274. *The Structure of Flavylium Salts.*

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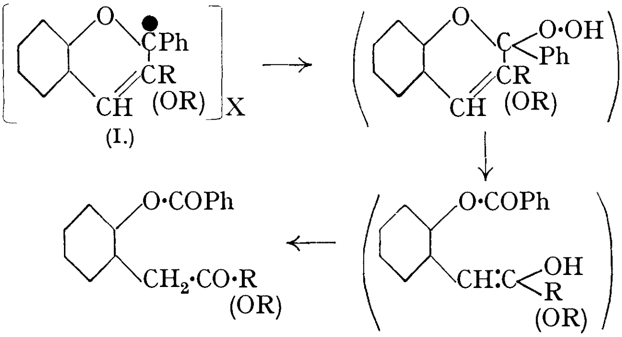
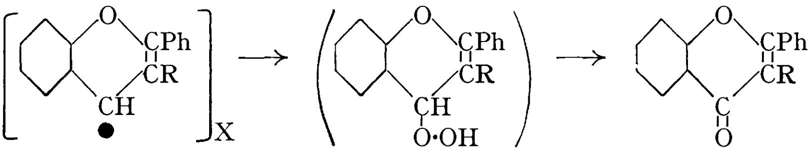
THE skeleton of the benzopyrylium salts and the related pyrylium and xanthylium salts has long been established, but the exact structure of the pyrone ring and the mode of attachment of the acid radical have given rise to much speculation and several different formulæ have been proposed. The latest is Dilthey's "Carbenium" formula, based upon a general theory of the relationship between structure and colour suggested by Dilthey and Wizinger (see Wizinger, "Organische Farbstoffe," Bonn, **1933**). According to this formula, the anion is linked to the pyrone ring at an ionised co-ordinatively unsaturated carbon atom, the heteropolar atom being indicated as in formula (I) by a point. Before the introduction of this formula a centric carbonium formula, in which no attempt was made to define the point of attachment of the acid, had come into general use. Quint and Dilthey (*Ber.*, **1931**, **64**, 2082), however, showed that in neutral or acid solution, xanthylium salts were oxidised by perhydrol, which first attacked the heteropolar atom with the formation of a peroxide, and by this means established that in these salts the *meso*-carbon was the heteropolar atom. When the reaction was applied by Dilthey and Quint (*J. pr. Chem.*, **1931**, **131**, 1) and Dilthey and Hoeschen (*ibid.*, **1933**, **138**, 42) to 3-substituted flavylium salts, the peroxide formed was unstable, and oxidation proceeded further with the production of benzoyl esters of *o*-hydroxybenzyl ketones (or *o*-hydroxyphenylacetic acid) according to the following scheme, which shows conclusively that the double linkage in these salts is in the 3 : 4-position and that the 2-carbon is the heteropolar atom.


(I.)

Had the 4-carbon atom, for example, been the heteropolar atom, the oxidation must have produced flavones :



The complete absence of the formation of flavones in their experiments led Dilthey and Hoeschen (*loc. cit.*) to conclude that, when localisable, the heteropolar atom in flavylium salts is the 2-carbon.

Indications are not lacking in previous work that attachment of the anion may also take place at other points, and it has already been suggested by one of us (this vol., p. 85) that, in some instances, the 4-carbon may be the heteropolar atom. We have now clearly established the formation of two distinct series of pyranols derived from two types of flavylium salts, one of which we have also succeeded in converting into the corresponding flavones.

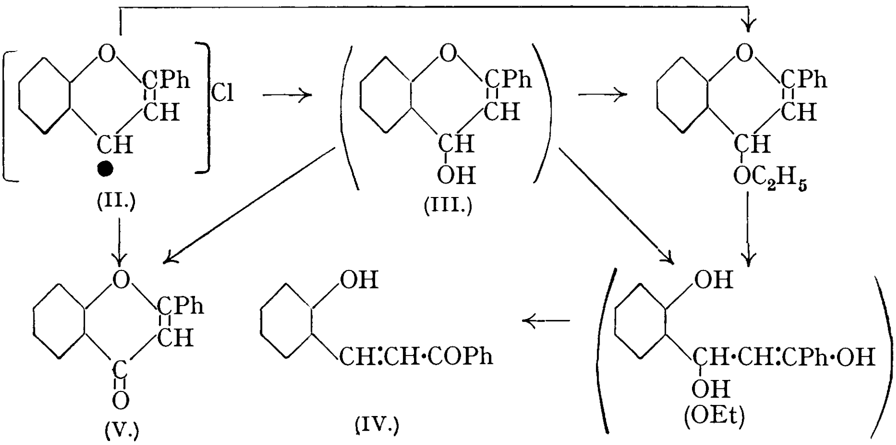
Prolonged treatment of 6-methoxy-, 7-methoxy-, 4′-methoxy-, and β-naphtha-flavylium chlorides and unsubstituted flavylium chloride itself with sodium carbonate or sodium hydroxide solution at room temperature led to a mixture of products from which the corresponding chalkones and flavones were isolated in each case. The isolation of the flavones was accomplished by taking advantage of an observation made in the course of the work that insoluble double compounds are formed with calcium chloride. Thus, a glacial acetic acid solution of flavone on treatment with a saturated solution of calcium chloride in hydrochloric acid deposited, on standing, long colourless needles of the flavone–calcium chloride double salt. Applying this to ethereal solutions, it was found that both flavone itself and pentamethylquercetin could be removed quantitatively from the solution, and subsequently recovered by decomposition of the double salt with water.

