

PAEONIFLORIN, A MONOTERPENE GLUCOSIDE OF  
CHINESE PAEONY ROOT

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(Received 8 June 1964)

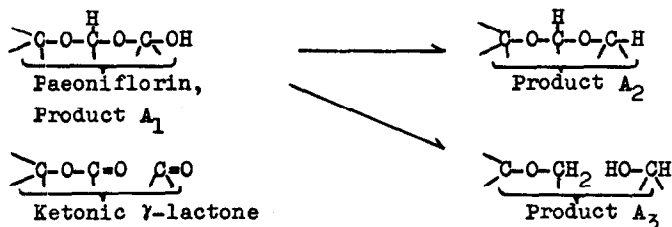
PAEONIFLORIN (I), obtained from Chinese Paeony root, has been found as being a glucoside of benzoylated  $C_{10}$ -compound, whose aglycone cannot be obtained by the usual methods due to its instability to acid and resistance to enzymatic hydrolysis. It has been reported previously<sup>(1,2)</sup> that mono-methyl ether of desbenzoyl paeoniflorin (IV) yields on acid hydrolysis D-glucose and 2-(2,5-dihydroxy-4-methylphenyl)-propionic acid (XII). This aromatic acid (XII) was noted as it retained all the ten carbon atoms of the assumed aglycone part of paeoniflorin which is by no means aromatic.

By the action of  $LiAlH_4$ , paeoniflorin tetraacetate and pentaacetate gave three products,  $C_{16}H_{24}O_{10}$ , m.p.  $186^\circ$ ,  $C_{16}H_{24}O_9$ , m.p.  $163^\circ$ , and  $C_{16}H_{26}O_9$ , m.p.  $267^\circ$ , which were tentatively named product  $A_1$  (V),  $A_2$  (VI) and  $A_3$  (VII), respectively. The product  $A_1$  (desbenzoyl paeoniflorin)(V), gave the aromatic compound (XII) on acid hydrolysis, whereas the product  $A_3$  (VII) afforded a non-aromatic aglycone,  $C_{10}H_{16}O_4$ , m.p.  $223^\circ$  (VII').

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The reaction of  $\text{LiAlH}_4$  mentioned above would reasonably be explained by the presence of an acetal-hemiketal combining system in paeoniflorin and the product  $A_1$ , which is subjected to a reductive change to give the products  $A_2$  and  $A_3$ . The acetal-hemiketal system has also been supported by the chromic acid oxidation of paeoniflorin tetraacetate (II) affording a ketonic  $\gamma$ -lactone (VIII) ( $\text{IR } \nu_{\text{max}}^{\text{CHCl}_3} 1780 \text{ cm}^{-1}$ ); 2,4-dinitrophenylhydrazone,  $\text{C}_{37}\text{H}_{38}\text{N}_4\text{O}_{18}$ , m.p.  $208^\circ$ .



On heating the ketonic  $\gamma$ -lactone (VIII) in aq.  $\text{Na}_2\text{CO}_3$ , hydrolytic opening of the lactone ring, deacetylation, desbenzoylation and dehydration occurred simultaneously to give an  $\alpha\beta$ -unsaturated keto-carboxylic acid (IX); pentaacetate,  $\text{C}_{26}\text{H}_{32}\text{O}_{15}$ , m.p.  $182^\circ$  (IX') ( $\text{IR } \nu_{\text{max}}^{\text{CHCl}_3} 1765$  (acetate  $\text{C}=\text{O}$ ),  $1730$  ( $\text{COOH}$ ),  $1700 \text{ cm}^{-1}$  ( $\alpha\beta$ -unsaturated  $\text{C}=\text{O}$ )).

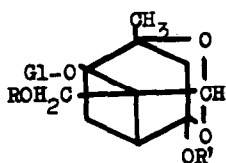
The ultraviolet spectra of the  $\alpha\beta$ -unsaturated keto-carboxylic acid (IX) ( $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} 249 \text{ m}\mu$ ) and its acetate (IX') ( $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} 242 \text{ m}\mu$ ,  $\log \epsilon 3.86$ ) showed a close similarity with that of verbenone (X) ( $\text{UV } \lambda_{\text{max}}^{\text{EtOH}} 252 \text{ m}\mu$ ,  $\log \epsilon 3.80$ ).

Catalytic hydrogenation of the acetate of  $\alpha\beta$ -unsaturated keto-carboxylic acid (IX') afforded a dihydro derivative,  $\text{C}_{26}\text{H}_{34}\text{O}_{15}$ , m.p.  $222^\circ$  (XI) whose infrared spectrum ( $\text{IR } \nu_{\text{max}}^{\text{CHCl}_3} 1715 \text{ cm}^{-1}$ ) showed that the ketone group is located on a saturated six-membered ring.

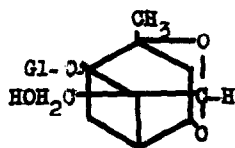
A singlet methyl signal in the NMR spectrum of paeoniflorin tetraacetate ( $\tau$ :8.66) was retained in the ketonic  $\gamma$ -lactone (VIII) ( $\tau$ :8.38) to indicate the presence of  $>\overset{\text{CH}_3}{\text{C}}-$  system in these compounds. In the NMR spectrum of the  $\alpha\beta$ -unsaturated keto-carboxylic acid (IX), the methyl signal was shifted to lower field overlapping with the acetyl signal ( $\tau$ :7.9) showing the methyl group is standing on a double bond. On hydrogenation of the double bond, a doublet signal centred on  $\tau$ :8.95 ( $J=7$  c.p.s.) appeared in the NMR spectrum of XI to indicate the occurrence of  $-\overset{\text{CH}_3}{\text{C}}-$  system in its molecule.

