrogen to give tetrahydroswertiamarin acetate (V) as a liquid, whose infrared spectrum showed no bands at 5.88, 6.18, and 11.9 μ.

3) III and IV showed the presence of four acetoxy groups in the molecules by hydrolysis with sulfuric acid or with p-toluenesulfonic acid followed by titration of the resulting volatile acid with alkali. When III and IV were hydrolyzed with an excess of 0.1 N potassium hydroxide for twenty four hours at room temperature, five moles of alkali were consumed. On vigorous hydrolysis (two hours' refluxing with 0.1 N potassium hydroxide) III consumed six moles of alkali. When this hydrolysate was acidified with sulfuric acid followed by steam distillation, the distillate consumed five moles of alkali and formic acid was detected in the distillate.

4) The Kuhn-Roth determination showed the presence of four C-methyl groups in III and five C-methyl groups in IV. While the ozonization of III gave formaldehyde together with formic acid and carbon dioxide, the ozonization of IV merely gave formic acid and carbon dioxide. When IV was hydrolyzed with dilute hydrochloric acid followed by chromium trioxide oxidation of the resulting liquid, one mole equivalent of a mixture of volatile fatty acids was obtained, from which acetic acid and propionic acid were detected (paper chromatography and p-bromophenacyl esters).

IV had no infrared bands at 3.25, 9.93, and 10.66 μ, which were originally present in the infrared spectrum of III. These evidences suggests that swertiamarin has CH_2=CH- group.

5) The ultraviolet absorption maximum (233.5-234 mμ) of III and IV shows too great a bathochromic shift to be considered as α,β-unsaturated-δ-lactone with trisubstituted double bond, and in the infrared spectrum, the intensity of the band at 6.18 μ is anomalously strong. These phenomena can be explained by considering that the carbon atom in the α- or β-position of the unsaturated lactone group is attached to an oxygen linkage.[6,7] Furthermore, the anomalous infrared band (5.89 μ) of the α,β-unsaturated-δ-lactone of III and IV is in agreement with the known bathochromic shift which occurs by the appearance of an oxygen linkage in the β-position of an α,β-unsaturated ketone.[8] Since the oily products obtained from III and IV by acid hydrolysis gave a negative reaction with ferric chloride, we

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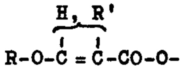
[6] F. E. Bader, Helv.Chim.Acta 36, 216 (1953); H. Schmid et al, ibid. 41, 1109 (1958); F. Korte and K. H. Bückel, Chem.Ber. 92, 877 (1959).

[7] K. Nakanishi, 'Jikken-kagaku-koza' vol I, p. 336, Maruzen Co. (1957).

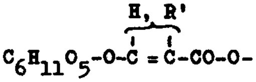
[8] K. Nakanishi, Kagaku-no-ryoiki Extra edition vol. 21, 122 (1956).

can exclude the formula (B) from two possible partial formula, (A) and (B), for III and IV.



$$\text{R-O-}\overbrace{\text{C}=\text{C}}^{\text{H, R}'}\text{-CO-O-}$$

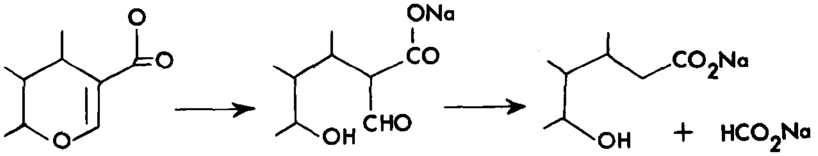
(A)



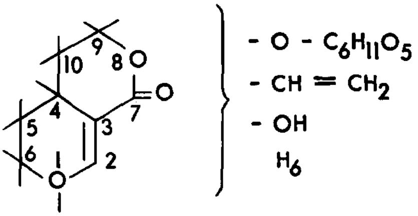
$$C_6H_{11}O_5\text{-O-}\overbrace{\text{C}=\text{C}}^{\text{H, R}'}\text{-CO-O-}$$

(B)

6) **The empirical formula of swertiamarin suggests that the R-** group in the formula (A) must incorporate a five or six-membered ring **If we assume a dihydropyran ring as the R-group, the peculiarity of swertiamarin and its derivatives in their spectroscopic properties and their various reactions may be easily explained. For instance, the formation of formic acid by alkaline hydrolysis of swertiamarin acetate** (cf. 3) **can be showed as following sequence:**



We can now show the partial structure IC for swertiamarin.



