92. The Synthesis of Resveratrol and its Derivatives.*

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(Comm. by R. MAJIMA, M.I.A., Oct. 12, 1940.)

Recently two phenolic substances,¹⁾ resveratrol and hydroxyresveratrol, have been isolated from roots of white hellebore. Synthesis of derivatives and degradation products of these phenolic substances have been recorded and the evidence afforded by synthesis of dibromo-derivative of 3·5·4'-trimethoxydiphenylethane and tribromo-derivative of 3·5·2'·4'-tetrahydroxydiphenylethane, identical with the bromo-compounds derived from natural products, amply suffice to determine the constitution of resveratrol (I, R=H) and hydroxyresveratrol (II).

Later on rhapontigenin (V), aglucone of rhapontin which was isolated from Turkish rhubarb and was investigated by S. Kawamura,²⁾ was also confirmed to be a stilbene derivative³⁾ as in the case of resveratrol and hydroxyresveratrol.

Some intermediates of the above bromo-compounds, however, have not been obtained in crystalline form and the present writer therefore decided to continue the investigation of this subject. Resveratrol and its methyl as well as acetyl-derivative have now been synthesised.

Condensation of sodium 3·5-dihydroxyphenylacetate with 4-hydroxybenzaldehyde in presence of acetic anhydride gave 3·5·4'-triacetoxystilbene- α -carboxylic acid (III) which was converted into triacetoxystilbene by decarboxylation.

3·5·4'-Triacetoxystilbene thus obtained, melting at 114-116°, was identical with triacetyl resveratrol (I, R=OCCH₃) and this was next hydrolysed to 3·5·4'-trihydroxystilbene as below.

* On the Phenolic Substances of White Hellebore (*Veratrum grandiflorum* Loes. fil.) Part II.

1) M. Takaoka, Jour. Fac. Sci. Hokkaido Univ., Series III, **3**, 1 (1940).

2) J. Pharm. Soc. Japan, **58** (1938), 83.

3) M. Takaoka, Proc. **16** (1940), 408.

The synthetic stilbene was found to be identical with natural resveratrol in all respects. On methylation with methyl sulphate 3·5·4-trihydroxystilbene furnished trimethyl ether, m. p. 56–57° which was also confirmed to be trimethyl-resveratrol by direct comparison.

Reference must be made to the recent work of E. Späth and J. Schläger.¹⁾ These authors isolated a phenolic substance, pterostilbene, $C_{16}H_{16}O_3$, from red sandalwood and oxidised it with potassium permanganate, obtaining 3·5-dimethoxybenzoic acid. Oxidation of methylpterostilbene furnished 4-methoxybenzoic acid in addition to 3·5-dimethoxybenzoic acid. Pterostilbene was thus stated to be 3·5-dimethoxy-4'-hydroxystilbene (VIII). Methylpterostilbene, according to E. Späth and J. Schläger, melts at 56–57°, having the same melting point as the above trimethylresveratrol (I, $R=CH_3$) which has now been synthesised. Pterostilbene seems therefore to be 3·5-dimethoxy-4'-hydroxystilbene as they considered.

In 1909 Y. Asahina²⁾ isolated an acid, hydrangeic acid $C_{15}H_{12}O_4$ along with hydrangenol $C_{15}H_{12}O_4$ from *Hydrangea Hortensia* DC. var. *Otakusa* Maxim. and the former was established to be a stilbene derivative (IV) by Y. Asahina and J. Asano.³⁾ Since then as was already mentioned in Part I, rhapontigenin⁴⁾ (V), resveratrol (I, $R=H$), hyoroxeresveratrol (II), pinosylvin⁵⁾ (VI, $R=H$), and monomethylpinosylvin⁵⁾ (VI, $R=CH_3$) had been found in the botanical kingdom. Since then another stilbene hydroxyderivative, 3·3'-dimethoxy-4·4'-dihydroxystilbene⁶⁾ (VII) was added to the naturally occurring stilbene group. Stilbene hydroxy-derivatives are now becoming common constituents of resinous matters. Pterostilbene is therefore not the first or one of the first representatives of the rarely occurring natural stilbenes as previous writers state.

1) Ber. **73** (1940), 881.

2) J. Pharm. Soc. Japan, **24** (1909), 330, p. 3.

3) Ber. **63** (1930), 429; 2059.

4) loc. cit.

5) H. Erdtmann, A. 539 (1939), 116.

6) H. Richtenzehain and C. V. Hofer, Ber. **72** (1939), 1890.

*Experimental.**3·5·4'-Triacetoxystilbene- α -carboxylic acid (III).*

A mixture of sodium 3·5-dihydroxyphenylacetate (2.1 g), 4-hydroxy-benzaldehyde (2.1 g) and acetic anhydride (12.6 cc) was heated at 165–170° for 8 hours. The condensation product, recrystallised from benzene, melted at 178–179° (Found: C, 63.11; H, 4.44. $C_{21}H_{18}O_8$ requires C, 63.29; H, 4.56%), soluble in usual organic solvents except light petroleum.

3·5·4'-Triacetoxystilbene (I, $R=OCCH_3$)

The stilbene- α -carboxylic acid (III) (1.3 g) in quinoline (13 cc) was heated at 200–210° in presence of Naturkupfer C (1.3 g) for 40 minutes. The decarboxylated stilbene (II) was crystallised from methyl alcohol and then ethyl alcohol, melting alone or with a specimen from natural product at 114–116° (Found: C, 68.00; H, 5.37. Calc. for $C_{20}H_{18}O_6$ C, 67.81; H, 5.12%).

3·5·4'-Trihydroxystilbene (I, $R=H$).

The triacetoxystilbene (I, $R=OCCH_3$) (0.2 g) was hydrolysed with alcoholic sodium hydroxide (20 cc) in a current of nitrogen. From water crystallised out the trihydroxystilbene in needles and melted at 216° (Found: C, 73.43; H, 5.25. Calc. for $C_{14}H_{12}O_3$. C, 73.65; H, 5.32%). It was identified as resveratrol from the resinous matters of white hellebore by mixed melting point method.

3·5·4'-Trimethoxystilbene (I, $R=CH_3$)

3·5·4'-Trihydroxystilbene above mentioned was treated with methyl sulphate and potassium hydroxide and the trimethyl ether, m. p. 56–57° (Found: C, 75.47; H, 6.31. Calc. for $C_{17}H_{18}O_3$. C, 75.52; H, 6.72%), was obtained which melted without depression on admixture with a specimen derived from resveratrol.

The author is indebted to Professor H. Suginome for his interest in this work. The cost of this investigation was partly met by a grant from the Imperial Academy Tokyo, hereby gratefully acknowledged.