Treatment of the reaction mixture in the above experiments with ether, therefore, extracted everything but the chalkones, which remained dissolved in the aqueous alkaline solution and were recovered therefrom on acidification. The flavones were separated by simple drying of the ethereal solutions over calcium chloride, which simultaneously removed them as double salts. The ether was then filtered and the flavones regenerated as above. A considerable quantity of material remained in the ether; it could not be purified but is believed to consist largely of impure pyranols, although their instability prevented their isolation (see below). Naturally, in view of the number of easily formed by-products, the yield of flavones was low, usually in the neighbourhood of 10%. In spite of this low yield, we have never failed in the course of a great many experiments, carried out under various conditions, to obtain flavones from these compounds.

The same procedure applied to flavylium salts with a substituent in the 3-position led only to the production of pyranols, with no indication whatever of flavone formation (cf. Dilthey and Hoeschen, *loc. cit.*). In view of the success attending the isolation of flavones in the former cases, and of the fact that the calcium chloride method is capable of separating quantities of flavone as low as 0·02—0·03 g., there can be no doubt that flavones are not produced from 3-substituted flavylium salts.

The explanation of this difference in behaviour is to be found in the properties of the pyranols derived from these two series of salts. Flavylium salts unsubstituted in position 3 could not be induced to yield simple pyranols on account of their great instability. They were, however, isolated as their ethyl ethers by the action of sodium hydroxide in alcohol at low temperatures. Even this was attended by considerable difficulty, and close attention must be paid to the experimental conditions. The ethers were spontaneously converted into salts in the presence of acids and must be preserved in an atmosphere completely free from acid. Their most characteristic property is that, although comparatively stable in absolute alcohol, they are invariably converted quantitatively in hot aqueous alcohol into the corresponding chalkones. The 3-substituted flavylium salts, on the other hand, were readily converted into the free pyranols by sodium acetate or sodium hydroxide, and the pyranols were converted into their ethyl ethers on boiling in alcohol. Neither the free pyranols nor the ethyl ethers were decomposed by prolonged boiling in dilute alcohol. It is evident, therefore, that the two series of pyranols are fundamentally different, and this difference must also be exhibited by the salts from which they are derived.

The formation of flavones from salts unsubstituted in position 3 is sufficient evidence that they are flavylium 4-chlorides and the instability of the pyranols obtained from them leads to the following scheme of the changes involved:



The chloride (II) is first hydrolysed to the unstable pyranol (III), which is then partly further hydrolysed to chalkone (IV), by opening of the pyrone ring, and partly oxidised to flavone (V).

The salts from which stable pyranols were obtained are those which Dilthey and his collaborators have already shown to be flavylium 2-chlorides and it is apparent that they cannot undergo the reactions outlined above.

EXPERIMENTAL.

2-*Phenylbenzopyranol* 4-*Ethyl Ether*.—Freshly prepared flavylium chloride (from 5 g. of chalkone) was dissolved in alcohol (100 c.c.), and 10% sodium hydroxide solution (50 c.c.) added. The clear, orange-coloured solution was kept for 24 hours, during which a colourless crystalline solid was deposited. This was collected, washed with alcohol, and twice crystallised from light petroleum (b. p. 40—60°). It separated as large colourless cubes (3·4 g.); m. p. 76° (Found: C, 80·9; H, 6·4; OEt, 18·5. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·3; OEt, 17·9%). Acidification of the mother-liquors gave a small quantity of chalkone (0·6 g.).

The foregoing *ether* is unstable, and must be kept in an acid-free atmosphere. It dissolves in hydrochloric or glacial acetic acid to deep yellow solutions from which flavylium ferrichloride and perchlorate were obtained on addition of ferric chloride and perchloric acid respectively. It may be crystallised unchanged from absolute alcohol, but on refluxing with 50% alcohol (0·5 g. in 200 c.c.) for 3 hours the solution became yellow, and on cooling it deposited a quantitative yield of chalkone as a mass of fine yellow needles (m. p. and mixed m. p. 153°).

