

CCXII.—*The Condensation of α -Formylphenylacetonitriles with Phenols. Part I.*

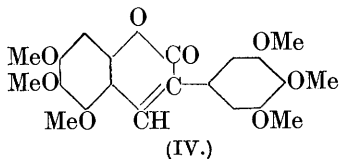
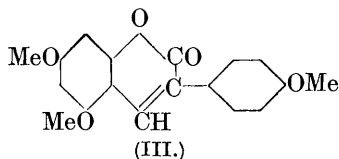
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THE condensation of α -formylphenylacetonitrile and derivatives with resorcinol or other phenols under the conditions of the Hoesch reaction leads to the production of 3-phenylcoumarins and not the isomeric 3-phenylchromones (*isoflavones*). The Hoesch reaction in these cases takes an abnormal course, condensation occurring between the cyano-group and a phenolic hydroxyl group to give a lactone (compare Fischer and Nouri, *Ber.*, 1917, **50**, 613). The yields are generally very poor.

The condensation of α -formylphenylacetonitrile, CHO·CHPh·CN (I), with resorcinol in presence of phosphoryl chloride gives 7-hydr-

oxy-3-phenylcoumarin (II) (Baker, J., 1927, 2898), and under the conditions of the Hoesch synthesis it is now found that the same substance is produced as the only product isolable in the pure state. The Hoesch condensation between resorcinol monomethyl ether and (I) gave the methyl ether of (II), but in one experiment a trace of 7-methoxyisoflavone (Baker and Robinson, J., 1925, 127, 1981) was also isolated. Later experiments did not yield the isoflavone, and the conditions for the production of this substance cannot therefore be laid down.

Phloroglucinol and (I) yielded 5 : 7-dihydroxy-3-phenylcoumarin (Bargellini, *Gazzetta*, 1927, 57, 460). Phloroglucinol dimethyl ether and α -formyl-p-methoxyphenylacetonitrile gave 5 : 7 : 4'-trimethoxy-3-phenylcoumarin (III), the analogue of genistein trimethyl ether (Bargellini, *ibid.*, p. 464); and α -formyl-3 : 4 : 5-trimethoxyphenylacetonitrile and 3 : 4 : 5-trimethoxyphenol (antiarol) gave 5 : 6 : 7 : 3' : 4' : 5'-hexamethoxy-3-phenylcoumarin (IV), the analogue of irigenin trimethyl ether (Baker, J., 1928, 1028). No condensation occurred between α -formyl-3 : 4 : 5-trimethoxyphenylacetonitrile and 1 : 2 : 3 : 5-tetramethoxybenzene.



A number of experiments were carried out with the *O*-benzoyl derivative of (I), benzoyloxymethylenephénylacetonitrile, CH(O·COPh):CPh·CN (V), which generally gave cleaner and more homogeneous products than (I). The condensation of (V) with resorcinol gave the coumarin (II) and a compound, m. p. 145—146°, of unknown constitution. The condensation of (V) with the dibenzoate, dimethyl ether, dibenzyl ether, and diethylcarbonato-derivative of resorcinol led to no definite results, a trace of (II) being isolated in some cases. The product formed from (V) and pyrogallol was 7 : 8-dihydroxy-3-phenylcoumarin, and from (V) and orcinol was formed 7-hydroxy-3-phenyl-5-methylcoumarin (formerly described by Ghosh as the chromone, J., 1916, 109, 117).

Under the conditions of the Hoesch reaction (V) did not react with quinol, catechol, or phenol, nor when the substances were dissolved in concentrated sulphuric acid and poured into water. By condensing (V) with resorcinol diacetate, hydrogen chloride, and zinc chloride in acetic acid, 4 : 6-diacetylresorcinol was produced; a similar condensation between (V) and the acetyl derivative of resorcinol monomethyl ether gave 7-methoxy-3-phenylcoumarin.

EXPERIMENTAL.

Condensation of Resorcinol with α -Formylphenylacetonitrile (I).—A mixture of resorcinol (7.6 g.), α -formylphenylacetonitrile (10 g.), and anhydrous zinc chloride (4 g.) in dry ether (60 c.c.) was saturated at 0° with hydrogen chloride and again after 24 hours, and kept at 0° for 3 days. The product was washed with dry ether, boiled for 2 hours with water (100 c.c.), and filtered hot. The remaining red solid was boiled with 20% sulphuric acid for 3 hours and then refluxed for 2 hours with 20% alcoholic sulphuric acid and poured into water. The sticky product (5 g.) was dissolved in boiling 5% aqueous sodium hydroxide (70 c.c.), cooled, and filtered, and the filtrate saturated with carbon dioxide. The yellow precipitate (0.5 g.) could not be obtained crystalline; it had m. p. about 245—255°, gave a brown colour with ferric chloride in alcoholic solution, and a weak green fluorescence in concentrated sulphuric acid. Its non-crystalline acetyl derivative had m. p. 150—156°. The final filtrate on acidification gave a precipitate which after repeated crystallisation had m. p. 208° and was proved to be (II).

