CCLXXVI.—*A Synthesis of Pyrylium Salts of Anthocyanidin Type. Part XIII. Some Monohydroxyflavylium Salts.*

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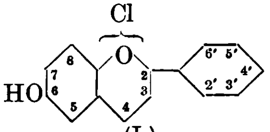
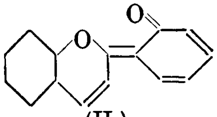
IT was thought that a study of some of the simpler hydroxyflavylium salts might throw light on the effects produced by hydroxy-groups in different positions in the three nuclei, especially from the point of view of anhydro-base and pseudo-base formation. Solutions of 3-hydroxyflavylium chloride have been obtained by demethylation of the methyl ether (Pratt and Robinson, J., 1923, **123**, 748), but this salt showed such a strong tendency to pass into the pseudo-base that it could not be isolated in a pure condition. It dissolves in sulphuric acid to a solution that exhibits intense plum-coloured fluorescence. 6-Hydroxyflavylium chloride (I) is less readily hydrolysed, but also yields a colourless pseudo-base, a quinonoid anhydro-base not being possible without the postulation of "bridge-bonds." This is merely one more example among many which



(I.)



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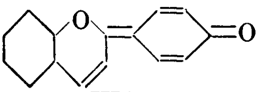
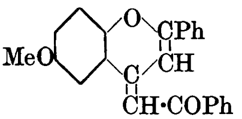


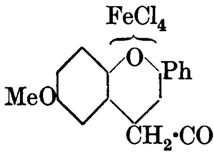
(III.)

show that aromatic structures assume a bridge-phase with the greatest reluctance. In the cases of 2′- and 4′-hydroxyflavylium salts, anhydro-bases of the types (II) and (III) are possible. Actually the anhydro-bases derived from 2′-hydroxyflavylium chloride and 2′-hydroxy-8-methoxyflavylium chloride are violet substances that could not be isolated owing to their marked tendency to pass into pseudo-bases by hydration. Thus the quinones are not formed by dehydration of pyranols, but are directly obtained from the kations of the pyrylium salts by removal of a proton under the influence of anions. The colour-base from 4′-hydroxyflavylium chloride is apparently a quinhydrone having the composition $C_{15}H_{10}O_2,C_{15}H_{12}O_3,2H_2O$; by analogy with the suggestions of Schneider and Meyer (*Ber.*, 1921, **54**, 1484) it may be named *4′-hydroxyflavanhydrone*. The molecular weight of the anhydrous compound corresponded with this formula, and similar results were obtained in the study of *4′-hydroxy-8-methoxyflavanhydrone*.

Incidentally *6-methoxy-4-phenacylideneflavene* (IV) has been examined and found to yield a *hydroferrichloride* (V) which is readily hydrolysed by water.

(IV.)





(V.)

Moreover, the carbonyl group in (IV) is inactive, so that the resemblance to the pyrones is complete, the system −O−C=C−C=O being extended to −O−C=C−C=C−C=O. Probably the phenacylideneflavenes are dipoles and anhydronium bases in the sense in which that expression was used by Armit and Robinson (J., 1925, **127**, 1607). In view of the remarkable rearrangement of the anhydro-base from 2 : 6-diphenyl-4-*o*-hydroxyphenylpyrylium chloride to phenacylideneflavene (Dilthey and Floret, *Annalen*, 1924, **440**, 95), alternative formulæ for the latter substance would appear to require consideration. However, Dilthey and Floret have excluded possibilities based on the triphenylpyrylium skeleton on the ground that phenacylideneflavene gives a small quantity of flavone when oxidised by permanganate.

EXPERIMENTAL.

8-*Methoxyflavylium Chloride.*—Under slightly modified conditions, the direct condensation of *o*-vanillin, acetophenone, and hydrogen chloride in acetic acid solution (Roberts and Robinson, J., 1924, **125**, 209) gave a 70% yield of the flavylium salt, which crystallised from dilute hydrochloric acid in brown needles which blackened at 170° and melted at 190° (decomp.) (Found in material dried in a vacuum : C, 66·2; H, 5·2. $C_{16}H_{13}O_2Cl,H_2O$ requires C, 66·1; H, 5·1%). The *iodide* crystallises from dilute, colourless hydriodic acid in puce-coloured needles, m. p. 134°. All attempts to demethylate these salts were unsuccessful.

