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ANTHOCYANINS AND RELATED COMPOUNDS—VI

FLAVYLIUM SALT—PHLOROGLUCINOL CONDENSATION PRODUCTS

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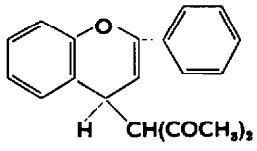
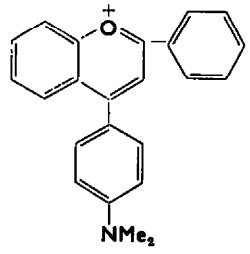
Abstract—8-Methoxy-4'-hydroxy-3-methylflavylium chloride and phloroglucinol rapidly react in aqueous media at pH 4–7 to form 8-methoxy-4'-hydroxy-3-methylflav-2-ene (VIa) and colourless, crystalline C_{23} and C_{40} condensation products. On the basis of chemical and NMR spectral data structures XIIa and XIVa have been assigned to these condensation products. 8,4'-Dimethoxy-3-methyl-, 4'-hydroxy-3-methyl- and 4'-hydroxyflavylium chlorides react with phloroglucinol to form structurally similar compounds.

IT HAS been reported that flavylium perchlorate reacts with acetyl acetone and other β-diketones[1] in alkaline solutions and with dimethylaniline[2] and malonic acid[3,4] in acetic solutions to yield products of type I, II and III respectively. Flavylium salts substituted in the 3- or 5-positions by methyl, phenyl or methoxyl groupings, however, do not[4] apparently react with these nucleophilic reagents. Furthermore, the malonic



I



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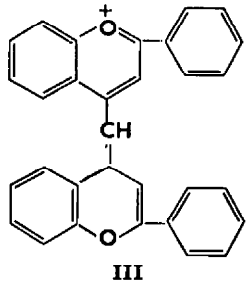


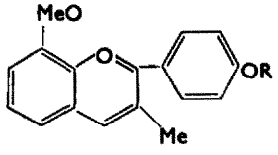
III

* A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture.

[1] F. Kröhnke and K. Dickore, *Chem. Ber.* **92**, 46 (1959).
[2] R. L. Shriner and J. A. Shotton, *J. Amer. Chem. Soc.* **74**, 3622 (1952).
[3] R. Wizinger and A. Luthiger, *Helv. Chim. Acta* **36**, 526 (1953).
[4] M. Blackburn, G. B. Sankey, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1573 (1957).

acid reaction involves atmospheric oxidation and does not[4] occur under nitrogen. Flavylium salt–polyphenol condensation reactions of a similar nature could be of some significance as possible synthetic and biosynthetic routes to certain types of natural bisflavonoid and polymeric flavonoid compounds. Such flavylium salt–polyphenol condensation reactions, however, have not previously been demonstrated, although it has been suggested[4] that the phytochemical production of dracorubin (IV) a complex anhydro base from Dragon's blood resin, probably involves an oxidative coupling of a flavylium salt with a phenolic flavan. We have now determined that phloroglucinol, resorcinol and D-catechin rapidly react with flavylium salts in aqueous media at pH 4–8 to yield complex mixtures of condensation products, the structures of some of which have been elucidated.

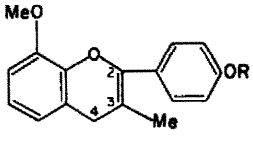
Unexpectedly, it was noted early in this investigation that these phenol condensation reactions are accompanied by *reduction* of appreciable quantities of the flavylium salt. Thus, solutions of 8-methoxy-4'-hydroxy-3-methyl-flavylium chloride Va and phloroglucinol, resorcinol or D-catechin in aqueous methanol at pH 5·8 or in dilute aqueous acetic acid rapidly deposit a colourless, crystalline monohydroxy compound, $C_{17}H_{16}O_3$. On the basis of its molecular formula and the fact that it could also be

