69. *A New Synthesis of Benzopyrylium Salts.*

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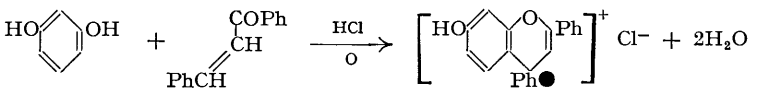
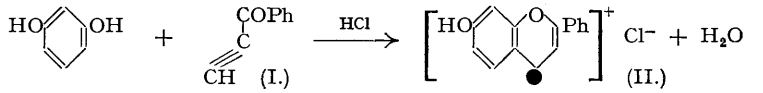
Benzopyrylium salts including flavylium salts and some pyrylium salts are synthesised by a new reaction which consists of the interaction of phenols with ethynyl ketones in the presence of acids. The general nature of the reaction is illustrated by the use of resorcinol, *m*-methoxyphenol, pyrogallol, phloroglucinol, β-naphthol, 2-hydroxycarbazole, 6-ethoxythioindoxyl, phenol, *p*-cresol, and *p*-methoxyphenol with phenyl ethynyl ketone, *m*-methoxyphenyl ethynyl ketone, and methyl ethynyl ketone.

The condensation reactions of β-diketo-compounds, $R{\cdot}CO{\cdot}CH_2{\cdot}COR'$, involving both of the keto-groups with the elimination of water can often be carried out equally well with the αβ-acetylenic carbonyl compounds, $R{\cdot}CO{\cdot}C{:}CR'$ (or $R{\cdot}C{:}C{\cdot}COR'$). Thus, these compounds with hydrazines give pyrazole derivatives, with hydroxylamine give *iso*oxazole derivatives, and with amidines, guanidines, or urea give pyrimidines. β-Keto-acids and their derivatives often behave similarly to the corresponding αβ-acetylenic acids. Also, the αβ-acetylenic compounds can be employed in reactions which are normally carried out with the corresponding ethylenic compounds in the presence of an oxidising agent, *e.g.*, many of the well-known quinoline syntheses. Thus, by analogy, further reactions of the αβ-acetylenic compounds can often be predicted.

Benzopyrylium salts (Hill, *Chem. Reviews*, 1936, **19**, 27) have been obtained by the condensation of β-diketones or β-keto-aldehydes with reactive phenols (von Bülow *et al.*, *Ber.*, 1901, **34**, 1189, 1782, 2368, 3889, 3916; Hill, *loc. cit.*) and by the condensation of αβ-ethylenic ketones with reactive phenols in the presence of an oxidising agent such as chloranil (Robinson and Walker, *J.*, 1934, 1435; 1935, 941), *e.g.* :



It therefore appeared probable that benzopyrylium salts would be obtained from the reaction of αβ-ethynyl ketones and phenols in the presence of acids; *e.g.*, resorcinol and phenyl ethynyl ketone (I) should yield 7-hydroxyflavylium (7-hydroxy-2-phenylbenzopyrylium) (II) salts :

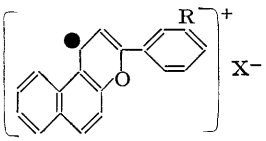
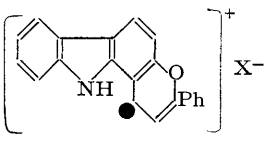


The probability that benzopyrylium salts would be obtained in this way was supported by an observation by Kalff (*Rec. Trav. chim.*, 1927, **46**, 594) who mentioned that the reaction of phenylpropiolic aldehyde with resorcinol in ethereal or glacial acetic acid solution in the presence of a trace of hydrogen chloride gave a bright red solution, although he did not identify any product.

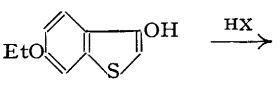
This probability has now been examined experimentally and as a result a useful method for the production of benzopyrylium salts has been elaborated.