Phenyl 2-Hydroxy-5-methoxystyryl Ketone.—2-Hydroxy-5-methoxybenzaldehyde (5·1 g.; 1 mol.) and acetophenone (4 g.; 1 mol.) in ethyl alcohol (30 c.c.) were mixed with a warm solution of potassium hydroxide (13 g.; 7 mols.) in water (13 c.c.) and left in a warm place over-night. The solution was poured into water (400 c.c.), kept for an hour until the waxy precipitate (A) had solidified, and then filtered. The filtrate and washings were acidified with 50% acetic acid and the chalkone was collected and dried (yield, 4·25 g. or 50%). It crystallised from benzene or from 50% alcohol in clusters of fine, golden-yellow needles, m. p. 104° (Found : C, 75·5; H, 5·4. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

The residue (A) was thrice recrystallised from alcohol; it formed stellate clumps of short, white needles, m. p. 125° (Found : C, 77·0; H, 6·0. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%). The yield (2·6 g.) of this *2-hydroxy-5-methoxybenzylidenediacetophenone* was 40% of that theoretically possible. A larger percentage was formed when the temperature during the alkaline condensation was higher; but it was not found possible, by varying the molecular proportion of the alkali employed, to obtain a higher yield of the chalkone.

6-*Methoxyflavylium Salts.*—Phenyl 2-hydroxy-5-methoxystyryl ketone was converted into 6-methoxyflavylium chloride by means of hydrogen chloride in acetic acid solution. The reaction proceeded to completion in the cold, passing through the red ketone-hydrochloride stage. The flavylium salt partly crystallised and was partly precipitated by the addition of ether. It was collected and dried to constant weight in a vacuum (Found : C, 62·3; H, 5·5. $C_{16}H_{13}O_2Cl,2H_2O$ requires C, 62·2; H, 5·5%). The salt crystallised from 5% hydrochloric acid in dark greenish-brown, shining needles, m. p. 97°. Its yellow solution in concentrated sulphuric acid exhibited a weak green fluorescence, but the orange-yellow alcoholic solution was non-fluorescent. The *ferrichloride* crystallised from acetic acid in glistening, brown platelets with green nuance, m. p. 203° (Found : C, 44·0 ; H, 3·2 ; Fe, 12·7. $C_{16}H_{13}O_2Cl_4Fe$ requires C, 44·1 ; H, 3·0 ; Fe, 12·9%). The *iodide* crystallised from alcohol in almost black, microscopic needles, m. p. 143°, whilst the *periodide* had m. p. 86—87°. The *perchlorate* crystallised from 60% methyl alcohol in short, dark brown needles, m. p. about 200° (decomp.).

6-*Hydroxyflavylium Salts*.—The demethylation required rather careful control. A mixture of 6-methoxyflavylium chloride dihydrate (8·8 g.), phenol (40 g.), and hydriodic acid (*d* 1·74 ; 150 c.c.) was heated in a glycerol-bath at 110°, until the effluent stream of carbon dioxide no longer contained methyl iodide (45 minutes). The mixture was diluted with an equal volume of water and of ether, cooled in ice, and filtered ; the black crystals (6·4 g.) had a green lustre. After the ethereal layer had been separated, the remainder (about 3·6 g.) of the iodide, mixed with periodide, could be recovered by evaporating the filtrate under reduced pressure in an atmosphere of hydrogen. The demethylated product (7 g.) was dissolved in the minimum volume of hot alcohol (700 c.c.) and concentrated hydrochloric acid (200 c.c.), and freshly precipitated silver chloride (from 7 g. of silver nitrate) added. The mixture was gently boiled during 5 minutes while being stirred ; it was then filtered hot, and the residue washed with hot ethyl-alcoholic hydrochloric acid. The filtrate and washings were concentrated to a small volume and cooled, and the 6-*hydroxyflavylium chloride* was collected ; it crystallised from alcohol or from 15% hydrochloric acid in orange needles. The chloride was very readily hydrolysed by water, and the pseudo-base was also formed when sodium acetate was added. The *ferrichloride* crystallised from glacial acetic acid in short, reddish-brown needles, m. p. 198° (Found : C, 43·1 ; H, 2·7 ; Fe, 13·2. $C_{15}H_{11}O_2Cl_4Fe$ requires C, 42·8 ; H, 2·6 ; Fe, 13·3%). The *chloroaurate* formed golden-brown needles which on heating turned grey at 180° but did not melt. 6-Hydroxyflavylium salts give, in concentrated sulphuric acid, orange solutions with a green fluorescence.