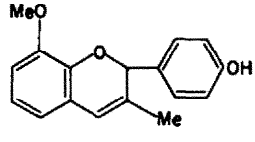


Va, R = H

Vb, R = Me

prepared by sodium borohydride reduction of the flavylium salt,[5] this colourless product is clearly either the flav-2-ene (VIa) or flav-3-ene (VII). UV and NMR spectral data establish structure VIa for this compound. Thus, Gramshaw *et al.*[6] recently demonstrated that the LAH reduction product of apigeninidin trimethyl ether is 4',5,7-trimethoxyflav-2-ene. The UV spectrum[6] of this flavene (λ_{max} 272, 247, 222 mμ, log ϵ, 3·90, 4·40, 4·41) is very similar to the spectra of the flavene from the flavylium





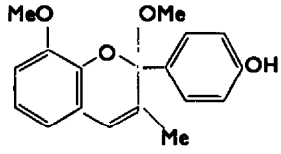
salt–phenol reaction and its methyl ether (VIb) (λ_{max} 270, 243, 222 mμ, log ϵ, 3·90, 4·30, 4·33), thus indicating the presence in these compounds of the same *para*-hydroxy (or methoxy) -styryl chromophore. It is noteworthy that the UV spectrum of the related flav-3-ene[7] VIII (λ_{max} 274, 263 mμ, log ϵ, 4·11, 4·13) distinctly differs from

[5] Reduction of flavylium salts with $NaBH_4$ does not appear to have been described. However, LAH reduction affords flavenes (P. Karrer and M. Seyhan, *Helv. Chim. Acta* 33, 2209 (1950)).

[6] J. W. Gramshaw, A. W. Johnson and T. J. King, *J. Chem. Soc.* 4040 (1958).

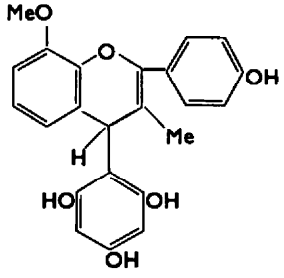
[7] Unpublished work.

these flav-2-enes. Structure VIa for the flavene was confirmed unequivocally by its NMR spectrum (Table 1), the 3-methyl and the benzylic protons absorbing as singlets at 8·26 and 6·55 τ respectively.

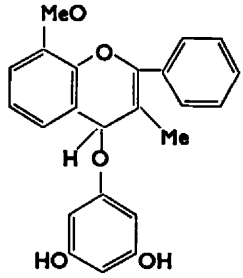


VIII

The major product formed in the reaction of 8-methoxy-4'-hydroxy-3-methyl flavylium chloride (Va) with excess of phloroglucinol at pH 5·8 was a colourless, crystalline compound of molecular formula $C_{23}H_{20}O_6$. This compound gave a positive Gibbs test and an intense red colour with vanillin in acidified ethanol. On complete acetylation and methylation it gave triacetyl and trimethyl derivatives respectively. The tetrahydroxyflavene structure IX, which might have been anticipated for this condensation product, is therefore excluded. The presence of only three hydroxyl groups could be accounted for by possible structures X, XI, XIIa or XIII. The



IX



X

condensation product and its trimethyl derivative, however, are not appreciably effected by hot, dilute aqueous mineral acids. Thus, phenyl benzyl ether structures of type X are excluded, since it is well known that ethers of carbinol bases are easily hydrolyzed to flavylium salts under these conditions.[8] The quinoidal structure XI may be excluded unequivocally on the basis of the UV spectrum of the condensation product (λ_{max} 273 mμ, log ϵ 3·64) and the observation that 8,4'-dimethoxy-3-methyl-flavylium chloride (Vb) reacts smoothly with phloroglucinol to give a crystalline dihydroxy compound, $C_{24}H_{22}O_6$, the dimethyl derivative of which is identical with the trimethyl derivative of the C_{23} product. From these considerations, therefore, the C_{23} compound has the oxygen bridged structure XIIa or XIII. Definitive chemical evidence in favour of one or the other of these two structures has not been obtained. However, by analogy with the acetyl acetone and malonic acid condensation products (I and II) it is most probable that the C_{23} compound is XIIa and is formed from the

[8] The carbinol base methyl ether (VIII) is rapidly and quantitatively hydrolysed to the flavylium salt (Va) in dil. HClaq.

