315. *A New Synthesis of Benzopyrylium Salts by Condensation of Reactive Phenols with Unsaturated Aldehydes or Ketones in the Presence of a Strong Acid and an Oxidising Agent. Part I. Typical Cases with Resorcinol as Phenolic Component.*

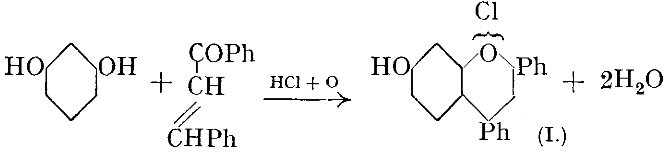
By Robert Robinson and James Walker.

Analogies naturally exist between the methods available for the synthesis of quinolines and benzopyrylium salts from aniline and phenol derivatives respectively; for instance, the direct methods from *o*-aminobenzaldehydes and *o*-hydroxybenzaldehydes and reactive keto-methylene compounds are closely parallel, and Combes's synthesis of quinolines finds a counterpart in Bülow's method in the benzopyrylium salt series. In these cases the components are in the correct state of oxidation and the condensations require the elimination of the elements of water only.

Some of the more useful general synthetic methods for the preparation of quinoline derivatives, however, utilise a component in a lower state of oxidation; *e.g.*, the processes of Graebe, Skraup, Doebner, Miller, and Beyer. Somewhat analogous methods have been used by Dilthey and his collaborators in the pyrylium series, but reactions of this type have not hitherto been employed for the synthesis of benzopyrylium salts.

Accordingly we made experiments to determine the conditions under which a reactive phenol could be condensed with an unsaturated aldehyde or ketone in acid solution and in the presence of an oxidising agent so as to yield a benzopyrylium salt. In the first place, we used resorcinol and unsaturated ketones of the aromatic series.

A German patent (D.R.-P. 357,755; Friedländer, 1921—5, XIV, 494) describes the condensation of resorcinol with benzylideneacetone but, under the conditions employed, the product, obtained in almost theoretical yield, is an amorphous solid which we were unable to convert into a benzopyrylium salt. There is no evidence for the improbable constitution suggested in this patent.



(I.)

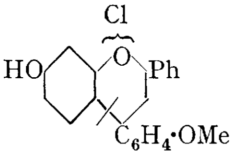
In our own experiments exploratory trials were made with benzylideneacetophenone, and eventually a good yield of 7-hydroxy-2 : 4-diphenylbenzopyrylium chloride (I) (prepared by Bülow and Sicherer, *Ber.*, 1901, **34**, 2373) was obtained by effecting the condensation in alcoholic hydrogen chloride solution and in the presence of chloranil. The general character of the reaction has been established under these conditions, but we have found in small-scale experiments that many variations are feasible and we are engaged in attempts to find a more economical and equally convenient oxidising agent.

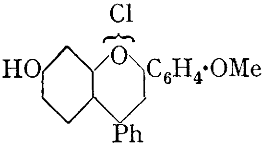
Obviously, this particular example can give no indication of the mechanism of the reaction, and, in order to determine whether the unsaturated carbon or the carbon of the carbonyl group becomes attached to the carbon of the resorcinol nucleus, we applied the method to anisylideneacetophenone and to benzylidene-*p*-methoxyacetophenone. These afforded 7-*hydroxy-2-phenyl-4-anisyl-* and 7-*hydroxy-4-phenyl-2-anisyl-benzopyrylium chlorides*, (II) and (III), respectively, each in homogeneous condition and possessing characteristic properties; this showed that the unsaturated ketones do not orient themselves in both of the possible ways, and also indicated that the method is likely to prove a useful accessory synthesis.

In explanation of the latter point, it may be added that benzoylanisoylmethane and resorcinol yield a mixture of salts which is very difficult to separate; even were this not the case and only one isomeride were formed, the new method has a clear advantage in that it gives us the power to synthesise either of the isomerides at will.