4′-*Hydroxyflavylium Salts*.—*p*-Methoxyacetophenone was condensed with salicylaldehyde to form *p*-methoxyphenyl *o*-hydroxystyryl ketone as described by Kostanecki and Zwayer (*Ber*., 1908, **41**, 1337) and the yield of the pure, recrystallised product was 81%. The chalkone (13·8 g.) was dissolved in a mixture of glacial acetic acid (50 c.c.) and concentrated hydrochloric acid (25 c.c.) by saturating this with hydrogen chloride, and the solution after an hour was gently warmed for 15 minutes and poured into water. An excess of potassium iodide was added to the filtered solution of the flavylium chloride and an orange precipitate of the anhydrous *4′-methoxyflavylium iodide* was formed (yield, 89%). This salt (17·2 g.) was gently refluxed for ½ hour with hydriodic acid (300 c.c.; *d* 1·74) and phenol (70 g.) in an atmosphere of carbon dioxide. On cooling, crystals (9·4 g.) separated which were pure enough for the next operation; for analysis, they were recrystallised from methyl alcohol, being thus obtained in dark purple prisms (Found: C, 29·8; H, 2·0; I, 62·7. $C_{15}H_{11}O_2I_3$ requires C, 29·8; H, 1·8; I, 63·1%). *4′-Hydroxyflavylium periodide* melts at 208—209° and decomposes suddenly at 285°; when pressed on glass, it has a beetle-green lustre. Freshly precipitated silver chloride (from 2·85 g. of silver nitrate) was added to a solution of the periodide (2 g.) in a hot mixture of methyl alcohol (125 c.c.) and 7·5% hydrochloric acid (100 c.c.), and the whole was boiled for 15 minutes and filtered. The filtrate and washings were concentrated and, on cooling, red needles separated (yield, 80%). This product was crystallised several times from dilute hydrochloric acid in order to remove traces of inorganic impurities which were tenaciously held. The clusters of fine, orange-red needles, after drying over sulphuric acid and potassium hydroxide, darkened at 135° and melted at 142° (decomp.) (Found: C, 61·2, 61·0; H, 5·1, 5·3. $C_{15}H_{11}O_2Cl,2H_2O$ requires C, 61·1; H, 5·1%). This salt dissolves in water or alcohol to an orange solution which becomes yellow on the addition of a drop of dilute hydrochloric acid or red with weakly alkaline reagents. The orange solution in concentrated sulphuric acid exhibits a green fluorescence. The *chloroaurate* crystallises in golden-orange needles, m. p. 177°.

4′-Hydroxyflavanhydrone.—A solution of 4′-hydroxyflavylium chloride in water was covered with benzene, and excess of sodium acetate added; on shaking, a portion of the violet-red substance was dissolved by the benzene, which was separated, dried with potassium carbonate, and filtered. The dark violet solid which remained on removal of the solvent could not be crystallised (Found: C, 72·0; H, 5·7; loss on heating at 110°/15 mm., 7·4. $C_{30}H_{22}O_5,2H_2O$ requires C, 72·3; H, 5·2; H_2O, 7·2%. Found in dried material: C, 77·6; H, 4·9; *M*, by micro-Rast, 472. $C_{30}H_{22}O_5$ requires C, 77·9; H, 4·8%; *M*, 462). On further heating, the deep red substance gradually sintered and was completely molten at 200°. The red solution in pyridine became colourless in a few seconds, probably as the result of the formation of the benzopyran ether (compare Dilthey, *J. pr. Chem.*, 1917, **95**, 113, 117). This flavanhydrone showed no tendency to combine with methyl iodide.

4′-Hydroxy-8-methoxyflavylium Salts.—The method of Nencki and

Stoeber (*Ber.*, 1897, **30**, 1769) for the preparation of *p*-hydroxyacetophenone only gives a 10% yield and the product is difficult to purify. The following modification is much more satisfactory: Powdered anhydrous ferric chloride (81 g.) was added to a solution of phenol (63 g.) in carbon disulphide (48 c.c.), and acetyl chloride (95 c.c.) was then introduced drop by drop with shaking. When the addition was complete, the mixture was shaken during 5 minutes and the carbon disulphide and acetyl chloride were then carefully removed by distillation. The residue was decomposed by water and rendered alkaline with sodium hydroxide, the solution decanted from the ferric hydroxide, which was washed by decantation, and the crude *p*-hydroxyacetophenone precipitated by acidification. After crystallisation from water, 30 g. (yield, 33%), m. p. 110°, were obtained. p-*Acetoxyacetophenone*, m. p. 54°, crystallises from alcohol and was obtained in 80% yield on agitating an aqueous solution of sodium *p*-acetylphenoxide (1 mol.) with acetic anhydride (1 mol.).