αβ-Ethynyl ketones (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) have been brought into reaction with phenols in ethereal or preferably glacial acetic acid solution in the presence of mineral acids to give benzopyrylium salts in excellent yields (flavylium salts were obtained from aryl ethynyl ketones and monocyclic phenols). In the early experiments hydrogen chloride was used as the mineral acid, but it was later found that the use of concentrated sulphuric acid was more convenient. In the procedure usually adopted the reactants were dissolved in glacial acetic acid and sulphuric acid was added; after 24 hours the crystalline benzopyrylium sulphate had usually separated but, if not, it was precipitated by the addition of dry ether. The sulphate could be converted into the chloride by crystallisation from dilute hydrochloric acid. Perchlorates and ferrichlorides were prepared from the chlorides for analytical purposes, since these salts give better analyses than the chlorides and more commonly have characteristic melting points.

The phenolic component was first shown to be variable within the usual limits of the term " reactive " phenol, and benzopyrylium salts have been obtained by the reaction of phenyl ethynyl ketone and the following phenols: resorcinol, *m*-methoxyphenol, pyrogallol, and phloroglucinol, to give 7-hydroxy-, 7-methoxy-, 7 : 8-*dihydroxy*- and 5 : 7-dihydroxy-flavylium salts, and with β-naphthol and 2-hydroxycarbazole to give 2-phenyl-β-naphthopyrylium (III; R = H) and 2-*phenylcarbazolo*(1′ : 2′ : 5 : 6)*pyrylium* (IV) salts respectively.

(III.)  (IV.) 

The interaction of phloroglucinol and phenyl ethynyl ketone is undoubtedly the most convenient method of synthesising 5 : 7-dihydroxyflavylium (chrysinidin) salts yet described. m-*Methoxyphenyl ethynyl ketone* and β-naphthol reacted to give 2-(3′-*methoxyphenyl*)-β-*naphthopyrylium* (III; R = OMe) salts, and methyl ethynyl ketone and β-naphthol reacted to give 2-methyl-β-naphthopyrylium salts. 6-Ethoxythioindoxyl reacted with phenyl ethynyl ketone in the presence of acids to give 2-*phenyl*-6′-*ethoxythionaphtheno*(2′ : 3′ : 5 : 6)*pyrylium* (V) salts, the 6-ethoxythioindoxyl presumably reacting in the enol form (VI) :

(VI.)  (V.)

No pyrylium salts have been isolated, when using the reaction conditions described, from phenyl ethynyl ketone and phenol, *m*-cresol, or thio-*p*-cresol, nor was there any reaction with the following " active " methylene compounds: 1-phenyl-3-methyl-5-pyrazolone, *N*-propyloxindole, 1 : 3-dihydroxy*iso*quinoline, 1 : 3-diketohydrindene, or 7-chloro-3-keto-5-methyl-2 : 3-dihydro-1 : 4-benzthiazine. Immediate deep red colourations were obtained in the reactions of phenyl ethynyl ketone with quinol, *m*-diethylaminophenol, and α-naphthol in acetic acid in the presence of sulphuric acid, although no products were isolated.

Although flavylium chloride itself cannot be prepared by the reaction of salicylaldehyde and acetophenone in the presence of hydrogen chloride, flavylium perchlorate can readily be prepared from these reactants in the presence of perchloric acid (Löwenbein and Rosenbaum, *Annalen*, 1926, **448**, 242). Similarly, benzopyrylium salts have been obtained from some apparently inoperable phenols by effecting the reaction with perchloric acid or with a solution of ferric chloride in hydrochloric acid as the condensing system. Thus, phenol and phenyl ethynyl ketone in the presence of a solution of ferric chloride in hydrochloric acid slowly reacted to give flavylium ferrichloride. The yield of flavylium ferrichloride was poor, possibly owing to simultaneous *p*-substitution of the phenol, since from *p*-cresol under similar conditions a high yield of 6-*methylflavylium ferrichloride* was rapidly obtained. It has also been shown that *p*-methoxyphenol and phenyl ethynyl ketone in the presence of acids give 6-methoxyflavylium salts. These later results show that the new reaction of ethynyl ketones can be used with phenols other than " reactive " phenols.

