58. *The Constitution of Tannins. Part I. Reduction Products of Chalkones and the Synthesis of a Typical Phlobatannin.*

By Alfred Russell.

If, as seems probable, the phlobatannins are constituted in a similar way to catechin (3 : 5 : 7 : 3′ : 4′-pentahydroxyflavan), there is nevertheless no reason to suppose that the pyranoid hydroxyls will always be found in position 3. Indeed, since catechin is the only member of its class known to occur naturally, it is likely that phlobatannins are related, not to 3-hydroxy- but to 4-hydroxy-flavans. It has therefore been thought of interest to prepare substances on the catechin model but hydroxylated in position 4 in order to compare their properties with those of typical natural phlobatannins. Experiments on the reduction of chalkones indicate that 2-hydroxychalkones, by reduction with zinc dust and dilute alcoholic acetic acid, give either 4-hydroxyflavans or the corresponding bimolecular pinacols (compare V and VI). To avoid confusion these reduction products will for the present be referred to as 4-hydroxyflavans.

The formation of 4-hydroxyflavans is shown by the following considerations :

(1) 2-Hydroxypolymethoxychalkones give amorphous reduction products insoluble in *N*-alkali; *e.g.*, the reduction products of 2-hydroxy-3 : 4 : 4′-trimethoxychalkone, 2-hydroxy-3 : 4 : 3′ : 4′-tetramethoxychalkone, and 2-hydroxy-3 : 4-dimethoxy-3′ : 4′-methylenedioxychalkone.

(2) 2 : 4′-Dihydroxy-3 : 4-dimethoxychalkone gives an amorphous alkali-soluble reduction product.

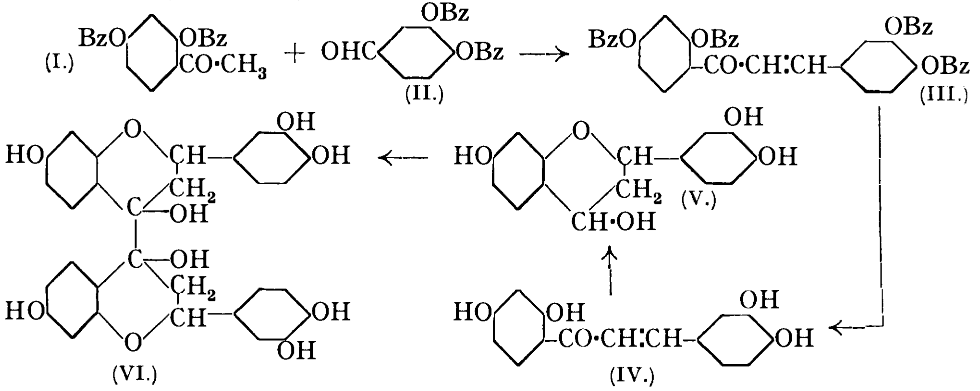
(3) Benzylideneacetophenone (chalkone) gives a crystalline colourless compound that must be at least bimolecular.

(4) 4′-Hydroxychalkone and 2 : 3 : 4 : 4′-tetramethoxychalkone give crystalline reduction products which are quite analogous to that obtained from chalkone itself and are, respectively, soluble and insoluble in alkali.

4-Hydroxypolymethoxyflavans display, so far as such poorly characterised substances can be compared, considerable resemblance to the products obtained by methylating natural phlobatannins. Both are amorphous, light-coloured substances when newly isolated, which darken superficially in daylight (when free phenolic hydroxyl groups are present, the colour change is much more marked and colour tests are given with ferric chloride, *e.g.*, 4 : 4′-dihydroxy-7 : 8-dimethoxyflavan and non-methylated tannins). Both melt indefinitely, slowly decompose on further heating, and give similar fission products with fused alkali, *viz.*, a polyhydric phenol and a phenolic acid.