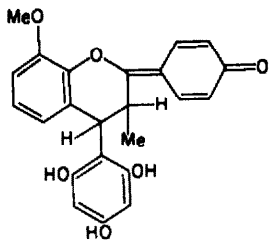
TABLE 1. NMR SPECTRAL* DATA OF FLAVYLIUM SALT–PHLOROGLUCINOL CONDENSATION PRODUCTS

	H_3 and H_3'	H_4 and H_4'	C-CH_3(s)	H(s) of Phloroglucinol nucleus
VIa	—	6·55 (s)	8·26 (s)	—
VIb	—	6·54 (s)	8·20 (s)	—
VIc	—	6·53 (s)	8·19 (s)	--
XIIb	7·67 (d, 2·5 quart., 7·0)	5·88 (d, 2·5)	9·25 (d, 7·0)	3·93 (d, 2·5) 3·77 (d, 2·5)
XIIc	7·4–7·8†	6·05 (d, 2·5)	9·22 (d, 7·0)	3·38 (d, 2·5) 3·25 (d, 2·5)
XIId	7·4–7·8†	6·05 (d, 2·5)	9·23 (d, 7·0)	3·38 (d, 2·5) 3·25 (d, 2·5)
XIIe	7·3–7·8†	6·15–6·25†	9·22 (d, 7·0)	2·7–3·5 (m)‡
XIIf	7·61 (d, 2·5 quart., 7·0)	5·85 (d, 2·5)	9·23 (d, 7·0)	3·80 (d, 2·5) 3·72 (d, 2·5)
XIIg	7·3–7·8†	6·05 (d, 2·5)	9·20 (d, 7·0)	3·36 (d, 2·5) 3·24 (d, 2·5)
XIIh	7·65 (d, 2·5)	5·75 (t, 2·5)	—	3·36 (d, 2·5) 2·26 (d, 2·5)
XIVb	7·3–7·9 (overlapped multiplets)	5·86 (d, 2·5) 5·66 (d, 2·5)	9·27 (d, 7·0) 9·17 (d, 7·0)	 3·75 (s)
XIVc	7·4–7·8†	6·16 (d, 2·5) 5·60 (d, 2·5)	9·22 (d, 7·0) 9·14 (d, 7·0)	 3·46 (s)
XIVd	7·4–7·8†	6·18 (d, 2·5) 6·59 (d, 2·5)	9·21 (d, 7·0) 9·13 (d, 7·0)	 3·48 (s)
XIVe	7·5–7·8†	5·91 (d, 2·5) 5·68 (d, 2·5)	9·30 (d, 7·0) 9·20 (d, 7·0)	 3·75 (s)
XIVf	7·5–7·8†	6·05–6·30† 5·65 (d, 2·5)	9·30 (d, 7·0) 9·20 (d, 7·0)	 3·47 (s)

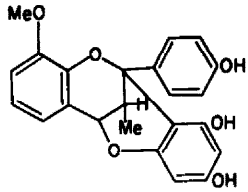
* The NMR spectra, shielding values recorded in τ (multiplicity, coupling constant in cps) were taken in $CDCl_3$ with tetramethylsilane as internal references.

† The absorption peak(s) of the proton(s), although accounted for by integration, was partially or completely overlapped with CH_3CO- or CH_3O- absorptions.

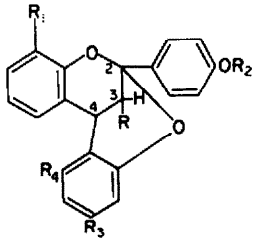
‡ Protons of resorcinol nucleus.