In order to demonstrate the identity of the benzopyrylium salts obtained by the new reaction, a number have been compared with the products of condensation of the appropriate

o-hydroxy-aldehyde and acetophenone by the conventional method (Perkin, Robinson, and Turner, *J.*, 1908, **93**, 1085; Hill, *loc. cit.*) [*e.g.*, 2 : 4-dihydroxybenzaldehyde and acetophenone in the presence of hydrogen chloride give (II)]. Identity has thus been established for the 7-hydroxy-, 7 : 8-dihydroxy-, and 6- and 7-methoxy-flavylium salts and for the 2-phenyl-β-naphthopyrylium salts.

All the benzopyrylium salts from the ethynyl ketones were pure compounds usually obtained in high yields, and there were no indications of the formation of mixtures of salts, such as are often formed by the von Bülow method (Hill, *loc. cit.*) or may be formed by the Perkin method (Hill and Melhuish, *J.*, 1935, 88). The new method cannot be used for the synthesis of 3-substituted flavylium salts, however, which include most of the naturally occurring anthocyanins.

Experimental.

M. p.'s are uncorrected. In all crystallisations of benzopyrylium salts, the suspension of the salts in the solvent was heated slowly, preferably on the steam-bath, as many of the salts were easily decomposed by heat.

The "ferric chloride solution" referred to throughout this paper was prepared by dissolving anhydrous ferric chloride (100 g.) in concentrated hydrochloric acid (150 c.c.).

2-*Phenyl-β-naphthopyrylium Chloride.*—(*a*) Dry hydrogen chloride was passed into a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in acetic acid (10 c.c.) for 1 hour and the mixture left overnight. 2-Phenyl-β-naphthopyrylium chloride (0·8 g.) separated as long orange needles and was crystallised from 3% hydrochloric acid. The product had m. p. 133—134° alone and mixed with an authentic specimen prepared by the condensation of 2-hydroxy-1-naphthaldehyde and acetophenone in the presence of hydrogen chloride (Kondo and Segawa, *J. Pharm. Soc. Japan*, 1931, **51**, 859, give m. p. 135°; Russell and Speck, *J. Amer. Chem. Soc.*, 1941, **63**, 851, give m. p. 118°). The product dissolved in concentrated sulphuric acid to give a yellow solution with a strong fluorescence. A flocculent red precipitate was obtained on addition of alkali to an aqueous solution of the chloride.

(*b*) Concentrated sulphuric acid (1 c.c.) was added to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). The solution became deep red and a crystalline solid separated after 1 minute. Next day, the solid was separated and crystallised from 3% hydrochloric acid (75 c.c.). A further quantity was obtained from the acetic acid mother liquors by dilution with dry ether (30 c.c.). 2-Phenyl-β-naphthopyrylium chloride (1·1 g.), m. p. 132—133°, was obtained as orange needles. The ferrichloride formed orange-red needles from acetic acid, m. p. 188° alone and mixed with an authentic specimen (Decker and Fellenberg, *Annalen*, 1907, **364**, 42, give m. p. 187·5°). The *perchlorate* formed orange needles from acetic acid, m. p. 245° alone and mixed with a specimen prepared from authentic 2-phenyl-β-naphthopyrylium chloride (Found: C, 63·8; H, 3·9; Cl, 9·8. $C_{19}H_{13}O_5Cl$ requires C, 63·95; H, 3·65; Cl, 9·95%).

(*c*) 2-Phenyl-β-naphthopyrylium ferrichloride (1·4 g.) was also obtained by the addition of ferric chloride solution (5 c.c.) to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The perchlorate (1·0 g.) was obtained similarly by the addition of 70% perchloric acid (1 c.c.) to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.).

