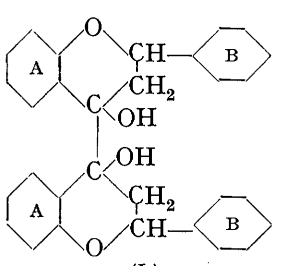
90. *The Constitution of Tannins. Part V. The Synthesis of some Flavpinacols.*

By Alfred Russell and John Todd.

In previous communications (J., 1934, 218, 1066, 1506, 1940) several polyhydroxy-derivatives of flavpinacol (I), in which B consisted of a catechol residue and A was built up from a resorcinol, phloroglucinol, or pyrogallol nucleus, were shown to be qualitatively indistinguishable from typical natural phlobatannins and to be capable, in aqueous solution, of tanning sheepskin. The series of synthetic flavpinacols has been extended with a view to the determination of the simplest structure of the flavpinacol type to exhibit the properties of a tannin, and we now describe corresponding series of flavpinacols in which B has been derived from (*a*) vanillin and (*b*) *p*-hydroxybenzaldehyde. Without exception, the products in each of these series are insoluble in water and therefore not directly comparable with natural phlobatannins.



(I.)

On the other hand, the flavpinacol obtained by the reduction of 2 : 3′ : 4′-trihydroxychalkone, *i.e.*, the flavpinacol containing *o*-hydroxyl groups in the 3′ : 4′-positions in residue B but without hydroxyl groups in residue A, is soluble in water and was shown by qualitative reactions to be related to natural phlobatannins. An aqueous solution of this preparation transformed a piece of sheepskin into a leather-like mass which showed no sign of decomposition after exposure for several months. Thus the presence of two hydroxyl groups in residue B, provided they are situated at the 3′ : 4′-positions, is sufficient to enable the flavpinacol to show tanning properties. We are now seeking to determine whether this condition is essential or not.

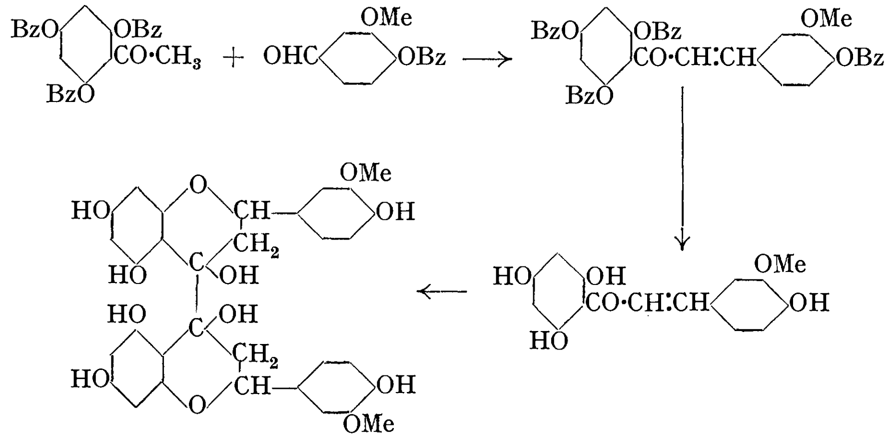
The number and disposition of hydroxyl groups in residue B influence the solubility of a flavpinacol in water to a much greater extent than similar groups in residue A. The number and orientation of such groups in residue A, on the other hand, have the greater effect on the colour : an increase in the number intensifies it and the effect is greatest when the groups are vicinal to each other.