The constitutions of (II) and (III) follow from the fact that salts having the same properties are accessible respectively from 7-hydroxyflavone and anisylmagnesium bromide and from 7-hydroxy-4′-methoxyflavone (pratol) and phenylmagnesium bromide; (III) differs from (II) in showing intense green fluorescence in sulphuric acid solution.

(II.)



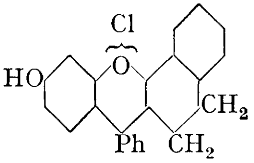


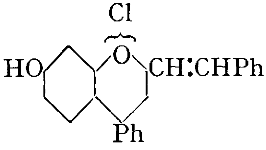
(III.)

On hydrolysis by means of boiling aqueous potassium hydroxide, (II) gave a mixture of acetophenone and *p*-methoxyacetophenone. This is evidently due to scission at the dotted line with formation of resorcinol (isolated) and benzoylanisoylmethane. The occurrence of a similar reaction in the case of certain umbelliferone derivatives has been established by Baker (J., 1925, **127**, 2349). The following examples suffice to illustrate the wide scope of the method, and further extensions are being made. 2-Benzylidene-1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene yields (IV), dibenzylideneacetone yields (V), dibenzylidene*cyclo*pentanone yields (VI), diveratrylidene*cyclo*hexanone yields (VII); furthermore, small-scale experiments have shown that the reaction succeeds with orcinol, naphtharesorcinol, and phloroglucinol as phenolic components, and with unsaturated ketone components containing substituted amino-groups with formation of intensely coloured basic dyes in suitable cases.

Betaines of fluorescein type may be obtained by the use of sulphonated or carboxylated intermediates.

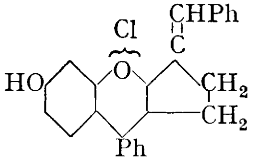
(IV.)

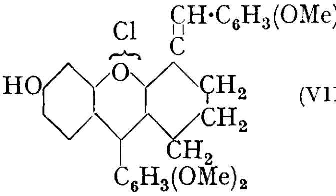




(V.)

(VI.)





(VII.)

EXPERIMENTAL.

Condensation of Resorcinol and Benzylideneacetone (G.P. 357,755).—A mixture of benzylideneacetone (5·8 g.) and glacial acetic acid (11 c.c.) was saturated with hydrogen chloride at room temperature, and resorcinol (5·2 g.) added. On gentle heating on the steam-bath, a dark brown solution was obtained, and when this was poured into water after 2 hours an orange solid was precipitated (yield, 10·9 g.); it could not be crystallised, and attempted oxidation, *e.g.*, with bromine water, gave no indications of the formation of a benzopyrylium salt.

By a similar procedure, benzylideneacetophenone (7·5 g.) furnished a bright red amorphous solid (yield, 10·8 g.), the acid filtrate from which was treated with an excess of sodium acetate, giving a crimson precipitate, which was collected, washed with water, and dried (0·2 g.). This gave a yellow solution with intense green fluorescence in sulphuric acid, and doubtless consisted of the anydronium base related to 7-hydroxy-2 : 4-diphenylbenzopyrylium chloride. The main product contained only traces of any pyrylium salt.

Oxidative Condensation of Resorcinol and Benzylideneacetophenone.—(A) A mixture of benzylideneacetophenone (4·2 g.), resorcinol (2·2 g.), anhydrous ferric chloride (10 g.), and ethyl-alcoholic hydrogen chloride (50 c.c. of 11—12%) was kept for 4 days and then poured into water. A large excess of sodium acetate was added to the solution, which was extracted with a mixture of ether and benzene. The extract was shaken with hydrochloric acid, and the precipitated pyrylium salt was collected and the solvent again applied to extract more quinone base from the deep red ferric acetate solution. This cycle was repeated, and the salt (0·7 g.) on examination proved to be crude 7-hydroxy-2 : 4-diphenylbenzopyrylium chloride, but the yield was inferior and the product impure.