2-*Methyl-β-naphthopyrylium Ferrichloride.*—Ferric chloride solution (3 c.c.) was added to a solution of β-naphthol (0·5 g.) and methyl ethynyl ketone (0·25 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in acetic acid (5 c.c.). A crystalline solid was rapidly formed, and next day the solid was separated and crystallised from acetic acid. The *ferrichloride* was thus obtained as pale green needles (0·75 g.), m. p. 141—143° (Found: Cl, 35·7. $C_{14}H_{11}OCl_4Fe$ requires Cl, 36·1%).

m-*Methoxyphenylethynylcarbinol.*—Purified acetylene was rapidly passed into liquid ammonia (1000 c.c.) with stirring and cooling, and sodium (17 g.) added in small pieces in such a manner that the blue colour never persisted for more than a few seconds. A solution of *m*-methoxybenzaldehyde (92 g.) in ether (100 c.c.) was then added during 1 hour and the mixture was stirred and cooled for a further 3 hours with continued passage of acetylene. The ammonia was allowed to evaporate overnight, and ether and cold dilute hydrochloric acid were added to the residue with stirring. The ethereal layer was separated and repeatedly washed with sodium hydrogen carbonate solution in order to remove the *m*-methoxybenzoic acid formed by the simultaneous Cannizzaro reaction. The solution was dried and the ether removed; fractionation of the residue gave the *carbinol* as a pale yellow oil, b. p. 103°/3 mm. (Found: C, 73·8; H, 6·0. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%). The carbinol readily gave a white insoluble silver derivative with ammoniacal silver nitrate.

m-*Methoxyphenyl Ethynyl Ketone.*—To a stirred solution of *m*-methoxyphenylethynylcarbinol (38 g.) in acetone (50 c.c.) a solution of chromium trioxide (21 g.) in water (67 c.c.) and concentrated sulphuric acid (18 c.c.) was slowly added in an atmosphere of nitrogen. The addition lasted one hour and the temperature of the reaction mixture was kept at 10—15° by external cooling. After being stirred for a further 30 minutes the mixture was diluted with water and the product extracted with ether. Evaporation of the ether gave a dark yellow oil which was distilled to give the *ketone* as a pale yellow oil, b. p. 92—93°/1 mm., which solidified on cooling and was crystallised from light petroleum (b. p. 60—80°); it then had m. p. 15—16° (Found: C, 74·8; H, 4·9. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%).

2-m-*Methoxyphenyl-β-naphthopyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of β-naphthol (0·5 g.) and *m*-methoxyphenyl ethynyl ketone (0·55 g.) in acetic acid (10 c.c.). After 2 days the deep red solution was diluted with ether and the precipitated salt crystallised from dilute hydrochloric acid (80 c.c.). It was thus obtained as small red prisms, m. p. 124—125° (1·03 g.). The *ferrichloride*, m. p. 178—179°, formed orange needles from acetic acid (Found: C, 49·35; H, 3·3; Cl, 29·15. $C_{20}H_{15}O_2Cl_4Fe$ requires C, 49·5; H, 3·1; Cl, 29·3%). The *perchlorate*, m. p. 210—211°, formed

small brown needles from acetic acid (Found : C, 62·1; H, 4·0; Cl, 9·2. $C_{20}H_{15}O_6Cl$ requires C, 62·1; H, 3·9; Cl, 9·2%). The ferrichloride (1·5 g.) and perchlorate (1·05 g.) were also obtained from the reaction of β-naphthol (0·5 g.) and *m*-methoxyphenyl ethynyl ketone (0·55 g.) in the presence of ferric chloride solution (3 c.c.) or 70% perchloric acid (1 c.c.) respectively.

7 : 8-*Dihydroxyflavylium Chloride.*—(*a*) Concentrated sulphuric acid (5 c.c.) was added to a solution of 2 : 3 : 4-trihydroxybenzaldehyde (1·54 g.) and acetophenone (1·2 g.) in acetic acid (20 c.c.). Crystals slowly separated from the dark red solution, and next day the whole was poured into dry ether. The deep purple-red salt which separated was washed with ether, collected (2·35 g.), and crystallised by dissolving in hot 3% hydrochloric acid (500 c.c.) and then adding concentrated hydrochloric acid (85 c.c.). The salt (1·65 g.) crystallised slowly as permanganate-coloured rods, m. p. 236—237° (decomp.). Its alcoholic solution acquired a deep blue colouration on the addition of sodium carbonate solution. The *perchlorate*, m. p. 223—224°, formed dark reddish-brown prisms from acetic acid (Found : C, 53·1; H, 3·35; Cl, 10·8. $C_{15}H_{11}O_7Cl$ requires C, 53·2; H, 3·25; Cl, 10·5%).