XI



XIII



XII

	R	R_1	R_2	R_3	R_4
a	Me	OMe	H	OH	OH
b	Me	OMe	Me	OMe	OMe
c	Me	OMe	Ac	OAc	OAc
d	Me	OMe	Me	OAc	OAc
e	Me	OMe	Me	OAc	H
f	Me	H	Me	OMe	OMe
g	Me	H	Ac	OAc	OAc
h	H	H	Ac	OAc	OAc

intermediate flavene IX by intramolecular addition of a phloroglucinol hydroxyl to the C_2, C_3 double bond. This latter reaction is similar to the well known addition of phenols to dihydropyran. The acid stability of XIIa may be accounted for by the fact that it is an intramolecular ketal which is apparently the preferred form in the equilibrium with IX. NMR spectral data are in full accord with structure XIIa for the C_{23} compound. Thus the spectrum (Fig. I and Table 1) of its trimethyl derivative (XIIb) showed a three proton doublet (J = 7·0 c/s) at τ = 9·25, a one proton octet (J = 2·5 and 7·0 c/s) at 7·67, a one proton doublet (J = 2·5 c/s) at 5·88, two *meta* coupled (J = 2·5 c/s) proton doublets at 3·93 and 3·77 respectively, and two apparent

doublet A_2B_2 system at 3·08 and 2·39 (apparent *ortho* coupling = 9·0 c/s). Since the spectrum does not indicate the presence of either vinyl methyl or quinoidal protons, structures X and XI may be eliminated. Of the two possible structures (XIIa and XIII) which remain, XIIa is favoured, since the doublet at 5·88 is most appropriately assigned to the bridgehead proton adjacent to two phenyl substituents.[9] The 9·25 doublet is assigned to the 3-methyl group and the 7·67 octet is the spin-spin coupling

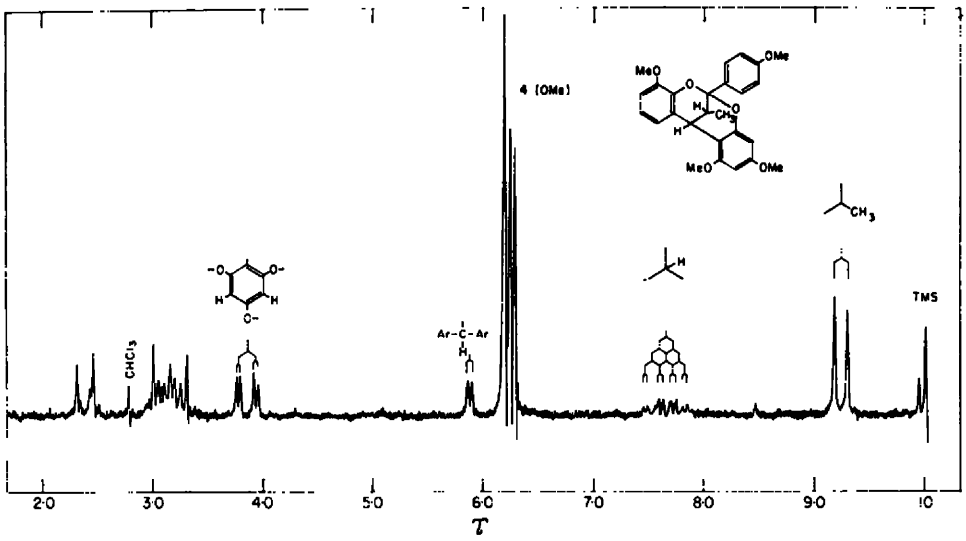


FIG. I. 60 Mc NMR Spectrum of XIIb.