The views of Asahina, Shinoda, and Inubuse (*Chem. Abs.*, 1928, **22**, 2946) on the constitutions of eriodictyol (fawn-coloured leaflets, m. p. 267°) and homoeriodictyol (pale yellow plates, m. p. 223°) have been confirmed. Power and Tutin, who isolated these substances from the leaves of *Eriodictyon californicum* and of *E. glutinosum*, considered them to be, respectively, 2 : 4 : 6 : 3′ : 4′-pentahydroxychalkone and its 3′-monomethyl ether (J., 1907, **91**, 887). The Japanese workers formulated them as the corresponding flavanones. Chalkones of the above constitutions have now been obtained by an unambiguous route; they crystallise from dilute alcohol, the former in orange-brown microscopic prisms, m. p. 245°, and the monomethyl ether in orange prisms, m. p. 214°. Each, when recrystallised from 70% acetic acid, is converted into the corresponding flavanone, 5 : 7 : 3′ : 4′-tetrahydroxyflavanone, fawn-coloured lustrous plates, m. p. 267°, evidently identical with eriodictyol, and 5 : 7 : 4′-trihydroxy-3′-methoyxflavanone, fawn-coloured plates, m. p. 219—220°, the homoeriodictyol of Power and Tutin.

The required chalkones were synthesised by condensation of appropriate benzoylated derivatives of *o*-hydroxyacetophenone and of benzaldehyde in ethyl acetate solution at 0° in the presence of anhydrous hydrogen chloride, the resulting benzoylated chalkone being hydrolysed with alkali in an atmosphere of nitrogen. Where possible, the benzoic acid was separated from the hydroxychalkone with boiling benzene. The solubility of the chalkones in benzene, however, increases as the number of hydroxyl groups decreases; so, in cases where the solubility of the chalkone in this solvent was appreciable, the separation from benzoic acid was accomplished with dilute sodium carbonate solution in an atmosphere of carbon dioxide.

The lower hydroxychalkones were reduced with zinc dust and acetic acid, but in the reduction of the more highly hydroxylated chalkones zinc dust and alcoholic hydrogen chloride were used, since the acidity of the hydroxychalkones increased with the number of hydroxyl groups.

The following scheme, which is typical for the series, shows the synthesis of 2 : 4 : 6 : 4′-tetrahydroxy-3′-methoxychalkone and its reduction to *bis*-(5 : 7 : 4′-*trihydroxy*-3′-*methoxy*)-*flavpinacol* :



Experimental.

2 : 4′-*Dibenzoyloxy*-3′-*methoxychalkone*.—The colourless solution of *o*-benzoyloxyacetophenone (9·6 g.) and vanillin benzoate (10·3 g. ; slight excess over 1 mol.) in dry ethyl acetate (100 c.c.), saturated at 0° with anhydrous hydrogen chloride, protected from moisture, and kept in ice for 24 hours, became yellow, orange, orange-red, and finally clear red. Dry air was then drawn through it during 2 hours, the solvent distilled off on the water-bath, and the residual reddish syrup taken up in boiling alcohol (*ca*. 100 c.c.). The cooled solution was decanted from the precipitated, pale yellow, semi-solid mass, which was washed twice with cold alcohol and used in the hydrolysis to the hydroxychalkone. A specimen crystallised from alcohol formed topaz-coloured prisms with pointed ends, m. p. 118—119° (Found : C, 75·5 ; H, 4·3. $C_{30}H_{22}O_6$ requires C, 75·3 ; H, 4·6%).

2 : 4′-*Dihydroxy*-3′-*methoxychalkone*.—The crude benzoate (13·5 g.), dissolved in alcohol (*ca*. 100 c.c.), was boiled with 4% aqueous caustic potash (200 c.c. ; 5 mols.) in an atmosphere of nitrogen for 4 hours, the alcohol then having distilled off. The cooled solution was acidified and saturated with sodium chloride, the pale yellow precipitate collected and shaken with dilute aqueous sodium carbonate (carbon dioxide atmos.), and the *chalkone* filtered rapidly, washed with water, and recrystallised from dilute alcohol (charcoal), forming pale orange-coloured needles, m. p. 128° (Found : C, 71·1 ; H, 5·1. $C_{16}H_{14}O_4$ requires C, 71·1 ; H, 5·2%).