Condensation of Resorcinol Monomethyl Ether with (I).—This was done as in the preceding case, resorcinol monomethyl ether (8.5 g.) being used. After 5 days the red mass was washed with ether, boiled for 2 hours with water (200 c.c.), refluxed with 5% alcoholic sulphuric acid (200 c.c.) for 3 hours, and poured into water. The insoluble product was heated with excess of 2% sodium hydroxide solution for 2 hours and filtered. The very small amount of undissolved residue was normally not crystalline but in one experiment was obtained crystalline from dilute alcohol. After repeated crystallisation it had m. p. 154—156°, which was not depressed on admixture with 7-methoxyisoflavone (Baker and Robinson, J., 1925, 127, 1986; 1929, 1473). Acidification of the alkaline solution gave a solid, which after crystallisation had m. p. 121—122° and was identified as 7-methoxy-3-phenylcoumarin (Found: C, 75.9; H, 4.5. Calc. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8%).

Condensation of Phloroglucinol with (I).—This was done under the conditions of the Hoesch reaction, phloroglucinol (10 g.), (I) (11.5 g.), zinc chloride (2 g.), and ether (60 c.c.) being used. The product was boiled with 10% aqueous sulphuric acid for 1 hour, and the filtered solution yielded 5:7-dihydroxy-3-phenylcoumarin, m. p. 260° (Found: C, 70.5; H, 4.1. Calc. for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9%). The acetyl derivative had m. p. 156° (Found: C, 67.2; H, 4.4. Calc. for $C_{19}H_{14}O_6$: C, 67.4; H, 4.1%) (compare Bargellini, *loc. cit.*).

α -Formyl-p-methoxyphenylacetonitrile.—To a solution of sodium

(2.4 g.) in absolute alcohol (75 c.c.) was added *p*-methoxyphenylacetonitrile (14.7 g.) and then ethyl formate (8.2 g.). After 2 hours, the mixture was heated at 60° for 2 hours, water (400 c.c.) and a little sodium hydroxide solution were added, and the mixture was warmed to 45° and filtered. The acidified filtrate deposited a colourless oil which rapidly solidified (11.5 g.). The substance crystallised from benzene (200 c.c.) in small irregular prisms, m. p. 120—121° (Found : N, 7.8. $C_{10}H_9O_2N$ requires N, 8.0%). α -Formyl-*p*-methoxyphenylacetonitrile gives in concentrated sulphuric acid a pale greenish-blue solution. Its alcoholic solution becomes Prussian blue with a trace of ferric chloride, but the colour fades appreciably in a few minutes; excess of ferric chloride produces an emerald-green colour.

5 : 7 : 4'-Trimethoxy-3-phenylcoumarin (III).—A solution of the preceding compound (2.4 g.) and phloroglucinol dimethyl ether (2.1 g.) in dry ether (100 c.c.) was saturated with hydrogen chloride in presence of anhydrous zinc chloride. After 2 days, dry ether was added and the precipitated product was boiled with dilute alcoholic sodium hydroxide (5%) for $\frac{1}{2}$ hour and reprecipitated by acidification. The viscous material slowly crystallised from a small amount of alcohol, and after it had been pressed on porous earthenware, washed with ether and alcohol, and crystallised from acetic acid and then from alcohol, there was obtained about 0.1 g. of exceedingly pale yellow needles, m. p. 166—168°, having the properties ascribed by Bargellini (*loc. cit.*) to 5 : 7 : 4'-trimethoxy-3-phenylcoumarin.

α -Formyl-3 : 4 : 5-trimethoxyphenylacetonitrile.—This was prepared, in the same way as the corresponding *p*-methoxy-derivative, from sodium (2.1 g.), alcohol (100 c.c.), 3 : 4 : 5-trimethoxyphenylacetonitrile (15.5 g.) (Baker and Robinson, J., 1929, 157), and ethyl formate (6.1 g.). It separated from benzene in colourless branching prisms (Found : N, 5.8. $C_{12}H_{13}O_4N$ requires N, 5.9%). The substance is probably dimorphous, since it melts at 83—85°, then resolidifies slowly, and melts again at 114—115°. Its reaction with ferric chloride resembles that of the *p*-methoxy-derivative. In concentrated sulphuric acid it gives a greenish-yellow solution, which slowly becomes emerald-green.