(*b*) Concentrated sulphuric acid (0·5 c.c.) was added to a solution of pyrogallol (0·3 g.) and phenyl ethynyl ketone (0·3 g.) in acetic acid (5 c.c.). The dark red solution solidified almost completely after 1 hour at room temperature. Next day, the solid was crystallised as in the previous experiment to yield 7 : 8-dihydroxyflavylium chloride (0·5 g.), m. p. 236—237° (decomp.). The corresponding perchlorate had m. p. 223—224° alone and mixed with the specimen obtained in the previous condensation.

5 : 7-*Dihydroxyflavylium Chloride* (*Chrysinidin Chloride*).—Concentrated sulphuric acid (1·0 c.c.) was added to a solution of phloroglucinol (1·0 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). A deep red colouration was produced and a red precipitate formed almost immediately. Next day, the precipitate was separated and extracted with 0·5% hydrochloric acid (3 × 250 c.c.); 5 : 7-dihydroxyflavylium chloride was thus obtained as small red needles (0·8 g.), m. p. > 250° (cf. Pratt, Robertson, and Robinson, *J.*, 1927, 1975). A considerable amount of insoluble red material remained after this extraction. The corresponding perchlorate formed reddish-brown platelets from acetic acid, m. p. 243—244° (Pratt, Robertson, and Robinson, *loc. cit.*, give m. p. 244°).

7-*Hydroxyflavylium Chloride.*—Concentrated sulphuric acid (1·0 c.c.) was added to a solution of resorcinol (0·9 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). The dark red solution was kept at room temperature for 4 days after which time a considerable amount of crystalline material had formed. This was separated and a further amount obtained by the addition of dry ether (50 c.c.) to the filtrate. The combined solids were recrystallised from 7% hydrochloric acid, and 7-hydroxyflavylium chloride was thus obtained as red-brown needles, m. p. > 260° (Perkin, Robinson, and Turner, *loc. cit.*, say the m. p. is indefinite. The value given by Bülow and Sicherer, *Ber.*, 1901, **34**, 3889, m. p. 152—153°, has not been confirmed by later workers). The corresponding *ferrichloride* was obtained as orange-red needles and, after crystallisation from acetic acid, had m. p. 166—167°; it caused sneezing, and was stable in air (Found : C, 42·95; H, 2·7; Cl, 33·7. $C_{15}H_{11}O_2Cl_4Fe$ requires C, 42·65; H, 2·85; Cl, 33·65%). The *perchlorate*, m. p. 220—221°, alone and mixed with a specimen prepared from authentic 7-hydroxyflavylium chloride, formed orange plates from acetic acid (Found : C, 55·8; H, 3·7; Cl, 10·85. $C_{15}H_{11}O_6Cl$ requires C, 55·64; H, 3·7; Cl, 10·95%).

7-*Methoxyflavylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of *m*-methoxyphenol (1·0 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). The deep red solution was kept at room temperature for two days, and the product was precipitated by the addition of dry ether (100 c.c.). The solid was separated and crystallised from 7% hydrochloric acid; 7-methoxyflavylium chloride was thus obtained as deep orange needles, m. p. 96—97° (Robinson and Crabtree, *J.*, 1918, **113**, 877, give m. p. 102—103°; Row and Seshadri, *Proc. Indian Acad. Sci.*, 1941, **13**, *A*, 510, give m. p. 105—106°). The yellow solution of the chloride in dilute hydrochloric acid showed a bright green fluorescence. The corresponding ferrichloride formed golden-brown needles from acetic acid, m. p. 150—151°; mixed m. p. with an authentic specimen, 149—150° (Hill, *J.*, 1935, 85, gives m. p. 147°). The *perchlorate*, m. p. 222—223°, alone and mixed with a specimen prepared from authentic chloride, formed pale yellow plates from acetic acid in which it dissolves with a deep green fluorescence (Found : C, 57·0; H, 4·4; Cl, 10·85. $C_{16}H_{13}O_6Cl$ requires C, 56·7; H, 4·15; Cl, 10·75%).

