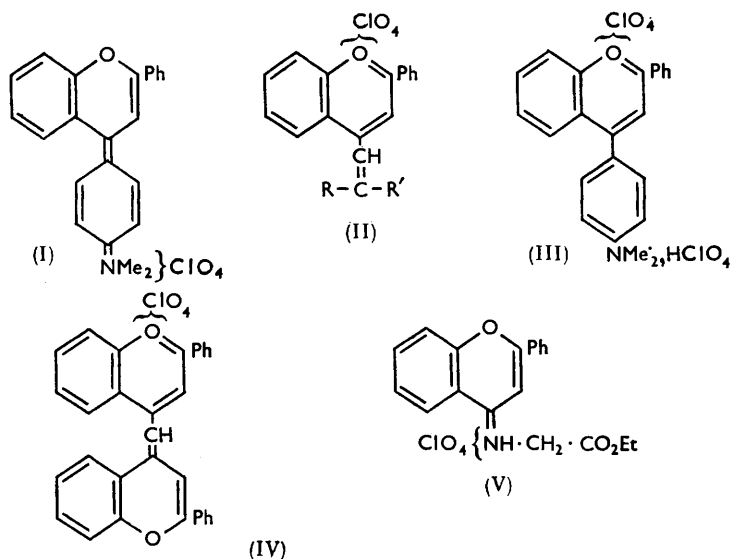


302. Reactions of Flavylium Salts with Dimethylaniline and Malonic Acid.

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The nature and scope of the condensation of selected flavylium salts with dimethylaniline and with malonic acid have been investigated.

THE condensation of dimethylaniline, diarylethylenes, and malonic acid with flavylium perchlorate in hot acetic acid to yield products of type (I), (II), and (IV) respectively has been recorded by Wizinger¹ who in collaboration with Luthiger² subsequently examined the formation of compounds (I) and (II) in some detail. This kind of condensation appeared to us to be of some significance in connexion with the structure of dracorubin³ and possible synthetical routes to this type of molecule, more especially because for some



time we have envisaged the phytochemical production of the dracorubin molecule to be essentially an oxidative coupling of the appropriate benzopyrylium salt (or base) with a flavan, or their equivalents. Accordingly the present investigation was initiated to determine the scope and nature of this coupling reaction exhibited by flavylium perchlorate, including the effects of substituents in the flavylium residue.

Thus, in agreement with the structure of the condensation products proposed by Wizinger and Luthiger,² flavylium salts with a substituent in the 4-position fail to react with dimethylaniline. With 3- or 5-substituted flavylium salts, *e.g.*, 3-methoxy-, 7-hydroxy-3-methoxy-, 3-phenyl-, 5:7-dimethyl-, and 5:7-dimethoxy-flavylium perchlorate the reaction was extremely slow and, although the mixture became highly coloured as in successful cases, only the starting materials could be isolated. On the other hand 7-hydroxy-, 7-methoxy-, 4'-hydroxy-, 4'-methoxy-, 6:7-dimethoxy-, and 7:4'-dihydroxy-8-methoxy-flavylium perchlorate readily furnished the appropriate *p*-dimethylamino-phenyl derivatives type (I) which have been characterised by the formation of salts. In agreement with structure (I) these products form a series of well-defined diperchlorates, of type (III), which, as would be expected on general grounds, are much paler than corresponding monoperochlorates.

¹ Wizinger, *Chimia (Switz.)*, 1952, **6**, 243.

² Wizinger and Luthiger, *Helv. Chim. Acta*, 1953, **36**, 526.

³ Robertson, Whalley, and Yates, *J.*, 1950, 3117.

Attempts to obtain degradative evidence for structures of type (I) were unsuccessful; *e.g.*, 4-*p*-dimethylaminophenylflavylium perchlorate is not readily oxidised with ozone, and with potassium permanganate or chromic oxide furnished only benzoic acid; degradation with alkali gave dimethylaniline and acetophenone.