Bis-(4′-*hydroxy*-3′-*methoxy*)*flavpinacol*.—To a boiling solution of 2 : 4′-dihydroxy-3′-methoxychalkone (2 g.) in alcohol (30 c.c.), alcoholic hydrogen chloride (15 c.c., saturated at 0°) was added, followed by zinc dust (5 g.). After 10 minutes' boiling, the solution, now colourless, was filtered hot, cooled rapidly, diluted with water, and extracted with ethyl acetate. The extract was washed with water until free from halogen, dried (sodium sulphate), and evaporated under diminished pressure. The *product* was a light red, amorphous powder, insoluble in water and in acids, soluble in alkalis and in the common organic solvents (Found : C, 71·2 ; H, 5·4. $C_{32}H_{30}O_8$ requires C, 70·8 ; H, 5·5%).

2 : 4 : 4′-*Trihydroxy*-3′-*methoxychalkone*.—Resacetophenone dibenzoate (7·2 g.) and vanillin benzoate (5·5 g.), condensed in the above-described manner, gave 2 : 4 : 4′-*tribenzoyloxy*-3′-*methoxychalkone* (12 g. approx.), which separated from alcohol in pale yellow, amorphous nodules, m. p. 148° (sintering 131°) (Found : C, 73·3 ; H, 4·5. $C_{36}H_{26}O_8$ requires C, 74·3 ; H, 4·35%). The benzoate was hydrolysed as before (nitrogen atmos.) and the pale yellow solid obtained after acidification of the reaction mixture was collected, dried, and extracted (Soxhlet), first with benzene to remove the benzoic acid and then with acetone. The acetone was removed on the water-bath, and the residue recrystallised from dilute alcohol, forming canary-yellow microscopic prisms, m. p. 210°. For analysis the substance was dried

over caustic soda for 2 hours at 120°/15 mm. (Found: C, 66·8; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

Bis-(7 : 4′-*dihydroxy*-3′-*methoxy*)*flavpinacol* was obtained by reduction of the preceding chalkone, as a deep red, amorphous solid, insoluble in water and in acids, soluble in alkalis to dark red solutions and in the usual organic solvents (Found in material dried over sodium hydroxide for 8 hours at 120°/15 mm.: C, 67·5; H, 5·4. $C_{32}H_{30}O_{10}$ requires C, 67·0; H, 5·2%).

2 : 4 : 6 : 4′-*Tetrahydroxy*-3′-*methoxychalkone*.—The *tetrabenzoate*, prepared by condensation of phloracetophenone tribenzoate (9·6 g.) and vanillin benzoate (5·5 g.), formed pale yellow, non-crystalline nodules (14 g. approx.) (Found in substance dried for 5 hours over sodium hydroxide at 80°/15 mm.: C, 73·8; H, 4·1. $C_{44}H_{30}O_{10}$ requires C, 73·5; H, 4·2%). The chalkone resulting from its hydrolysis in a nitrogen atmosphere was purified by the benzene extraction method and recrystallised from dilute alcohol; it formed deep orange-coloured, microscopic prisms, m. p. 214° (slight sintering at 210°) (cf. Mossler, *Annalen*, 1907, **351**, 243).

A mustard-yellow salt of the chalkone was obtained when carbon dioxide was passed into the alkaline solution after hydrolysis of the benzoate. The salt, on recrystallisation from 70% acetic acid, yielded the flavanone, homoeriodictyol.

Bis-(5 : 7 : 4′-*trihydroxy*-3′-*methoxy*)*flavpinacol*.—Acetic acid (10 c.c.) and zinc dust (5 g.) were added to a boiling solution of 2 : 4 : 6 : 4′-tetrahydroxy-3′-methoxychalkone (2 g.) in alcohol (10 c.c.). After boiling for 10 minutes, the hot solution was filtered, cooled, diluted with water, almost neutralised with aqueous bicarbonate, saturated with sodium chloride, and extracted with ethyl acetate. The clear red extract was dried (sodium sulphate) and evaporated to dryness under diminished pressure. The residue was dissolved in acetone, treated with charcoal, filtered, and the acetone removed under reduced pressure. The residual vitreous mass yielded, on grinding, a light red amorphous powder, soluble in alkalis to deep red solutions, insoluble in acids, sparingly soluble in hot water, and readily soluble in the usual organic solvents. For analysis, it was dried over sodium hydroxide for 2 hours at 120°/15 mm. (Found: C, 64·3; H, 4·8. $C_{32}H_{30}O_{12}$ requires C, 63·5; H, 4·95%).

