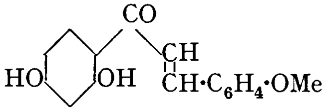
248. *Chalkones. Condensation of Aromatic Aldehydes with Resacetophenone. Part II.*

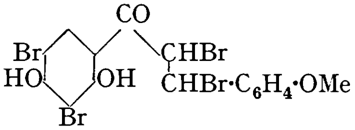
By D. R. NADKARNI and T. S. WHEELER.

In continuation of previous work, the direct synthesis of the corresponding polyhydroxychalkones from resacetophenone and *p*-anisaldehyde or *p*-hydroxybenzaldehyde has been examined; the possibility of passing directly from such chalkones to flavones, flavanones, and flavonols has also been investigated, and modified methods for the preparation of pratol, resokaempferide, and liquiritigenin are described.

IN continuation of Part I (J., 1937, 1737), Shinoda's statement (*J. Pharm. Soc. Japan*, 1928, **48**, 214; *Chem. Abs.*, 1928, **22**, 2947) that resacetophenone condenses with *p*-anisaldehyde in presence of alkali to give 2 : 4-dihydroxyphenyl 4-methoxystyryl ketone (I) has been confirmed, but our product has a higher m. p. This ketone yields pratol (7-hydroxy-4′-methoxyflavone) with selenium dioxide (cf. Mahal, Rai, and Venkataraman, J., 1935, 866) and resokaempferide (7-hydroxy-4′-methoxyflavonol) with alkaline hydrogen peroxide (cf. Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, **42**, *B*, 1). It is believed that this is the first occasion on which these methods have been applied to the direct production of, respectively, a hydroxyflavone and hydroxyflavonol.



(I.)



(II.)

The flavanone corresponding to (I) (7-hydroxy-4′-methoxyflavanone) could not be obtained pure by treatment of (I) with dilute alkali (Löwenbein, *Ber.*, 1924, **57**, 1515); the product always gave a coloration with ferric chloride. The application of Kostanecki's chalkone dibromide method for the production of flavones to polyhydroxychalkones does not appear to have been examined; work has been confined to alkoxy- and acetoxy-derivatives (cf. Tambor, *Ber.*, 1916, **49**, 1704). Bromination of (I) yielded 3 : 5-*dibromo*-2 : 4-*dihydroxyphenyl* αβ-*dibromo*-β-p-*anisylethyl ketone* (II). The position of the bromine atoms is assigned by analogy with the results of work on alkoxy-derivatives of 2-hydroxyphenyl styryl ketone (see Cullinane and Philpott, J., 1929, 1763; Nadkarni and Wheeler, *J. University Bombay*, 1937, **6**, 107); the directive influences of hydroxyl and alkoxyl are similar. On treatment with alkali and acetone in the cold, (II) gave 6 : 8-dibromo-7-hydroxy-4′-methoxyflavone (see Nadkarni *et al.*, J., 1937, 1800), which was also obtained by boiling with acetone alone.

Tambor (*loc. cit.*, p. 1708) synthesised 2 : 4-dihydroxyphenyl 4′-hydroxystyryl ketone (m. p. 187—188°; $2H_2O$) from resacetophenone and *p*-hydroxybenzaldehyde with 50% potassium hydroxide at the b. p. Shinoda and Ueeda (*Ber.*, 1934, **67**, 439) found that a similar product, m. p. 185—187°, obtained by condensation of *p*-carbethoxycinnamoyl chloride and resacetophenone, was contaminated with traces of colourless flavanone. Repetition of Tambor's method and also of a modification which involved working in the cold gave the chalkone free from flavanone; the crystals, m. p. 202—204°, were the *monohydrate*. The corresponding flavanone, liquiritigenin (7 : 4′-dihydroxyflavanone), which had been obtained from the chalkone by the acid method in an impure state by Tambor (*loc. cit.*; m. p. 182—183°; diacetyl derivative, m. p. 175—176°) and in a pure state by the Japanese workers (*loc. cit.*; m. p. 207°; diacetyl derivative, m. p. 184°) was readily obtained free from the chalkone with dilute alkali. Hydrolysis of the chalkone triacetate with potassium hydroxide solution gave a mixture of chalkone and flavanone; this result indicates that the method of preparing hydroxychalkones by the alkaline hydrolysis of the benzoyl derivatives (Russell and Todd, J., 1937, 421) may yield a mixture of the chalkone and flavanone.

EXPERIMENTAL.

Condensation of p-*Anisaldehyde with Resacetophenone* : 2 : 4-*Dihydroxyphenyl* 4-*Methoxystyryl Ketone* (I).—A solution of potassium hydroxide (50 g.) in water (35 c.c.) was gradually added at 0° to a mixture of *p*-anisaldehyde (4·3 g.), resacetophenone (5 g.), and alcohol (10 c.c.), which was then kept at room temperature out of contact with air for two days, diluted with an equal volume of water, and acidified, with cooling, with dilute hydrochloric acid. The resulting precipitate (4·5 g.) crystallised from alcohol in orange-red needles, m. p. 194° (lit.; 186°), giving a dark violet coloration with alcoholic ferric chloride (Found : C, 71·1; H, 5·1. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%).