(B) A mixture of benzylideneacetophenone (8·4 g.), resorcinol (4·4 g.), chloranil (9·8 g.), and ethyl-alcoholic hydrogen chloride (140 c.c. of 12%) was kept for 2 days at room temperature and ether (500 c.c.) was then added. The yellow-orange precipitate was well washed with ether, dried (yield, 15·5 g. of crude product, >100%), and extracted thoroughly with ether (Soxhlet). It was then crystallised twice from ethyl-alcoholic hydrogen chloride (4 vols. of 95% alcohol : 1 vol. of concentrated acid), separating as well-formed short prisms, which were dried in a vacuum over sulphuric acid (Found : Cl, 14·9%).

The solid was once more continuously extracted with ether and recrystallised from ethyl-alcoholic hydrogen chloride of somewhat lower concentration (7·5 vols. of 95% alcohol : 1·5 vols. of water : 1 vol. of 8% hydrochloric acid). The brownish-orange crystals effloresced to a light orange powder when dried in a vacuum over sulphuric acid. For analysis, they were dried over potassium hydroxide in a vacuum, forming a *monohydrate* (Found : C, 71·8; H, 5·1; Cl, 10·4. $C_{21}H_{15}O_2Cl,H_2O$ requires C, 71·5; H, 4·8; Cl, 10·1%).

Bülow and Sicherer (*loc. cit.*) describe a trihydrate of this salt (air-dried); it evidently loses $2H_2O$ in a vacuum desiccator. The substance is identical with the product of condensation of resorcinol and dibenzoylmethane. Its solution in sulphuric acid is pale greenish-yellow and exhibits an intense bluish-green fluorescence; on warming, the colour deepens slightly and the fluorescence is diminished (irreversible, see below). The fluorescence is diminished on dilution with 2 vols. of acetic acid, and discharged on dilution with water. The characteristic crystalline quinone-base was prepared.

7-*Hydroxy*-2-*phenyl*-4-*anisylbenzopyrylium Chloride* (II).—A heavy precipitate of microscopic needles separated from a mixture of anisylideneacetophenone (14·4 g.) (Kohler and Conant, *J. Amer. Chem. Soc.*, 1917, **39**, 1702), resorcinol (6·6 g.), chloranil (14·7 g.), and ethyl-alcoholic hydrogen chloride (250 c.c. of 12%). After 2 days at room temperature the solid was collected, washed with a little alcohol and much ether and dried (yield, 24 g. of crude material). After thorough extraction with ether (Soxhlet) (yield, 19·7 g.), a portion of the material was crystallised from glacial acetic acid–hydrochloric acid (9 : 1 by vol.), forming orange rectangular prisms; it was recrystallised in the same way and then dried over potassium hydroxide in a vacuum (Found : C, 67·1; H, 5·2; Cl, 8·2%). Again, when this material was recrystallised from 95% alcohol (4 vols.) and concentrated hydrochloric acid (1 vol.), orange needles separated (Found : Cl, 11·7%).

A portion was recrystallised twice in the same way (Found, in material dried in a vacuum over sulphuric acid and again over potassium hydroxide : Cl, 11·4%). These high values for chlorine content were at first attributed to chloranil contamination, but this is not the case, for they are due to the employment of too high a concentration of hydrogen chloride in the solvents. The replacement of a portion of the water of crystallisation by hydrogen chloride is a common phenomenon in the related anthocyanin group. Accordingly, the salt was recrystallised from 75% ethyl alcohol containing only 1% of hydrogen chloride, small orange needles being obtained (Found : C, 69·5; H, 5·0; Cl, 9·5. $C_{22}H_{17}O_3Cl,H_2O$ requires C, 69·0; H, 5·0; Cl, 9·3%). The benzene solution of the quinone-base is deep bluish-red in colour. The orange solution in acetic acid exhibits no fluorescence, and the characteristic behaviour in sulphuric acid is described below.