2 : 3 : 4 : 4′-*Tetrahydroxy*-3′-*methoxychalkone*.—Condensation of gallacetophenone tribenzoate (9·6 g.) and vanillin benzoate (5·5 g.) gave in the normal manner 2 : 3 : 4 : 4′-*tetrabenzoyloxy*-3′-*methoxychalkone* (approx. 14 g.) as a pale orange-yellow, friable solid, m. p. 95° after softening (Found: C, 72·5; H, 4·7. $C_{44}H_{30}O_{10}$ requires C, 73·5; H, 4·2%. $C_{44}H_{30}O_{10},C_2H_6O$ requires C, 72·4; H, 4·7%). The *hydroxychalkone* was obtained by hydrolysis of the above benzoate (nitrogen atmosphere), separated from benzoic acid by means of dilute sodium carbonate solution, and recrystallised from dilute aqueous alcohol, forming orange-brown prisms, m. p. 199—200° (Found: C, 64·2; H, 4·7. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%).

Bis-(7 : 8 : 4′-*trihydroxy*-3′-*methoxy*)*flavpinacol* was obtained, by reduction of the preceding chalkone with zinc dust and alcoholic hydrogen chloride, as a dark brown, amorphous powder, soluble in alkali to a very dark opaque solution, insoluble in acids, very sparingly soluble in hot water, and readily soluble in the common organic solvents (Found in substance dried for 6 hours over sodium hydroxide at 120°/15 mm.: C, 64·0; H, 5·1. $C_{32}H_{30}O_{12}$ requires C, 63·5; H, 4·95%).

2 : 4′-*Dihydroxychalkone*.—Condensation of *o*-benzoyloxyacetophenone (9·6 g.) and *p*-benzoyloxybenzaldehyde (9·1 g.) in dry ethyl acetate (*ca.* 100 c.c.) with anhydrous hydrogen chloride gave a pale orange, semi-solid mass. A dilute alcoholic solution of this *dibenzoate* slowly deposited pale yellow prisms, m. p. 120° (Found: C, 78·1; H, 4·2. $C_{29}H_{20}O_5$ requires C, 77·7; H, 4·46%). Hydrolysis with alcoholic caustic potash (nitrogen atmos.) and extraction of the product with dilute sodium carbonate solution (carbon dioxide atmos.) left the *chalkone*, which crystallised from dilute alcohol in pale yellow needles, m. p. 145° (Found in substance dried over sodium hydroxide in a vacuum desiccator: C, 75·4; H, 5·0. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

Bis-(4′-*hydroxy*)*flavpinacol*.—2 : 4′-Dihydroxychalkone (2 g.) was reduced with zinc dust (5 g.) and alcoholic hydrogen chloride (50 c.c.). The product (1·5 g.) was an orange-red friable solid, soluble in alkalis to clear red solutions, insoluble in acid and in water, readily soluble in alcohol and ether (Found: C, 75·0; H, 5·3. $C_{30}H_{26}O_6$ requires C, 74·7; H, 5·4%).

2 : 4 : 4′-*Trihydroxychalkone*.—Resacetophenone dibenzoate (7·2 g.) and *p*-benzoyloxybenzaldehyde (4·7 g.) gave in the usual manner 2 : 4 : 4′-*tribenzoyloxychalkone*, which formed pale yellow prisms, m. p. 114—115°, from alcohol (Found for substance kept over potassium hydroxide in a vacuum desiccator for 9 days: C, 75·2; H, 4·55. $C_{36}H_{24}O_7$ requires C, 76·1; H, 4·23%. $C_{36}H_{24}O_7,C_2H_6O$ requires C, 74·5; H, 4·9%).