A stream of hydrogen chloride was passed through a solution of *o*-vanillin (1·1 g.) and *p*-hydroxyacetophenone (1 g.) in formic acid (10 c.c.) for 1 hour, and the mixture kept until next day. The orange solid precipitated on the addition of ether crystallised from 10% hydrochloric acid (60 c.c.) in brick-red needles (1·6 g.) (Found in material dried in a vacuum: C, 62·3; H, 4·8. $C_{16}H_{13}O_5Cl,H_2O$ requires C, 62·6; H, 4·9%). This salt darkens at 170° and melts at 190° (decomp.); it dissolves in water to a yellow solution exhibiting a weak green fluorescence. The *ferrichloride* crystallised from acetic acid in reddish-brown needles, m. p. 217°, and the *periodide* crystallised in chocolate-coloured needles, m. p. 170—173° (decomp.), after darkening at 140°. The ruby benzene solution of the anhydro-base, prepared in the usual manner, was dried with potassium carbonate and, on removal of the solvent from the filtered solution, a deep purplish-red solid residue was obtained, which was dried in a vacuum (Found: C, 73·7; H, 5·4. $C_{32}H_{26}O_7$ requires C, 73·6; H, 5·0%). The molecular weight could not be determined by Rast's method and no solvent was found to be suitable for recrystallisation; in several solvents, for example, acetone and nitrobenzene, it gave bottle-green solutions. On heating, this 4'-*hydroxy*-8-*methoxyflavanhydrone* gradually sintered and decomposed at 206°.

2'-*Hydroxyflavylium Ferrichloride*.—The condensation of salicylaldehyde with *o*-hydroxyacetophenone (Fries and Pfaffendorf, *Ber.*, 1910, **43**, 215), under conditions similar to those mentioned below, gave a bright scarlet, very sparingly soluble solid, which is not a flavylium salt and is apparently of complex constitution.

The hydroxyl group in the ketonic component was therefore protected by acetylation (compare Friedländer and Neudorfer, *Ber.*, 1897, **30**, 1080; Lesser and Gad, *Ber.*, 1926, **59**, 233). A solution of *o*-acetoxyacetophenone (0·9 g.) and salicylaldehyde (0·6 g.) in formic acid (6 c.c.) was saturated with hydrogen chloride during 3 hours, and next day the red solid, which was precipitated on the addition of ether, was collected and extracted with 17% hydrochloric acid (60 c.c.), leaving a considerable residue. A *ferrichloride* prepared from the filtered solution crystallised from acetic acid in tufts of brown needles, m. p. 125° (Found : C, 42·6; H, 2·7; Fe, 13·3. $C_{15}H_{11}O_2Cl_4Fe$ requires C, 42·8; H, 2·6; Fe, 13·3%). The orange solution in sulphuric acid exhibits a weak green fluorescence. The solution of the ferrichloride in dilute hydrochloric acid gave, with a large excess of sodium carbonate solution, quickly added, a transient purple colour. The colourless filtrate from the ferric hydroxide apparently contained pseudo-base in solution, for on acidification it turned bright yellow, and then, on addition of a large excess of sodium carbonate, the purple colour flashed out, but the solution became almost instantaneously colourless. The purple colour was formed only if the sodium carbonate was added quickly and in large excess.