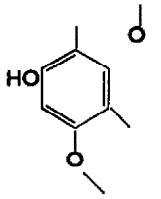
expected of H_3. There is no doubt that the 3·93 and 3·77 doublets arise from the two meta protons of the phloroglucinol nucleus while the A_2B_2 system is attributed to the 4 protons in the bridgehead aromatic ring.[10] Acetylation of XIIa produces the expected paramagnetic shifts for the aromatic protons in the phloroglucinol and bridgehead rings.

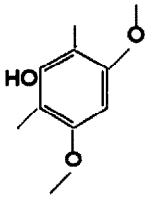
Like Va and Vb, 4′-hydroxy-3-methyl- and 4′-hydroxyflavylium chlorides react with phloroglucinol to form trihydroxy compounds, isolated as the triacetates XIIg and XIIh respectively. Similarly, Vb and resorcinol react to form a monohydroxy compound, isolated as its acetate (XIIe).

Treated with only 0·5 molecular equivs of phloroglucinol in aqueous methanol, 8-methoxy-4′-hydroxy-3-methyl flavylium chloride forms a complex mixture of products from which a colourless, crystalline compound, $C_{40}H_{34}O_9$, was isolated. This compound was also obtained, in better yields, by the further reaction of the C_{23} product (XIIa) with the flavylium salt (Va). The C_{40} compound forms a triacetate and a trimethyl derivative (m.p. 289°) and, therefore, is structurally similar to the C_{23} compound. The C_{40} product, however, has two flavan nuclei attached to phloroglucinol. These may be linked to phloroglucinol as in (a) or (b). Since the C_{40}

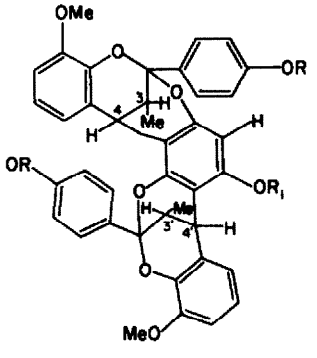
[9] The bridgehead proton in XIII would be expected to adsorb at a much lower field than 5·88τ. Thus, the bridgehead protons of cyanomaclurin and its derivatives appear at 4·6 to 4·9 τ (P. M. Nair and K.Venkataraman, *Tetrahedron Letters* 317 (1963)). The methylene protons of dihydroanthacene, on the other hand, absorb at 6·13 τ.

[10] A. C. Waiss, R. Ludin and D. Stern, *Tetrahedron Letters* 513 (1964).





compound does not give a positive Gibbs test, a structure of type (b), which contains an hydroxyl with a free *para*-position, is excluded[11] and structure XIVa is assigned to this compound. The NMR spectrum (Fig. II and Table 1) of the trimethyl derivative (XIVb) of the C_{40} product is very similar to that of the fully methylated C_{23} compound. As expected the two ter C-methyl groups absorb at 9·27 and 9·17 τ (doublets, J = 7·0 c/s). The two protons at C_3 and $C_{3'}$ appear as unresolved multiplets centering at 7·65 τ. Two bridgeheaded protons and only one phloroglucinol proton are observed.



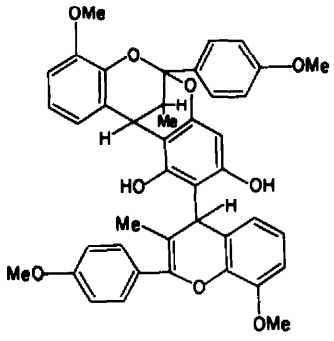
	R	R_1
XIVa	H	H
b	Me	Me
c	Ac	Ac
d	Me	Ac
e	Me	Me
f	Me	Ac

These appear at 5·86, 5·66 (both doublets with J = 2·5 c/s) and 3·75 (singlet) respectively. A paramagnetic shift of 0·3 τ is observed for the phloroglucinol proton in the triacetyl derivative.