The scope of the condensation of flavylium salts with malonic acid, recorded by Wizinger¹ without experimental details, to give 4-4'-flavenyldenemethylflavylium perchlorates of type (IV) has been found to follow closely the behaviour with dimethylaniline. We are indebted to Professor Wizinger for providing us with the details of his unpublished experimental conditions, *viz.*, the interaction of the components in acetic acid containing sodium acetate. This implies that the flavylium base is the active component and we have found that this reaction and also that with dimethylaniline is an oxidative coupling depending on the supply of atmospheric oxygen. The reaction does not take place in nitrogen, and, further, the condensation is equally productive when flavylium salts containing non-oxidising anions (*e.g.*, chloride) are employed.

Attempts to substantiate, by degradation, the 4-4'-flavenyldenemethylflavylium salt structure allocated to (IV) were unsuccessful; *e.g.*, ozonolysis gave only salicylic acid and fusion with alkali yielded benzoic acid. The exceptional stability to oxidation and alkali-fission encountered in these compounds, together with their intense colours, may be ascribed to the distribution of the cationic charge over the whole cation as in the case of the cyanine and triphenylmethane dyes.

The possibility that the observations described in this paper have biological significance has already been mentioned. The natural anthocyanidin pigments possess substituents in the 3- and the 5-position, and yet in the closely analogous and almost certainly biogenetically related natural flavones and flavanones there are several which do not have substituents in these positions, *e.g.*, flavone, 7-hydroxy-4'-methoxyflavone (pratol), 7:3':4'-trihydroxy- (butin), and 7:4'-dihydroxy-flavanone (liquiritigenin). This discrepancy may well be due in some measure to the reactivity towards "formyl equivalents" which 3- and 5-unsubstituted flavylium salts clearly exhibit and thus their existence in plant tissues might be transitory. Whilst malonic acid seldom occurs in plant tissues and is an inhibitor of the tricarboxylic acid cycle, its role in the condensations described is clearly the provision of one carbon atom, *i.e.*, the "formyl equivalent." It might be expected that the biological processes responsible for the frequent provision of one carbon atom fragments in phytochemical processes could function in this role. In this connexion it may be noted that the brief report⁴ of the oxidative coupling of flavylium perchlorate and glycine ethyl ester to furnish compound (V) is a further example and extension of the reactions now discussed.

EXPERIMENTAL

Several of the picrates and perchlorates, especially the diperchlorates, melt with violent decomposition and consequently analyses have been difficult or impossible in some cases. Salts which have not been analysed for this reason are marked with an asterisk.

4-*p*-Dimethylaminophenyl-2-phenylbenzopyranol.—A solution of flavylium perchlorate (1 g.) in methanol (13 ml.) containing dimethylaniline (0.5 g.), was refluxed for 90 min. On cooling, the intense blue mixture deposited 4-*p*-dimethylaminophenylflavylium perchlorate (0.3 g.) which separated from methanol in purple needles, m. p. 250° (decomp.), and from acetic acid in green plates, m. p. 250° (decomp.) (Found: C, 65.0; H, 4.8; N, 3.3; Cl, 8.6. Calc. for C₂₃H₂₀O₅NCl: C, 64.8; H, 4.8; N, 3.3; Cl, 8.2%) (Wizinger and Luthiger² give m. p. 254°). The same compound separated in green plates (0.5 g.), m. p. 250° (decomp.), when boiling methanol was replaced by boiling acetic acid. The colour of a warm solution of this perchlorate (2 g.) in methanol (20 ml.) was discharged by the drop-wise addition of 2N-aqueous sodium hydroxide. Purification of the crystalline product (1.5 g.) from methanol furnished the *methyl ether* of 4-*p*-dimethylaminophenyl-2-phenylbenzopyranol in stout tablets, m. p. 118° (Found: C, 79.9; H, 6.3; N, 3.9; OMe, 8.4. C₂₄H₂₃O₂N requires C, 80.7; H, 6.4; N, 3.9; OMe, 8.7%).

⁴ Shriner, XIVth Internat. Congr. Pure Appl. Chem., Congress Handbook, 1955, p. 265.