4′-*Methoxy*-2-*phenylbenzopyranol* 4-*Ethyl Ether*.—4′-Methoxychalkone was converted into the flavylium chloride in the usual way and treated as described above. After standing in the ice-chest for 24 hours, a pale yellow oil had separated. This could not be crystallised, so was washed with water by decantation and taken up in ether. The ethereal solution was placed over solid potassium hydroxide for several days, then filtered from a small quantity of reddish-brown solid, and the ether removed at room temperature. The residual oil now solidified readily, and was twice crystallised from absolute alcohol, being obtained as long flat colourless plates (2·3 g.), m. p. 86° (Found: C, 76·84; H, 6·4; OEt + OMe, 26·7. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4; OEt + OMe, 27·0%).

The *ether* resembled the preceding one in solubilities, and afforded 4′-methoxyflavylium ferrichloride as orange-red needles, m. p. and mixed m. p. 155—156°. Refluxed for 30 minutes with 33% alcohol (0·5 g. in 300 c.c.), it was converted into 4′-methoxychalkone (0·4 g.), m. p. and mixed m. p. 147°.

2-*Phenylnaphthapyranol* 4-*Ethyl Ether*.—Naphthaflavylium chloride (5 g.) was treated as described previously. The colourless needles which separated from the cold alkaline alcoholic solution were twice recrystallised from light petroleum (b. p. 40—60°); slender colourless needles (2·6 g.), m. p. 131—133° (Found: C, 83·7; H, 5·9; OEt, 15·2. $C_{21}H_{18}O_2$ requires C, 83·4; H, 6·0; OEt, 14·9%). The *ether* is soluble in acids and affords on refluxing with 50% alcohol for 30 minutes a quantitative yield of 2-*hydroxynaphthylideneacetophenone*, which separates from alcohol as deep yellow, small needles; m. p. 143—144° (Found: C, 83·0; H, 5·1. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

6-Methoxy- and 7-methoxy-flavylium chlorides when treated with alcoholic alkali in the above manner gave oils which could not be crystallised. In common with the other members of this series, they are easily converted into the corresponding chalkones by refluxing with dilute alcohol.

2-*Phenyl*-3-*methylbenzopyranol* 2-*Ethyl Ether*.—3-Methylflavylium chloride (12·7 g.) was covered with alcohol (100 c.c.), and potassium hydroxide solution added. The colourless oil which separated was only induced to solidify after standing for some days in ethereal solution over solid potassium hydroxide. It was crystallised from absolute alcohol and separated as large colourless needles, m. p. 44° (Found: C, 81·4; H, 6·8; OEt, 16·6. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8; OEt, 16·9%).

2 : 3-*Diphenylbenzo*-2-*pyranol*.—3-Phenylflavylium perchlorate (11·5 g.) was boiled with sodium acetate solution (23 g. in 100 c.c. water) until the brown oil which separated had solidified. The solid was filtered off, powdered, and reboiled until it became colourless. Recrystallised from benzene–light petroleum and finally from petroleum (b. p. 40—60°), it separated as colourless rectangles (8·5 g.), m. p. 125—126° (Found: C, 84·25; H, 5·3. Calc. for $C_{21}H_{16}O_2$: C, 84·0; H, 5·3%) (Decker and Fellenberg, *Annalen*, 1909, **364**, 35, give m. p. 121—122°). The pyranol is soluble in acids and readily yields flavylium salts. When refluxed with alcohol (5 g. in

100 c.c.) for 1 hour, it was quantitatively converted into the *ethyl ether*, which separated from light petroleum (b. p. 40—60°) as a colourless solid. For analysis it was twice crystallised from alcohol and obtained as colourless cubes, m. p. 80° (Found : C, 84·3; H, 6·1; OEt, 13·5. $C_{23}H_{20}O_2$ requires C, 84·2; H, 6·1; OEt, 13·7%).

3-*Methoxy*-2-*phenylbenzo*-2-*pyranol*.—3-Methoxyflavylium perchlorate (2·5 g.) was refluxed with sodium acetate solution (5 g. in 25 c.c. water) until the brown oil which formed had solidified to a light brown solid. After being collected and dried, this was crystallised first from benzene and light petroleum and then from the latter (b. p. 40—60°) alone. It separated as small white needles (2·3 g.), m. p. 122° (Found : C, 74·2; H, 5·5; OCH_3, 11·9. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5; OCH_3, 12·2%). It is easily soluble in acids and readily converted into flavylium salts; on refluxing in alcoholic solution, it is converted into its ethyl ether, colourless plates from 50% alcohol; m. p. and mixed m. p. with sample prepared by method of Dilthey and Hoeschen (*loc. cit.*) 123°; mixed m. p. with pyranol 103°. The ether was unchanged by refluxing with 50% alcohol for 30 hours.