This salt (4 g.) was mixed with potassium hydroxide (7 g.) and water (5 c.c.), and the red solution was slowly steam-distilled for 4 hours. The ketones in the distillate were collected by ether, fractionated (0·6 g. of amber-coloured oil), and converted into semicarbazones. On recrystallisation from 95% alcohol, plates, m. p. 170—173° (softening and partial melting from 164°), were obtained [acetophenone semicarbazone, m. p. 198—203°; *p*-acetylanisole semicarbazone, m. p. 181—182° (?) and 195—198°] (Found: C, 59·7; H, 6·3; MeO, 10·3. Calc. for acetophenone semicarbazone, $C_9H_{11}ON_3$: C, 61·0; H, 6·2%. Calc. for acetylanisole semicarbazone, $C_{10}H_{13}O_2N_3$: C, 58·0; H, 6·3; MeO, 15·0%).

The steam-distillation still-residue was acidified, and extracted 7 times with ether. The extracts contained a substance which sublimed as white crystals (0·8 g.), m. p. 114°, possessing the properties of resorcinol (cf. Bülow and Sicherer, *loc. cit.*, p. 2376).

7-*Hydroxy*-4-*phenyl*-2-*anisylbenzopyrylium Chloride* (III).—Benzylidene-*p*-methoxyacetophenone (9·6 g.), resorcinol (4·4 g.), and chloranil (9·8 g.) were dissolved in alcohol (150 c.c.) containing *ca.* 12% of hydrogen chloride. After 2 days at room temperature, the *salt* was precipitated with ether (500 c.c.), collected, washed, and dried (yield, 13·1 g. of crude product). The bright orange, microcrystalline powder was extracted with ether (Soxhlet) for about 12 hours and then recrystallised twice from 85% alcohol containing 1% of hydrogen chloride, forming reddish-orange needles (Found, in material dried over sulphuric acid in a vacuum and then over potassium hydroxide: C, 72·5; H, 5·0; Cl, 9·7. $C_{22}H_{17}O_3Cl$ requires C, 72·4; H, 4·7; Cl, 9·7%). The yellow solution in sulphuric acid exhibited an immediate, intense yellow-green fluorescence; on heating, the colour was unaltered, but the fluorescence diminished and at a certain stage returned quickly and with a bluer shade. On cooling, the blue-green fluorescence was even more intense than the original. The fluorescence was not destroyed by 7-fold dilution with acetic acid but was hardly perceptible after dilution with 5 vols. of water. The yellow solutions in acetic acid or methyl alcohol exhibit a pronounced green fluorescence. The quinone-base closely resembles that from 7-hydroxy-2 : 4-diphenylbenzopyrylium chloride.

7-*Hydroxy*-2 : 4-*dianisylbenzopyrylium Chloride.*—The solution from anisylidene-*p*-methoxyacetophenone (5·4 g.) and half the quantities of other reagents described above quickly turned crimson, and a heavy crimson precipitate had separated after about 2 hours. After 12 hours, the salt was precipitated by means of ether (500 c.c.) and the terra-cotta-coloured powder was well washed with ether, dried (yield, 7·6 g.), and extracted for 12 hours with ether. Recrystallisation from absolute methyl alcohol containing 1% of hydrogen chloride gave fine reddish-orange needles (Found, in material dried as before: C, 67·1; H, 5·3; Cl, 8·8. $C_{23}H_{19}O_4Cl,H_2O$ requires C, 66·9; H, 5·1; Cl, 8·6%). This *salt* is sparingly soluble in the usual solvents for the class of compound. The orange solution in acetic acid exhibits a weak green fluorescence. The orange-yellow solution in sulphuric acid has a weak green fluorescence, which is almost discharged on warming, but reappears at its original intensity (but bluer-green in tone) on cooling. The quinone-base is bluish-crimson, pink in dilute benzene solution.