Addition of perchloric acid to a methanolic solution of this ether regenerated the parent perchlorate. Prepared in alcohol, the *picrate* separated from acetic acid containing 1% picric acid in golden-brown needles, m. p. 244° (decomp.) (Found: C, 63.1; H, 4.2; N, 9.8. $C_{29}H_{23}O_8N_4$ requires C, 62.8; H, 4.0; N, 10.1%). The *ferrichloride* separated from acetic acid in purple plates, m. p. 149° (decomp.) (Found: C, 52.9; H, 3.9; N, 2.6; Fe, 10.2. $C_{23}H_{20}ONCl_4Fe$ requires C, 52.7; H, 3.8; N, 2.7; Fe, 10.7%). A solution of 4-*p*-dimethylaminophenylflavylium perchlorate (0.1 g.) in 60% perchloric acid (3 ml.) slowly deposited the *diperchlorate* (0.1 g.) in bright yellow plates, m. p. 100—170° (violent decomp.) (Found: N, 2.6. $C_{23}H_{21}O_9NCl_2$ requires N, 2.7%). Diluted with water a solution of this salt became purple owing to the regeneration of the monoperochlorate.

Dimethylaniline reacted with 4'-methoxyflavylium perchlorate to yield green needles, m. p. 134° (decomp.), of 4-*p*-dimethylaminophenyl-4'-methoxyflavylium perchlorate (Found: C, 60.7; H, 5.4; N, 2.6. $C_{24}H_{22}O_6NCl_2H_2O$ requires C, 60.9; H, 5.1; N, 3.0%) which gave a *diperchlorate** in orange needles, m. p. 120—140° (decomp.). The *picrate* separated from acetic acid in golden-brown needles, m. p. 226° (decomp.) (Found: N, 9.6. $C_{30}H_{24}O_9N_4$ requires N, 9.6%).

7-Hydroxyflavylium perchlorate gave 4-*p*-dimethylaminophenyl-7-hydroxyflavylium perchlorate in dark green needles, m. p. 273° (decomp.) (Found: Cl, 8.8. $C_{23}H_{20}O_6NCl$ requires Cl, 7.9%). The *diperchlorate* formed yellow plates, m. p. 135—180° (decomp.) (Found: Cl, 14.6. $C_{23}H_{21}O_{10}NCl_2$ requires Cl, 13.1%), and the *picrate* golden needles, m. p. 250—260° (decomp.) (Found: C, 60.7; H, 3.9; N, 9.7. $C_{29}H_{23}O_9N_4$ requires C, 61.0; H, 4.0; N, 9.8%).

4-*p*-Dimethylaminophenyl-4'-hydroxyflavylium perchlorate formed dark green needles, m. p. 280° (decomp.) (Found: N, 3.0. $C_{23}H_{20}O_6NCl$ requires N, 3.1%), giving a *diperchlorate** which separated from 60% perchloric acid in golden-yellow plates, m. p. 110—150° (decomp.). The *picrate* crystallised from acetic acid in chocolate-coloured prisms, m. p. 256° (decomp.) (Found: N, 9.6. $C_{29}H_{22}O_9N_4$ requires N, 9.8%).

4-*p*-Dimethylaminophenyl-7-methoxyflavylium perchlorate formed purple plates, m. p. 246—248° (decomp.), from acetic acid (Found: N, 3.0. $C_{24}H_{22}O_6NCl$ requires N, 3.1%); the *picrate* separated from alcohol in dark blue plates, m. p. 258° (decomp.) (Found: N, 10.3. $C_{30}H_{24}O_9N_4$ requires N, 9.6%).

7: 4'-Dihydroxyflavylium perchlorate yielded dark green needles of 4-*p*-dimethylaminophenyl-7: 4'-dihydroxyflavylium perchlorate, m. p. 350° (Found: N, 2.5. $C_{23}H_{20}O_7NCl$ requires N, 3.3%).