Flavone from Flavylium Chloride.—Freshly prepared flavylium chloride (from 5 g. of chalkone) was dissolved in 0·5% hydrochloric acid (100 c.c.), and the solution filtered and treated with sodium hydroxide (150 c.c. of 10%) and ether (75 c.c.). After standing at room temperature for a week, the deep purple ethereal solution was separated, well washed with water, and placed over calcium chloride for 24 hours. The calcium chloride was filtered off, washed with ether, and dissolved in water. The insoluble solid was filtered off, redissolved in ether, and the calcium chloride process repeated. The solid was finally twice crystallised from 33% alcohol; colourless needles (0·6 g.), m. p. and mixed m. p. 96—97° (Feuerstein and Kostanecki, *Ber.*, 1898, **31**, 1760, give m. p. 97°). It showed a typical pale blue fluorescence in concentrated sulphuric acid. The aqueous solution from the mother-liquors gave, on acidification, 0·7 g. of chalkone.

Replacement of the alkali in the reaction mixture by water led to the production of 0·75 g. of flavone.

6-*Methoxyflavone from* 6-*Methoxyflavylium Chloride*.—The chloride (4·5 g.) was dissolved in 0·5% hydrochloric acid (300 c.c.), the solution filtered, and 10% sodium hydroxide (100 c.c.) and ether (150 c.c.) added. The deep red ethereal layer was treated as already described, and the 6-*methoxyflavone* was crystallised from dilute alcohol, forming long colourless needles (0·25 g.) exhibiting a deep blue fluorescence with concentrated sulphuric acid; m. p. 162° (Found : C, 76·4; H, 4·9; OCH_3, 12·3. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8; OCH_3, 12·3%).

7-*Methoxyflavone from* 7-*Methoxyflavylium Chloride*.—The chloride (5 g.) was dissolved in water (500 c.c.), and 5% sodium carbonate solution (150 c.c.) added. After a week, ether (300 c.c.) was added, and the solid which had separated dissolved to a deep blue solution. The ethereal solution was removed after 12 days, washed with water, and treated with calcium chloride as described above. After three such treatments, during which much material was discarded, the product was twice crystallised from 33% alcohol, forming colourless needles (0·4 g.) with deep blue fluorescence in concentrated sulphuric acid; m. p. and mixed m. p. 109—110° (Emilewicz and Kostanecki, *Ber.*, 1899, **32**, 312, give m. p. 110—111°) (Found : C, 76·1; H, 4·8; OCH_3, 12·3. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8; OCH_3, 12·3%). An experiment in which water alone was used as hydrolytic agent gave 0·25 g. of 7-methoxyflavone and 2·2 g. of 4-methoxychalkone.

4′-*Methoxyflavone from* 4′-*Methoxyflavylium Chloride*.—The flavylium chloride (from 5 g. of 4′-methoxychalkone) was kept for a week with water. Addition of ether did not completely dissolve the solid which had separated and sodium carbonate (5 g.) was therefore added. The ethereal solution was treated with calcium chloride as previously described. By this means 0·6 g. of 4′-*methoxyflavone* was obtained, which crystallised from dilute alcohol as almost colourless needles, m. p. 156°, giving a blue fluorescence in concentrated sulphuric acid (Found : C, 76·0; H, 4·8; OCH_3, 12·3. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8; OCH_3, 12·3%).

β-*Naphthaflavone from* β-*Naphthaflavylium Chloride*.—The chloride (5 g.) was covered with 5% sodium carbonate solution (500 c.c.) and kept for a week. Ether was added and the mixture set aside for a further week. The naphthaflavone, obtained by the usual method, crystallised from dilute alcohol in long colourless needles (0·4 g.), m. p. 162°, giving a deep blue fluorescence with concentrated sulphuric acid (Ruhemann, *Ber.*, 1914, **47**, 120, gives m. p. 164—165°) (Found : C, 83·6; H, 4·4. Calc. for $C_{19}H_{12}O_2$: C, 83·8; H, 4·4%). β-Naphthachalkone (1 g.) was recovered from the mother-liquors.

Attempts to convert 3-methyl- and 3-methoxy-flavylium salts into the corresponding flavones by the above methods were unsuccessful, the sole products being the pyranols.

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