IC

7) **The oily products obtained from III and IV by acid hydrolysis** have no infrared bands (11.9μ corresponding to a trisubstituted double bond conjugated to the lactone group. **The oily product obtained by acid hydrolysis of V gave a positive reaction with 2,4-dinitrophenylhydrazine. These facts show that the glucoside residue of swertia-**

marin is bonded in the form of an acetal linkage. We assume that the glucoside linkage may be located at the C_6-position of two possible positions, C_2 and C_6, from analogy to aucubin and plumieride. Infrared bands at 10.8, 11.2, and 13.2 μ of swertiamarin show the presence of β-glucoside linkage.[9]

8) Swertiamarin acetate (III) was dehydrated with potassium hydrogen sulfate and acetic anhydride or with boron triflouride and acetic acid to give monoanhydroswertiamarin acetate (VI), $C_{24}H_{28}O_{13}$, m.p. 143-144°C, which had absorption maxima, 246 mμ (logε 3.44) and 269 mμ (logε 3.37). The latter maximum shows the presence of a conjugated triene in VI. This suggests that the tertiary hydroxyl group in III must be located at the α- or β-carbon atom of the vinyl group. The absorption maximum (243 mμ) of monoanhydrodihydroswertiamarin acetate, m.p. 161-162°C, which is obtained by dehydration of IV with potassium hydrogen sulfate and acetic anhydride, also suggests that the vinyl group is bonded to the carbon atom of the C_5- or C_{10}-position and the tertiary hydroxyl group is bonded to the carbon atom of the C_4-, C_5- or C_{10}- position. The formation of erythrocentaurin from swertiamarin, however, can more easily be explained as showed below, when the tertiary hydroxyl group is bonded to the C_4-carbon atom.

9) The above evidences show that swertiamarin has structure IB*, which may explain the mechanism of the formation of erythrocentaurin (II) as showed in the following sequence.

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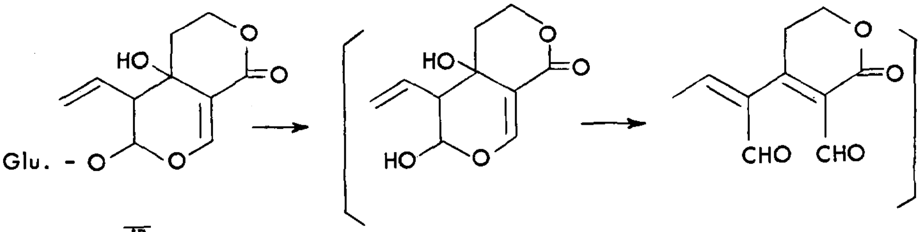
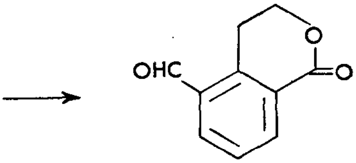
* Prof. G. Büchi has pointed out structure I as a possible structure of swertiamarin in his private communication which was sent us immediately after the preparation of this manuscript.

We, however, can not eliminate formula ID[10] for swertiamarin, since the negative color reaction of I and III with tetranitromethane may indicate an allylic structure of I.[12]



IB



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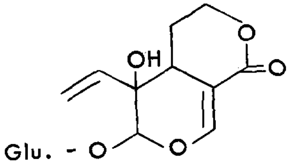

ID

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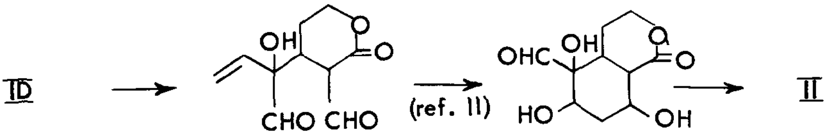
[10] **Formula ID may explain the formation of erythrocetaurin as follows:**



[11] Cf. E. Arnsdale, L. A. Mikesska, Chem.Rev. **51**, 505 (1952).

[12] E. Heilbronner, Helv.Chem.Acta **36**, 1121 (1953).

10) Biogenetic considerations led us to the conclusion that swertiamarin may form through the precursor, from which gentianin is considered to be formed in plants of Gentianaceae.[13] We assume that erythrocentaurin is *not* formed through the above precursor but formed from swertiamarin by hydrolysis, although erythrocantaurin has been isolated from *commercial* samples of *Erythrea centaullium*.[14]

Acknowledgements - We wish to thank Professor G. Büchi for his valuable suggestion and also Professor D. H. R. Barton and Dr. T. Matsuura for kind discussions.

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[13] E. Wenkert, *J.Am.Chem.Soc*. **81**, 1474 (1959).
[14] J. Mehu, *Chem.Zent*. 677 (1866), 877 (1870).