These results were sufficiently encouraging to justify the extension of the work to similar polyhydroxy-compounds and there has now been obtained 4 : 7 : 3′ : 4′-tetrahydroxyflavan, indistinguishable by all its reactions from typical phlobatannins. Demethylation of the polymethoxy-compounds already described was not considered feasible for the preparation of polyhydroxyflavans because of the instability of the latter in acid. Attempts to prepare the parent chalkones by direct condensation of polyhydric ketones with aldehydes gave only highly coloured phenolic condensates; acetoxy-derivatives were not used because of the difficulty of obtaining pure acetoxybenzaldehydes; finally the use of fully benzoylated derivatives has proved completely satisfactory.

Resacetophenone dibenzoate (I) was condensed with protocatechualdehyde dibenzoate (II) by means of hydrogen chloride in dry ethyl acetate. The resulting 2 : 4 : 3′ : 4′-tetrabenzoyloxychalkone (III), on debenzoylation, gave 2 : 4 : 3′ : 4′-tetrahydroxychalkone (IV), the properties of which are in exact agreement with those of natural butein (compare Perkin and Hummel, J., 1904, **85**, 1459; Göschker and Tambor, *Ber.*, 1911, **44**, 3502). This, by reduction with zinc dust in alcohol and acetic acid gave 4 : 7 : 3′ : 4′-tetrahydroxyflavan (V) or the pinacol (VI).



The properties of 4 : 7 : 3′ : 4′-tetrahydroxyflavan are identical with those of natural phlobatannins; a comparison with two natural phlobatannins is given below. The tests were carried out in 0·5% aqueous solution with the exception of the first one. The solution in each case was pale yellow.

Reagent.	4 : 7 : 3′ : 4′-Tetrahydroxyflavan.	Hemlock tannin.	Mimosa tannin.
Alcoholic $FeCl_3$	Dark green colour	Dark green colour	Dark blue-violet colour
Aqueous $FeCl_3$	Dark green colour, changing to dark blue ppt.	Dark green colour, changing to dark ppt.	Dark blue-violet colour, changing to dark ppt.
Gelatin	Ppt.	Ppt.	Ppt.
Lead acetate	Light-coloured ppt., darkening; sol. in acetic acid	Light-coloured ppt., darkening; sol. in acetic acid	Light-coloured ppt., darkening; sol. in acetic acid
Boiling 5% HCl (phlobaphene reaction)	Soln. reddens slowly and red ppt. separates	Soln. reddens slowly and red ppt. separates	Soln. reddens slowly and red ppt. separates
Bromine water	Immediate heavy orange ppt.	Immediate heavy yellow ppt.	Immediate heavy orange ppt.
Calcium hydroxide	Green colour, faint green ppt.	Pink colour, faint pink ppt.	Purple ppt.
Sodium sulphite	Pink colour.	Pink colour	Pink colour
HCHO + HCl	Ppt. on warming	Ppt. on warming	Ppt. on warming
Nitrous acid	Immediate brown ppt.	Immediate brown-red ppt.	Immediate brown-red ppt.
Copper sulphate	Faint green colour	Faint green colour	Faint blue-green colour
Copper sulphate + NH_3 aq.	Heavy dark ppt.	Heavy dark ppt.	Heavy dark ppt.
Aqueous ammonia	Soln. darkens slowly	Soln. darkens slowly	Soln. darkens slowly
Pine wood shaving + HCl	Orange-pink, 24 hours	Pink, 24 hours	Faint pink, 24 hours

Solvent.	Solubilities.		
Water	Soluble: conc. solns. red; dil. solns. yellow	Soluble: conc. solns. red; dil. solns. yellow	Soluble: conc. solns. red; dil. solns. yellow
EtOH, MeOH, $MeCO_2Et$, Me_2CO	Readily sol. to dark red soln.	Readily sol. to dark red soln.	Readily sol. to dark red soln.
Et_2O, C_6H_6, etc., ligroin, $CHCl_3$, etc.	Insoluble	Insoluble	Insoluble
Sodium hydroxide solution	Readily sol.; dark soln. bleached by acid	Readily sol.; dark soln. bleached by acid	Readily sol.; dark soln. bleached by acid

The synthetic product is rapidly and quantitatively absorbed by hide powder from 3% aqueous solution, in exact agreement with the absorption of hemlock and mimosa tannins. Moreover, small pieces of cleaned and scraped sheepskin, placed in concentrated aqueous solutions, darken slightly, swell, toughen, take on all the appearance of leather, and show no signs of decomposition after several months. In blank tests with hide steeped in water, decomposition proceeded rapidly after a few days. All the tests were controlled by blanks.