2′-*Hydroxy*-8-*methoxyflavylium Salts*.—Several attempts to prepare 2′-hydroxy-8-methoxyflavylium chloride by condensing *o*-vanillin (1 mol.) and *o*-acetoxyacetophenone (1 mol.) in anhydrous formic acid with hydrogen chloride failed during the recrystallisation from hot dilute hydrochloric acid (in order to remove the acetyl group in the 2′-position), probably because some complex substance, not a pyrylium salt, was formed in this case also. The use of unacetylated *o*-hydroxyacetophenone led to better results in this instance. A solution of *o*-hydroxyacetophenone (1·4 g.) and *o*-vanillin (1·5 g.) in formic acid (6 c.c.) was saturated with hydrogen chloride for 1·5 hours and on the following day ether precipitated a reddish-brown solid, which crystallised from methyl alcohol in long, red needles; these darkened above 100° and had m. p. 188° (decomp.) (Found : C, 66·3; H, 4·7. $C_{16}H_{13}O_5Cl$ requires C, 66·5; H, 4·5%). This salt dissolved in sulphuric acid to an orange solution exhibiting a weak green fluorescence. When water was added to the solid chloride or to its solution in alcohol, the pseudobase was obtained; this dissolved with difficulty in dilute hydrochloric acid. Sodium acetate, added in excess to an acid solution of this salt, produced the violet colour-base, which could be extracted by benzene; the colour of the violet solution, however, soon faded. Again, when the colour-base was quickly separated, the filtrate was always found to contain pseudo-base. This remarkable ease of hydration of the anhydro-base derived from a flavenol has not previously been observed in the absence of a substituent in position 3.

6-*Methoxyphenacylideneflavene* (V).—Following the details given by Feuerstein and Kostanecki (*Ber.*, 1898, **31**, 710) in the case of the parent substance, 2-hydroxy-5-methoxybenzylidenediacetophenone (7·5 g.) was converted into acetophenone (1·1 g.), *phenyl* β-2-*hydroxy*-5-*methoxyphenylethyl ketone* (2·3 g.), and 6-*methoxyphenacylideneflavene* (3·8 g.). The last compound crystallised from alcohol or benzene in yellow, feathery clusters of fine needles, m. p. 146° (Found: C, 80·7, 80·8; H, 5·0, 5·0; MeO, 8·8. $C_{24}H_{18}O_3$ requires C, 81·4; H, 5·1; MeO, 8·8%). In the micro-Zeisel determination, the mixture required to be heated almost twice as long as usual. The solution in cold sulphuric acid was yellowish-orange and non-fluorescent, and on warming a transitory purple colour appeared, succeeded by a ruby one.

Pure 6-methoxyphenacylideneflavene (1·8 g.) was suspended in acetic acid (10 c.c.), and a stream of dry hydrogen chloride passed during 3 minutes; on shaking, all the solid dissolved to a red solution. The addition of a solution of anhydrous ferric chloride (0·8 g.) in glacial acetic acid (5 c.c.) produced an immediate red precipitate, which soon became brownish-orange and crystalline. After keeping for an hour, the flask being stoppered, the solid was collected and dried over sulphuric acid and potassium hydroxide (yield, 2·54 g. or 92%) (Found: C, 52·0; H, 3·5; Fe, 10·0; MeO, 5·8. $C_{24}H_{19}O_3Cl_4Fe$ requires C, 52·1; H, 3·4; Fe, 10·1; MeO, 5·6%).

6-*Methoxy*-4-*phenacylflavylium ferrichloride* forms microscopic, elongated prisms which melt, with blackening, at 170° (on slow heating). It is sparingly soluble in water to an orange solution which slowly deposits 6-methoxyphenacylideneflavene; this hydrolysis is, however, very rapid in presence of alcohol. The ferrichloride gives an orange, non-fluorescent solution in sulphuric acid.

6-Methoxyphenacylideneflavene (1 mol.) did not react when refluxed in benzene solution for $\frac{1}{4}$ hour with magnesium phenyl bromide (1 mol. prepared in ether).

The *phenyl* β-2-*hydroxy*-5-*methoxyphenylethyl ketone* was a brown syrup with a strong green reflex. Although its hydroxyl group could not be acetylated or benzoylated, its carbonyl group was reactive, and the *semicarbazone* and p-*nitrophenylhydrazone* were readily prepared. The former crystallised from alcohol in white, elongated prisms, m. p. 184° (Found: C, 65·1; H, 6·5; N, 13·5. $C_{17}H_{19}O_3N_3$ requires C, 65·2; H, 6·1; N, 13·4%), and the latter separated from alcohol in microscopic, orange needles, m. p. 163—

165°. The ketone itself could not be crystallised. The same hydrochalkone was obtained, also as a syrup, and identified as the semicarbazone, m. p. 184° (alone or mixed), by the catalytic reduction of phenyl 2-hydroxy-5-methoxystyryl ketone with a palladium catalyst.

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