6: 7-Dimethoxyflavylium perchlorate gave 4-*p*-dimethylaminophenyl-6: 7-dimethoxyflavylium perchlorate in dark green needles, m. p. 286° (decomp.) (Found: N, 3.1. $C_{25}H_{24}O_7NCl$ requires N, 2.8%). The *picrate* formed bronze needles, m. p. 270° (decomp.) (Found: N, 10.0. $C_{31}H_{26}O_{10}N_4$ requires N, 9.4%).

Condensation of Flavylium Chloride and Dimethylaniline.—Flavylium chloride (1 g.) and dimethylaniline (0.5 g.) were heated in boiling methanol for 90 min. but, on cooling, the intense blue solution did not deposit a product. The mixture was treated with excess of methanolic sodium acetate followed by water (200 ml.), and a colourless semisolid precipitate was isolated with ether and treated with perchloric acid in acetic acid, giving the perchlorate of 4-*p*-dimethylaminophenylbenzopyranol, identical with an authentic specimen.

Attempts to effect this reaction in an atmosphere of nitrogen were unsuccessful and gave only very pale-blue reaction mixtures containing only the starting materials; admission of air at once produced the intense blue colour.

5: 7-Dimethylflavylium Perchlorate.—Prepared by the condensation of 2-hydroxy-4: 6-dimethylbenzaldehyde⁵ and acetophenone according to standard practice, 5: 7-dimethylflavylium perchlorate separated from acetic acid in yellow needles, m. p. 229° (decomp.) (Found: C, 60.7; H, 4.7. $C_{17}H_{15}O_5Cl$ requires C, 61.1; H, 4.5%).

6: 7-Dimethoxyflavylium perchlorate was prepared from 2-hydroxy-4: 5-dimethoxybenzaldehyde and acetophenone and separated from acetic acid in needles, m. p. 298° (decomp.) (Found: C, 54.6; H, 4.1. $C_{17}H_{15}O_7Cl$ requires C, 55.7; H, 4.1%).

*Alkali-degradation of 4-*p*-Dimethylaminophenylbenzopyranol.*—(a) When a solution of the perchlorate (1 g.) in methanol (15 ml.) containing 33% aqueous potassium hydroxide (10 ml.) was refluxed for 7½ hr. in a stream of nitrogen, and the effluent gas passed into aqueous 2: 4-

⁵ Gattermann, *Annalen*, 1907, 357, 328.

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dinitrophenylhydrazine sulphate, the hydrazone (10 mg.) of acetophenone was obtained in orange needles, m. p. 242°, after purification from alcohol. Separation of the hydrolysate into neutral, phenolic, and acidic components furnished acetophenone (20 mg.), identified as the 2 : 4-dinitrophenylhydrazone, as the only characterisable product.

(b) Fusion of the perchlorate (2 g.) with potassium hydroxide (6 g.) in water (5 ml.) in a stream of nitrogen at 320° during 30 min., followed by separation of the hydrolysate into neutral, acidic, and phenolic components, gave acetophenone, characterised as the 2 : 4-dinitrophenylhydrazone, and dimethylaniline characterised as the picrate.

Condensation of Flavylium Perchlorates with Malonic Acid.—Interaction of flavylium perchlorate (6.2 g.), malonic acid (1.04 g.), and sodium acetate (1.5 g.) in boiling acetic acid (150 ml.) for 20 min. or at room temperature for 12 hr. gave a crystalline product which on purification from acetic acid containing 1% of perchloric acid furnished 4-4'-flavenyldenemethylflavylium perchlorate (4 g.) in lustrous, green needles, m. p. 254° (decomp.) (Found : C, 70.0; H, 4.1; $C_{31}H_{21}O_8Cl$ requires C, 70.7; H, 4.0%). Wizinger⁶ found m. p. 250—254°. Prepared by the addition of sodium hydroxide solution to a solution of the perchlorate in methanol, the pyranol base separated from light petroleum (b. p. 60—80°) in yellow needles, m. p. 148° (decomp.) (Found : C, 84.2; H, 5.5. $C_{31}H_{22}O_8$ requires C, 84.2; H, 5.0%). This compound was very unstable and the analysis had to be performed within a few hours of preparation. With perchloric acid it regenerated the perchlorate and with picric acid furnished the picrate in dark red needles, m. p. 270° (Found : N, 6.5. $C_{37}H_{23}O_9N_3$ requires N, 6.4%).