It does not follow from the work described that all 4-hydroxy-polyhydroxyflavans are phlobatannins; tanning properties probably depend on the number and orientation of free phenolic hydroxyl groups present. The first synthetic phlobatannin was not intended to compare with any individual natural phlobatannin, but it may well be identical with one (probably Quebracho tannin, which gives corresponding fission products); the catechol group was included because most phlobatannins contain it. Apart from a few individuals which differ sufficiently from the main body for comparison with synthetic products, it is clear that the properties of the members of the phlobatannin group are too alike to make comparison of synthetic products with individuals satisfactory. Ultimate comparisons such as m. p. and analyses cannot be regarded as of much value for amorphous substances that cannot be rigidly purified. In view of this, the research is being extended by a comprehensive examination of the possible 4-hydroxy-polyhydroxyflavans with variously oriented phenolic hydroxyl groups. This should include the synthesis of most natural phlobatannins. It has already been noted that the so-called 4-hydroxyflavans may really be the corresponding pinacols. Since analytical figures are not of sufficient accuracy to settle this point and molecular-weight determinations are not practicable, it is being studied, indirectly, through the examination of the crystalline reduction product of chalkone itself; and, directly, through chalkone reduction in a closed system, where the quantity of absorbed hydrogen can be measured.

EXPERIMENTAL.

2-Hydroxy-3 : 4-dimethoxy-3′ : 4′-methylenedioxychalkone, prepared from gallacetophenone 3 : 4-dimethyl ether and piperonal (yield, 60%), formed orange needles, m. p. 175°, from dilute alcohol (Found : C, 65·6; H, 5·1. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%). *2 : 4′-Dihydroxy-3 : 4-dimethoxychalkone*, from gallacetophenone 3 : 4-dimethyl ether and *p*-hydroxybenzaldehyde (yield, 45%), formed bright yellow, hair-like needles, m. p. 106°, from dilute alcohol (Found : C, 63·5; H, 5·7. $C_{17}H_{16}O_5,H_2O$ requires C, 64·1; H, 5·7%). *2 : 3 : 4 : 4′-Tetramethoxychalkone*, from gallacetophenone trimethyl ether (obtained as an oily by-product in the methylation of gallacetophenone) and anisaldehyde (yield, 80%), crystallised from alcohol in light yellow, fine needles, m. p. 94° (Found : C, 69·4; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

4-Hydroxy-7 : 8 : 4′-trimethoxyflavan.—To a boiling solution of 2-hydroxy-3 : 4 : 4′-trimethoxychalkone (5 g.) in alcohol (400 c.c.) and acetic acid (50 g.), zinc dust (25 g.) was added during 1 hour. The solution, now colourless or very light green, was cooled and poured into water (2 l.). The colourless precipitate (5 g.) was collected, dissolved in alcohol (charcoal), and reprecipitated with water. The light cream-coloured amorphous *product* was insoluble in acids and boiling *N*-alkali and readily soluble in organic solvents, except ligroin, but could not be crystallised therefrom. It gradually darkened on keeping, and charred when heated above its melting point 85—95° [Found : C, 68·2; H, 6·4; OMe, 28·4. $C_{15}H_{11}O_2(OMe)_3$ requires C, 68·4; H, 6·3; OMe, 29·4%].

4-Hydroxy-7 : 8 : 3′ : 4′-tetramethoxyflavan, m. p. 90—110° (Found : C, 65·8; H, 6·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%), and *4-hydroxy-7 : 8-dimethoxy-3′ : 4′-methylenedioxyflavan*, m. p. 110—125° (Found : C, 65·4; H, 5·5. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·45%), were similarly obtained from the corresponding chalkones in 80% and 90% yield respectively.