5 : 6 : 7 : 3' : 4' : 5'-Hexamethoxy-3-phenylcoumarin (IV).— α -Formyl-3 : 4 : 5-trimethoxyphenylacetonitrile (2.4 g.) and 3 : 4 : 5-trimethoxyphenol (1.9 g.) (Chapman, Perkin, and Robinson, J., 1927, 3028) were suspended in ether (200 c.c.), and hydrogen chloride was passed in without cooling till all had dissolved. Finally, anhydrous zinc chloride was added and the mixture was cooled to 0° and rapidly saturated with hydrogen chloride. After 48 hours, water

was added, the mixture heated for 1 hour and cooled, the oily product washed with warm dilute sodium hydroxide solution, and the insoluble residue collected and crystallised from alcohol. It separated in bunches of pale yellow, minute needles (0.1 g.), m. p. 157° (Found: C, 62.7; H, 5.6. $C_{21}H_{22}O_8$ requires C, 62.7; H, 5.5%). The properties of the substance are distinct from those of the isomeric irigenin trimethyl ether. It is insoluble in boiling dilute sodium hydroxide solution, exhibits no basic properties towards concentrated hydrochloric acid, and gives a marked yellow solution in concentrated sulphuric acid.

Benzoyloxymethylenephnylacetonitrile (V).—To a suspension of finely divided sodium (10 g.) in dry ether (250 c.c.) cooled in ice and salt, a mixture of phenylacetonitrile (52 g.) and ethyl formate (38 g.) was added in the course of an hour with occasional shaking. The whole was left for 12 hours, and benzoyl chloride (70 g.) was then added in small portions, the ice-cooled mixture being shaken and kept alkaline by the addition of concentrated sodium hydroxide solution. After 2 hours, the solid was collected, washed with water, and crystallised from alcohol (1 l.). The product had m. p. 117—118°; yield 65—70 g. (compare *J. pr. Chem.*, 1897, **55**, 340; *Annalen*, 1901, **316**, 334).

Condensation of Resorcinol with (V).—This was effected under the usual conditions, resorcinol (10 g.), (V) (22.6 g.), zinc chloride (3 g.), and ether (100 c.c.) being used. The product was boiled with 5% sodium hydroxide solution (250 c.c.) for $\frac{1}{2}$ hour, cooled, and filtered, and the yellow residue crystallised from 50% acetic acid (charcoal). It separated in colourless needles (0.1 g.), m. p. 145—146°, which were not obtained quite pure (Found: C, 77.9; H, 4.4%). The substance is non-phenolic and gives a weak greenish-blue fluorescence in concentrated sulphuric acid. The alkaline solution when saturated with carbon dioxide gave a yellow solid, which after crystallisation from dilute acetic acid was identified as 7-hydroxy-3-phenylcoumarin, m. p. 209—210° (Found: C, 75.3; H, 4.6. Calc. for $C_{15}H_{10}O_3$: C, 75.6; H, 4.2%); acetyl derivative, m. p. 184° (Found: C, 72.5; H, 4.5. Calc. for $C_{17}H_{12}O_4$: C, 72.7; H, 4.3%).

Condensation of Pyrogallol with (V).—This was done under the usual conditions, pyrogallol (15 g.), (V) (30 g.), zinc chloride, and ether (100 c.c.) being used. After hydrolysis with boiling water, the filtered solution deposited colourless needles, m. p. 212° (Found: C, 70.8; H, 4.1. Calc. for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9%). The diacetate had m. p. 180° (Found: C, 67.4; H, 4.2. Calc. for $C_{19}H_{14}O_6$: C, 67.5; H, 4.1%) (compare Bargellini, *loc. cit.*).

Condensation of Orcinol with (V).—Condensation readily occurred under the usual conditions, and after hydrolysis 7-hydroxy-3-phenyl-

5-methylcoumarin separated, which crystallised from alcohol in small needles, m. p. 228° (Found: C, 71.5; H, 5.4. Calc. for $C_{16}H_{12}O_3 \cdot H_2O$: C, 71.1; H, 5.1%). The acetyl derivative separated from alcohol in colourless needles, m. p. 158—159° (Found: C, 73.8; H, 5.0. Calc. for $C_{18}H_{14}O_4$: C, 73.4; H, 4.7%). Both substances give blue fluorescent solutions in alcohol and in concentrated sulphuric acid. The alcoholic solution when treated with a drop of ferric chloride becomes orange-yellow and the fluorescence becomes violet.

Condensation of Resorcinol Derivatives with (V) in Acetic Acid.—The interaction of resorcinol diacetate and (V), with zinc chloride and hydrogen chloride in acetic acid first at room temperature and then on the water-bath, gave 4 : 6-diacetylresorcinol, crystallising from alcohol in pale yellow needles, m. p. 182° (Found: C, 61.5; H, 5.3. Calc. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.2%); diacetate, m. p. 120° (Found: C, 60.8; H, 5.5. Calc. for $C_{14}H_{14}O_6$: C, 60.4; H, 5.1%). A small amount of 7-hydroxy-3-phenylcoumarin was also isolated.

A similar reaction with the acetyl derivative of resorcinol mono-methyl ether yielded ultimately 7-methoxy-3-phenylcoumarin, m. p. 120°.

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