7-*Hydroxy*-4-*phenyl*-2-*styrylbenzopyrylium Chloride* (V).—Distyryl ketone (4·7 g.) was used with the quantities of reagents employed in the preceding preparation. The blood-red solution gradually became brownish-red, and after 2 days the product was precipitated, collected, washed (yield, 4 g.), and extracted as before (3·5 g.). The *salt* crystallised from 1% aqueous hydrochloric acid, in which it was very sparingly soluble, in brownish-orange, prismatic needles (Found: C, 69·8; H, 5·3; Cl, 9·2. $C_{23}H_{17}O_2Cl,2H_2O$ requires C, 69·6; H, 5·3; Cl, 8·8%). The intensely yellow solution in sulphuric acid exhibits bright yellow-green, and the orange solution in acetic acid a dull green, fluorescence. The solution in methyl alcohol is red and becomes yellow on addition of a trace of hydrochloric acid; it is non-fluorescent. The crimson colour-base dissolves sparingly in benzene to a permanganate-coloured solution.

7-*Hydroxy*-4-*phenyl*-1′-*benzylidene*-2 : 3-cyclo*penteno*(2′ : 3′)-*benzopyrylium Chloride* (VI).—Dibenzylidene*cyclo*pentanone (5·2 g.) was condensed under the conditions used above. The salmon-pink solution gradually became red and then purple, and much solid separated. After 3 days at room temperature, this was precipitated, washed, dried (6·8 g.), and extracted (Soxhlet; for 10 hours) as before, and then recrystallised from methyl alcohol—concentrated hydrochloric acid (7 : 3 by vol.) (Found, in a specimen dried in a vacuum over sulphuric acid: C, 74·4; H, 5·6; Cl, 8·9. $C_{25}H_{19}O_2Cl,H_2O$ requires C, 74·2; H, 5·2; Cl, 8·8%). The well-developed purple needles (green reflex) are very sparingly soluble in the usual solvents. The orange-red solution in acetic acid or in methyl alcohol exhibits yellowish-green fluorescence. The solution in sulphuric acid is orange-red with intense green fluorescence; on warming, the colour deepens and the fluorescence is almost discharged, returning to some extent on cooling. Addition of water diminishes the fluorescence, which is perceptible after 7-fold dilution. The quinone-base has a fine purple colour and is sparingly soluble in benzene.

6-*Hydroxy*-9-*phenyl*-1 : 2-*dihydro*-3 : 4-*benzoxanthylium Chloride* (IV).—Benzylidene-α-tetralone (4·6 g.) and resorcinol (2·2 g.) were condensed as before. The formation of pyrylium salt was detected within a few minutes by means of the fluorescence in sulphuric acid After $1\frac{1}{2}$ days the salt was precipitated with ether (500 c.c.), collected, and dried (yield, 4·2 g. of a yellow powder containing chloranil). The powdered solid was extracted with ether (Soxhlet; 30 hours), dried (yield, 2·0 g.), and crystallised from methyl alcohol containing 1% of hydrogen chloride, forming light orange balls of very fine needles (Found, in air-dried material: C, 76·6; H, 4·7; Cl, 10·0, 9·6. $C_{23}H_{17}O_2Cl$ requires C, 76·6; H, 4·7; Cl, 9·8%).

The orange-red solution in acetic acid exhibits a very feeble green fluorescence. The greenish-yellow solution in sulphuric acid has a very intense yellowish-green fluorescence; on heating, the solution becomes orange and the fluorescence is greatly weakened. The fluorescence persists on 10-fold dilution with acetic acid, but is destroyed on the addition of 2 vols. of water. The quinone-base resembles that from 7-hydroxy-2 : 4-diphenylbenzopyrylium chloride, but is a little bluer-red.