On being refluxed for 15 min. a solution of flavylium ferrichloride (2 g.), malonic acid (0.26 g.), and sodium acetate (0.41 g.) in acetic acid (25 ml.) gave the ferrichloride, which separated from acetic acid in dark blue plates, m. p. 256° (decomp.) (Found : C, 59.7; H, 3.6. $C_{31}H_{21}O_2FeCl_4$ requires C, 59.7; H, 3.4%). The free base from this had m. p. 148° and was identical with that obtained from the perchlorate.

The condensation of various flavylium perchlorates with malonic acid furnished analogous products as follows :

6-Hydroxyflavylium perchlorate (2 g.) gave 6-hydroxy-4-(6-hydroxy-4-flavenyldenemethyl)-flavylium perchlorate (0.9 g.) dark green needles (from acetic acid), m. p. 306° (decomp.) (Found : C, 66.4; H, 4.0. $C_{31}H_{21}O_8Cl$ requires C, 66.9; H, 3.8%).

7-Hydroxyflavylium perchlorate (1 g.) gave 7-hydroxy-4-(7-hydroxy-4-flavenyldenemethyl)-flavylium perchlorate (0.5 g.) in olive-green needles, m. p. 283° (decomp.) from acetic acid (Found : C, 67.0; H, 4.2%).

7-Methoxyflavylium perchlorate (1 g.) gave 7-methoxy-4-(7-methoxy-4-flavenyldenemethyl)-flavylium perchlorate dihydrate (0.5 g.) in dark green needles, m. p. 289° (decomp.) from acetic acid (Found : C, 63.5; H, 4.9. $C_{33}H_{25}O_8Cl \cdot 2H_2O$ requires C, 63.9; H, 4.7%).

8-Methoxyflavylium perchlorate (1 g.) furnished 8-methoxy-4-(8-methoxy-4-flavenyldene-methyl)flavylium perchlorate dihydrate (0.48 g.) in plates, m. p. 296° (decomp.), with a magnificent sheen (from acetic acid) (Found : C, 63.4; H, 4.8%).

4'-Hydroxyflavylium perchlorate (1 g.) furnished 4'-hydroxy-4-(4'-hydroxy-4-flavenyldene-methyl)flavylium perchlorate (0.5 g.) in dark green needles, m. p. 280° (decomp.) (Found : C, 62.6; H, 4.4. $C_{31}H_{21}O_8Cl \cdot 2H_2O$ requires C, 62.8; H, 4.0%).

4'-Methoxyflavylium perchlorate (1 g.) gave 4'-methoxy-4-(4'-methoxy-4-flavenyldenemethyl)-flavylium perchlorate (0.5 g.) in deep green needles, m. p. 281° (decomp.) (Found : C, 67.3; H, 4.3. $C_{33}H_{25}O_8Cl$ requires C, 67.8; H, 4.3%).

4'-Hydroxy-8-methoxyflavylium perchlorate (1 g.) furnished 4'-hydroxy-4-(4'-hydroxy-8-methoxy-4-flavenyldenemethyl)-8-methoxyflavylium perchlorate (0.3 g.) in olive green needles, m. p. 330° (decomp.) (Found : C, 64.2; H, 4.2. $C_{33}H_{25}O_{10}Cl$ requires C, 64.3; H, 4.1%).

The free bases or the picrates from the foregoing products were not obtained crystalline.

3-Phenyl-, 3-methoxy-, 4-phenyl-, 5 : 7-dimethyl-, and 5 : 7-dimethoxy-flavylium perchlorate failed to condense with malonic acid and in most cases were recovered in 80—90% yield.

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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⁶ Wizinger, personal communication.