2-*Phenylcarbazolo*(1′ : 2′ : 5 : 6)*pyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of 2-hydroxycarbazole (0·6 g.; m. p. 272—273°) and phenyl ethynyl ketone (0·4 g.) in acetic acid (40 c.c.). A solid was rapidly precipitated from the dark red solution. After 2 days at room temperature, dry ether (100 c.c.) was added to the mixture and the solid separated and crystallised from 3% hydrochloric acid (2,500 c.c.). The chloride (0·7 g.) was obtained as a dark brown crystalline product which did not melt below 270°. The *ferrichloride* formed small dark red crystals, m. p. 235—236°, from acetic acid (Found : C, 50·6; H, 2·95. $C_{21}H_{14}ONCl_4Fe$ requires C, 51·0; H, 2·8%). The *perchlorate* formed black micro-crystals with a metallic lustre, m. p. 267—268°, from acetic acid (Found : C, 63·4; H, 3·2. $C_{21}H_{14}O_5NCl$ requires C, 63·7; H, 3·5%).

2-*Phenyl*-6′-*ethoxythionaphtheno*(2′ : 3′ : 5 : 6)*pyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of 6-ethoxythioindoxyl (0·75 g.; m. p. 122°) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). The dark red solution was kept overnight and then, after the addition of dry ether (100 c.c.), the precipitate was separated and crystallised from 3% hydrochloric acid. The chloride was thus obtained as a pale brown amorphous solid which was very susceptible to heat. The *ferrichloride* formed red needles, m. p. 170—171°, from acetic acid (Found : C, 44·7; H, 2·7; Cl, 28·1. $C_{18}H_{15}O_2Cl_4SFe$ requires C, 45·1; H, 3·0; Cl, 28·1%). The *perchlorate* formed small brown prisms, m. p. 231—233°, from acetic acid (Found : C, 56·2; H, 3·1. $C_{19}H_{15}O_6ClS$ requires C, 56·1; H, 2·7%).

6-*Methylflavylium Ferrichloride.*—Ferric chloride solution (3 c.c.) was added to a solution of *p*-cresol (0·4 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The dark yellow solution soon deposited a crystalline product. Next day this was separated and crystallised from acetic acid; 6-*methylflavylium ferrichloride* (0·7 g.) was thus obtained as long yellow needles, m. p. 171—172° (Found : C, 46·2; H, 3·4; Cl, 34·0. $C_{16}H_{13}OCl_4Fe$ requires C, 45·8; H, 3·1; Cl, 33·9%).

6-*Methoxyflavylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of *p*-methoxyphenol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). No precipitate

separated from the dark brown solution after 2 days at room temperature. The flavylium salt was precipitated with dry ether (30 c.c.) and crystallised from 7% hydrochloric acid; 6-methoxyflavylium chloride (0·5 g.) was thus obtained as dark brown needles, m. p. 95—96° (Irvine and Robinson, *J.*, 1927, 2086, give m. p. 97°). The corresponding ferrichloride, m. p. 202—203° (Irvine and Robinson, *loc. cit.*, give m. p. 203°), formed brown platelets from acetic acid. The ferrichloride (1·1 g.) was also obtained by the addition of ferric chloride solution (3 c.c.) to a solution of *p*-methoxyphenol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The precipitated product was separated and crystallised from acetic acid.

Flavylium Ferrichloride.—Ferric chloride solution (3 c.c.) was added to a solution of phenol (0·35 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). After 3 days at room temperature the crystalline product (0·1 g.) was separated and crystallised from acetic acid; flavylium ferrichloride was thus obtained as long yellow needles, m. p. 138—139° (Hill *et al.*, *J.*, 1935, 85; 1937, 41, give m. p. 140°).

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