6-*Hydroxy*-9-*veratryl*-4-*veratrylidene*-1 : 2 : 3 : 4-*tetrahydroxanthylium Chloride* (VII).—A mixture of diveratrylidene*cyclo*hexanone (6·4 g.), resorcinol (1·6 g.), chloranil (3·2 g.), and saturated alcoholic hydrogen chloride (160 c.c.) was kept with frequent shaking for 12 hours, and a large volume of ether was then added. The solvent was decanted, the dark crimson residue mixed with very dilute hydrochloric acid, and the deep mauve-coloured solid collected, drained, and washed with benzene–anisole (1 : 1) until chloranil was removed; it was then washed with ether. The *substance* crystallised from a mixture of methyl alcohol (30 c.c.) and concentrated hydrochloric acid (4 c.c.) and then from 1% methyl-alcoholic hydrogen chloride in dark mauve-violet, microscopic prisms, almost black in mass and exhibiting a dull bronze reflex (Found: C, 66·2; H, 5·8; MeO, 22·4; Cl, 6·0. $C_{30}H_{29}O_6Cl,1{\cdot}5H_2O$ requires C, 65·8; H, 5·3; 4MeO, 22·7; Cl, 6·4%). The aqueous acid solutions of this salt, which is very sparingly soluble, are dull bluish-crimson and the alcoholic solutions are permanganate-coloured. The solution in sulphuric acid is mauve-red and non-fluorescent; on keeping, the shade becomes redder.

The colour-base forms a dark red-violet precipitate, and is sparingly soluble in the usual neutral organic solvents to intense dull mauve-crimson solutions.

Independent Syntheses of (II) *and* (III).—As already explained (p. 1436), the strikingly different properties of the two isomerides enabled us to determine their constitutions by qualitative synthesis.

Pure 7-hydroxyflavone was boiled with dry benzene (*ca.* 120 c.c.) (it is extremely sparingly soluble), and a large excess of anisylmagnesium bromide in ether (*ca.* 50 c.c.) was added, producing a light buff-coloured gelatinous precipitate. The mixture was heated on the steam-bath for about $\frac{1}{2}$ minute, and then decomposed with water; the red (quinone) colour passed into the benzene layer, which was separated and filtered. The aqueous layer was washed several times with ether, and the washings were filtered and added to the benzene extract. The solution of the quinone-base was shaken with 5% hydrochloric acid, and a yellow chloride was precipitated. The organic solvent was decanted, and the aqueous acid layer filtered through a small sintered-glass funnel. The pyrylium salt was extracted from the filter with boiling acetic acid (1 c.c.), and reprecipitated by the addition of ethereal hydrogen chloride. The salt was collected and its behaviour compared with that of the benzopyrylium salt from anisylidene-acetophenone and resorcinol (see p. 1437). Both substances dissolved in sulphuric acid to pale yellowish-green solutions without any initial fluorescence. On keeping, however, both solutions gradually developed green fluorescences at exactly the same rate and of precisely the same colour and intensity, the fluorescence ultimately becoming intense bluish-green.

Dilution with water destroyed the fluorescence. When an excess of sodium acetate was added, a pale yellowish-brown solution resulted, and *no* colour passed into benzene on extraction of this solution (due to sulphonation ?).

Dilution with acetic acid weakened the fluorescence, which was hardly perceptible after the addition of 4 vols. When the yellow fluorescent solutions were simultaneously strongly heated, the fluorescences disappeared at the same rate from both solutions, and on cooling, the fluorescences returned but not to the same extent as in the initial solutions; this alternation could be repeated.

In the above and other tests the specimens showed full identity of behaviour.

Similarly, 7-hydroxy-4′-methoxyflavone (pratol) and phenylmagnesium bromide furnished, after analogous treatment, an orange-yellow benzopyrylium salt, the behaviour of which in sulphuric acid tallied exactly with that of 7-hydroxy-4-phenyl-2-anisylbenzopyrylium chloride from benzylidene-*p*-methoxyacetophenone and resorcinol.

The authors thank the Carnegie Trust for the Universities of Scotland for a Research Fellowship (J. W.).

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July* 26*th*, 1934.]