4 : 4′-Dihydroxy-7 : 8-dimethoxyflavan, obtained from the corresponding chalkone in theoretical yield, was a light cream-coloured amorphous solid, m. p. 120—125°, soluble in alkali. It rapidly became dark red in daylight, but underwent no appreciable colour change when kept in darkness. In dilute aqueous-alcoholic solution it gave a permanent pink colour with ferric chloride (Found : C, 66·6; H, 6·1. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%).

Reduction Product of Chalkone.—Chalkone (5 g.) in boiling alcohol (100 c.c.) and acetic acid (15 c.c.) was reduced with zinc dust (20 g.) by the method described above. The colourless solution, filtered hot, deposited on cooling a mass of white woolly crystals. This, washed with boiling water and recrystallised from alcohol, gave felted needles (4 g.), m. p. 192°. The *product* was unsaturated and gave no reactions for a keto-group. It was insoluble in water, acids, and alkalis, but soluble in organic solvents (Found : C, 85·9; H, 6·35. $C_{30}H_{26}O_2$ requires C, 86·1; H, 6·2%).

4′-Hydroxychalkone and 2 : 3 : 4 : 4′-tetramethoxychalkone, similarly reduced, gave products which crystallised from alcohol in fine colourless needles, m. p. 204—205° (Found : C, 79·0; H, 6·0. $C_{30}H_{26}O_4$ requires C, 80·0; H, 5·8%), and stout colourless needles, m. p. 168°, respectively.

2 : 4 : 3′ : 4′-*Tetrahydroxychalkone* (*Butein*).—A colourless solution of resacetophenone dibenzoate (3·6 g.; 1 mol.) and protocatechualdehyde dibenzoate (3·6 g.; slight excess over 1 mol.) in dry ethyl acetate (70 c.c.), when saturated at 0° with dry hydrogen chloride (2 hours), became yellow, orange, orange-red, and finally light red. It was kept in ice for 24 hours, protected from moisture; ligroin (330 c.c.) then precipitated a dark red oil. This was washed with water and warm alcohol (20 c.c.), dissolved (7 g.) with great difficulty in boiling alcohol (75 c.c.), and refluxed for 3 hours with potassium hydroxide (5·5 g.; 10 mols. approx.) dissolved in water (100 c.c.). Water (100 c.c.) was then added, most of the alcohol removed by evaporation, and the dark orange-red solution cooled and acidified. The precipitate (2·5 g.), recrystallised from dilute alcohol, formed brilliant orange needles, m. p. 212°. The product dissolved in aqueous alkali to deep orange-red solutions. In alcoholic solution, it gave a deep red precipitate with lead acetate (compare butein), and a transient saffron colour, which darkened rapidly, with ferric chloride.

4 : 7 : 3′ : 4′-*Tetrahydroxyflavan.*—2 : 4 : 3′ : 4′-Tetrahydroxychalkone (1·6 g.) was dissolved in alcohol (25 c.c.) and acetic acid (5 c.c.), and to the boiling solution zinc dust (5 g.) was added in five portions during 15 minutes. The deep orange-red solution became very light yellow, but during filtration the colour darkened to reddish-brown. The solution was diluted to 250 c.c. with water, treated with bicarbonate, saturated with sodium chloride, and extracted with ethyl acetate (once, 40 c.c.). The clear red extract was dried (sodium sulphate) and evaporated to dryness below 50°. The residual light red-brown, vitreous mass (1·5 g.) was dissolved in acetone, shaken with charcoal, and the filtered solution evaporated in a vacuum. The residue was a clear golden-red vitreous mass and became a light red, amorphous solid on grinding. It retained traces of solvents very obstinately (Found : C, 65·2; H, 5·25. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%. $C_{30}H_{26}O_{10}$ requires C, 66·0; H, 4·76%).

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