2 : 4 : 4′-*Trihydroxychalkone*, obtained by hydrolysis of the above product by means of alco-

holic caustic potash (nitrogen atmos.) and separation of the benzoic acid with dilute aqueous sodium carbonate solution (carbon dioxide atmos.), formed pale yellow needles, m. p. 187—188°, from dilute alcohol (Found : C, 70·1; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

Bis-(7 : 4′-*dihydroxy*)*flavpinacol* was prepared by reduction (zinc dust–acetic acid) of an alcoholic solution of 2 : 4 : 4′-trihydroxychalkone and isolated as a deep orange-red, amorphous powder, insoluble in water and in acids, soluble in alkalis and in alcohol and ether. The substance for analysis was dried over sodium hydroxide at 120°/15 mm. for 5 hours (Found : C, 70·0; H, 5·05. $C_{30}H_{26}O_8$ requires C, 70·0; H, 5·05%).

2 : 3 : 4 : 4′-*Tetrahydroxychalkone*.—2 : 3 : 4 : 4′-*Tetrabenzoyloxychalkone* was obtained by condensation of gallacetophenone tribenzoate (9·6 g.) and *p*-benzoyloxybenzaldehyde (4·7 g.) and isolated in pale yellow, non-crystalline nodules, m. p. 105° after softening (Found : C, 74·0; H, 4·1. $C_{43}H_{28}O_9$ requires C, 74·9; H, 4·1%). 2 : 3 : 4 : 4′-*Tetrahydroxychalkone*, prepared by hydrolysis (alcoholic potassium hydroxide; nitrogen atmos.) of the above benzoate (benzoic acid removed by benzene extraction), crystallised from dilute aqueous alcohol in reddish-brown needles, m. p. 117° (Found : C, 65·8; H, 4·5. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

Bis-(7 : 8 : 4′-*trihydroxy*)*flavpinacol* was obtained, by reduction of the chalkone with zinc dust and alcoholic hydrogen chloride, as a deep brown, amorphous solid, sparingly soluble in hot water, insoluble in acids, soluble in alkalis to dark brown solutions and in alcohol, acetone, and ether (Found for substance dried over sodium hydroxide for 1½ hours at 120°/15 mm. : C, 66·0; H, 4·95. $C_{30}H_{26}O_{10}$ requires C, 65·9; H, 4·80%).

2 : 4 : 6 : 4′-*Tetrahydroxychalkone*.—Phloracetophenone tribenzoate (9·6 g.) and *p*-benzoyloxybenzaldehyde (4·7 g.) were condensed in the usual manner. The resulting 2 : 4 : 6 : 4′-*tetrabenzoyloxychalkone* was obtained in pale yellow nodules (12 g.) (Found : C, 74·6; H, 3·9. $C_{43}H_{28}O_9$ requires C, 74·9; H, 4·1%). Hydrolysis yielded 2 : 4 : 6 : 4′-*tetrahydroxychalkone*, which was separated from benzoic acid by benzene extraction and recrystallised from dilute alcohol, forming microscopic orange prisms, m. p. 205°. It was dried for 2 hours over sodium hydroxide at 120°/15 mm. (Found : C, 66·1; H, 4·5. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

Bis-(5 : 7 : 4′-*trihydroxy*)*flavpinacol* was obtained from the chalkone, by reduction with zinc dust and alcoholic hydrogen chloride, as an orange-brown, amorphous solid, soluble in alkalis to dark red solutions, insoluble in acids and in water, readily soluble in alcohol and in ether. A specimen was dried over sodium hydroxide for 2 hours at 120°/15 mm. (Found : C, 66·7; H, 4·9. $C_{30}H_{26}O_{10}$ requires C, 66·0; H, 4·8%).

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