The presence of acetal proton was shown in the NMR spectrum of paeoniflorin tetraacetate (II) at  $\tau$ :4.58 as well as in those of product A<sub>1</sub> (V) ( $\delta_{\text{aq.}}$  -0.76 p.p.m.) and product A<sub>2</sub> (VI) ( $\delta_{\text{aq.}}$  -0.82 p.p.m.). It disappeared in the NMR spectra of the ketonic  $\gamma$ -lactone (VIII) and product A<sub>3</sub> (VII). The NMR spectrum of product A<sub>1</sub> also showed that no proton is attached to the carbon atom which links glucose.

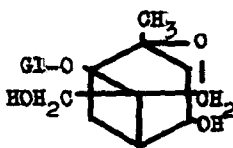
All the evidences mentioned above have agreed the structural formula (I) of paeoniflorin, which can provide a satisfactory explanation for the reaction products (II-IX, and XI).



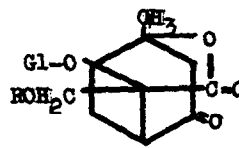
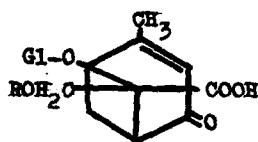
- (I) Gl = D-Glucosyl; R = C<sub>6</sub>H<sub>5</sub>CO; R' = H  
 (II) Gl = Tetraacetyl-D-glucosyl;  
 R = C<sub>6</sub>H<sub>5</sub>CO; R' = H  
 (III) Gl = Tetraacetyl-D-glucosyl;  
 R = C<sub>6</sub>H<sub>5</sub>CO; R' = CH<sub>3</sub>  
 (IV) Gl = D-Glucosyl; R = H; R' = CH<sub>3</sub>  
 (V) Gl = D-Glucosyl; R = R' = H



(VI) Gl = D-Glucosyl



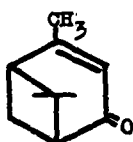
(VII) Gl = D-Glucosyl

(VIII) Gl = Tetraacetyl-D-glucosyl; R = C<sub>6</sub>H<sub>5</sub>CO

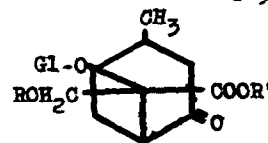
(IX) Gl = D-Glucosyl;

R = H

(IX') Gl = Tetraacetyl-D-glucosyl;

R = CH<sub>2</sub>CO

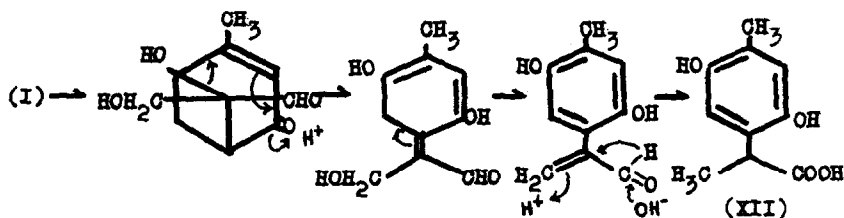
(X)



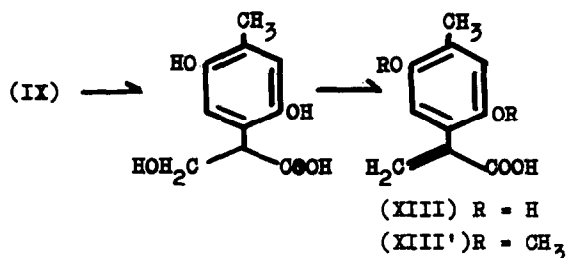
(XI) Gl = Tetraacetyl-D-glucosyl;

R = CH<sub>2</sub>CO; R' = H

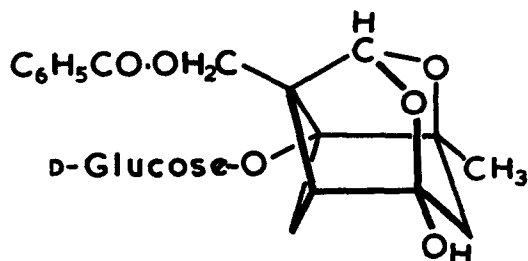
The conversion of desbenzoyl paeoniflorin monomethyl ether (IV) and the product A<sub>1</sub> (V) into the aromatic aglycone (XII) would reasonably be explained by the following mechanism:



On acid hydrolysis, the carboxylic acid (IX) afforded a hydroquinone derivative (XIII) whose dimethyl ether, m.p. 167° (XIII') was synthetically established. In this case, no intramolecular hydride shifting was observed in the side chain.



Thus paeoniflorin has been established as being a novel type monoterpene glucoside whose basic skeleton is a pinane derivative, and the stereochemical feature is illustrated below:



Acknowledgements: We are indebted to the members of the microchemical and spectroscopical laboratories of this Faculty and Institute of Applied Microbiology of University of Tokyo for microanalyses, and UV and IR spectral measurements, and to the research laboratories of Takeda Pharmaceutical Industry Co., Sankyo Co. and Mitsubishi-Kasei Co. for the NMR spectral measurements. We thank Yakuri-kenkyukai for grant.

#### REFERENCES

1. S. Shibata and M. Nakahara, Chem. Pharm. Bull. (Tokyo), 11, 372 (1963)
2. S. Shibata, N. Aimi and M. Nakahara, Ibid., 11, 379 (1963)