Preparation of 7-*Hydroxy*-4′-*methoxyflavone* (*Pratol*).—A mixture of (I) (3 g.), selenium dioxide (2 g.), and amyl alcohol (25 c.c.) was heated at 150° under reflux for 12 hours. After filtration, amyl alcohol was evaporated in steam. The residue (0·4 g.) crystallised from alcohol in colourless needles, m. p. 260—261° (lit., 262°); these gave a green fluorescence, turning blue on keeping, with concentrated sulphuric acid. The acetyl derivative had m. p. 174—176° (lit., two isomers, 166° and 176°) (Found : C, 69·2; H, 4·8. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5%).

7-*Hydroxy*-4′-*methoxyflavonol* (*Resokaempferide*).—A mixture of (I) (2 g.), alcohol (15 c.c.), and N/2-alcoholic potash (15 c.c.) was gradually treated with hydrogen peroxide (30%, 6 c.c.) with shaking, and kept until the orange colour of the mixture had changed to pale yellow (3 hours). The whole was diluted with water and acidified with dilute sulphuric acid. The precipitated flavonol (0·4 g.) crystallised from alcohol in greenish-yellow needles, m. p. 286—288° (lit., 284°). It gave a green fluorescence with concentrated sulphuric acid, and a violet coloration with alcoholic ferric chloride (Found : C, 67·2; H, 4·5. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%).

3 : 5-*Dibromo*-2 : 4-*dihydroxyphenyl* αβ-*Dibromo*-β-p-*anisylethyl Ketone* (II).—This *ketone* (1·4 g.) separated from a solution of bromine (4 g.) and (I) (2 g.) in chloroform (50 c.c.). It crystallised from benzene in pale yellow shining needles, m. p. 182—184° (Found : Br, 54·7. $C_{16}H_{12}O_4Br_4$ requires Br, 54·4%).

6 : 8-*Dibromo*-7-*hydroxy*-4′-*methoxyflavone*.—Aqueous potassium hydroxide (20%; 10 c.c.) was added at room temperature gradually with shaking to a suspension of the above dibromide (1 g.) in acetone (20 c.c.). The whole was kept for ½ hour, then diluted with water and acidified with dilute sulphuric acid. The precipitate crystallised from alcohol in yellow needles, m. p. 194°, not depressed when mixed with the *compound* obtained by boiling the above chalkone dibromide with acetone (Found : C, 45·0; H, 2·8; Br, 37·5. $C_{16}H_{10}O_4Br_2$ requires C, 45·1; H, 2·4; Br, 37·6%).

Condensation of p-*Hydroxybenzaldehyde with Resacetophenone.* 2 : 4-*Dihydroxyphenyl* 4′-*Hydroxystyryl Ketone*.—A mixture of *p*-hydroxybenzaldehyde (5 g.) and resacetophenone (6·25 g.) in alcohol (12 c.c.) which had been treated at 0° with aqueous potassium hydroxide (50 g. in 35 c.c. of water) and then kept at room temperature out of contact with air for 3 days was diluted with an equal volume of water and acidified, under cooling, with dilute hydrochloric acid. The resulting precipitate (2·8 g.) crystallised from dilute alcohol in yellow needles of the *monohydrate*, m. p. 202—204° (lit., *ca.* 187°) (Found : C, 65·7; H, 5·2; H_2O, 6·2. $C_{15}H_{12}O_4,H_2O$ requires C, 65·7; H, 5·1; H_2O, 6·6%), and gave a dark violet coloration with alcoholic ferric chloride; with magnesium powder and hydrochloric acid, it gave a similar colour, which disappeared in presence of excess of the acid. The acetyl derivative had m. p. 122° (lit., 123°). Repetition of Tambor's method (*loc. cit.*) gave the above chalkone with m. p. 201—203° (monohydrate).

Preparation of Liquiritigenin (7 : 4′-*Dihydroxyflavanone*) *from the Corresponding Chalkone*.—A mixture of aqueous sodium hydroxide (25 c.c.; 2·5%) and the above chalkone (1 g.) in alcohol (6 c.c.) which had been heated under reflux for 6 hours was diluted with water and acidified with dilute hydrochloric acid. The resulting precipitate separated from dilute alcohol in colourless shining plates, m. p. 207—208° ($1H_2O$) (lit., 182—183°; 207°; $1H_2O$), and gave a violet coloration with magnesium powder and excess of hydrochloric acid; it gave no coloration with alcoholic ferric chloride (Found : C, 65·2; H, 5·1; H_2O, 6·4. Calc. for $C_{15}H_{12}O_4,H_2O$: C, 65·7; H, 5·1; H_2O, 6·6%). The diacetyl derivative had m. p. 185° (lit., 175—176°; 184°).

Hydrolysis of 2 : 4-*Diacetoxyphenyl* 4′-*Acetoxystyryl Ketone : Formation of Flavanone and Chalkone*.—The chalkone triacetate (1 g.) dissolved in alcohol (6 c.c.) was boiled with aqueous potassium hydroxide (15 c.c.; 4%) in an atmosphere of coal-gas for 2 hours, and the cooled solution was diluted with water and acidified with dilute hydrochloric acid. The resulting precipitate on fractional crystallisation gave both the less soluble 7 : 4′-dihydroxyflavanone (m. p. 207—208°) and the more soluble 2 : 4-dihydroxyphenyl 4′-α-hydroxystyryl ketone (m. p. 202—204°), the identity of both products being confirmed by mixed m. p. determinations with authentic specimens.

ROYAL INSTITUTE OF SCIENCE, BOMBAY.

[*Received, June* 28*th*, 1938.]