In view of the number of asymmetric centers in XIV it would be expected that stereoisomers should be formed in these condensation reactions. In this connection it is noteworthy that the flavylium salt (VIb) reacts smoothly with 0·5 molecular equivs of phloroglucinol to give a mixture of products from which two isomeric monohydroxy compounds, $C_{42}H_{38}O_9$, and a dihydroxy compound of the same molecular formula were isolated in addition to a quantity of the C_{24} product (XIIg). One of the monohydroxy compounds (m.p. 315°) formed a monomethyl derivative (m.p 289°) identical with the trimethyl derivative of the above C_{40} condensation product. The isomeric monohydroxy compound (m.p. 243–245°; monomethyl derivative, m.p. 203°) did not give a Gibbs test and, except for minor differences in chemical shifts,

[11] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).

its NMR spectrum (Fig. III and Table 1) is virtually identical to that of the first isomer. This compound is thus one of the possible stereoisomers of XIVa. Insufficient of the dihydroxy compound was isolated for extensive investigation. The fact that it forms a diacetate suggests, however, that in this product the phloroglucinol is attached to a flavan and a flavene nucleus to give structure XV.



XV

EXPERIMENTAL

Unless otherwise stated, all UV spectra were determined in 95% EtOH in 1 cm silica cells.

8-Methoxy-4'-hydroxy-3-methylflavylium chloride (Va)

A solution of *o*-vanillin (60 g) and 4-hydroxypropiophenone (60 g) in ethyl acetate (400 ml) and EtOH (80 ml) was saturated with HCl and allowed to stand overnight. Orange-red crystals of the flavylium salt rapidly separated (102 g). These were collected and recrystallized from 10% HClaq. Va separated as orange needles, m.p. 213°, $\lambda_{max}^{EtOH-0.5\%HCl}$ 443 (4·28), 272 (4·15) mμ (log ϵ), R_F 0·92 (water–acetic acid–conc. HCl, 80:40:5 v/v), 0·94 (formic acid–3N HCl, 1:1 v/v).

The *ferrichloride* of the flavylium salt crystallized from acetic acid as yellow-brown needles, m.p. 159° (dec).

8-Methoxy-4'-hydroxy-3-methylflav-2-ene (VIa)

(a) *From* Va *and resorcinol.* A solution of Va (5·0 g) and resorcinol (10 g) in MeOH (50 ml) and aqueous buffer, pH 5·8 (100 ml) was warmed to 70° for 5 min and allowed to stand at room temp for 24 hr. Almost colourless crystals separated (1·08 g). They were recrystallized from MeOHaq (norite) whereupon VIa separated as colourless needles, which begin to turn red at 115–120° and melt to a deep red liquid at 150–152°; λ_{max} 270 (3·90), 243 (4·30), 222 (4·33) mμ (log ϵ). (Found: C, 76·1; H, 5·99; MeO-, 11·6. Calc. for $C_{17}H_{16}O_3$: C, 76·1; H, 6·01; 1 MeO-, 11·6%.)

The *acetate* (VIc) of the flavene, prepared by reaction with acetic anhydride and pyridine at room temp, crystallized from MeOH as long, colourless needles, m.p. 129°, λ_{max} 275 (3·82), 220 (4·41), inflection at 240 (4·19) mμ (log ϵ). (Found: C, 73·7; H, 5·91; MeO-, 10·3; CH_3CO-, 13·7. Calc. for $C_{19}H_{18}O_4$: C, 73·5; H, 5·85; 1 MeO-, 10·0; 1 CH_3CO-, 13·9%.)

The methyl ether (VIb) of the flavene was prepared by reaction with MeI and K_2CO_3 in acetone. VIb separated from acetone–MeOH as long, colourless needles, m.p. 121–122°, λ_{max} 270 (3·91), 242 (4·33), 222 (4·36) mμ (log ϵ). (Found: C, 76·6; H, 6·51; MeO-, 21·9. Calc. for $C_{18}H_{18}O_3$: C, 76·6; H, 6·43; 2 MeO-, 22·0%.)

The *benzyl ether* of the flavene, prepared by reaction with benzyl chloride in acetone in the usual

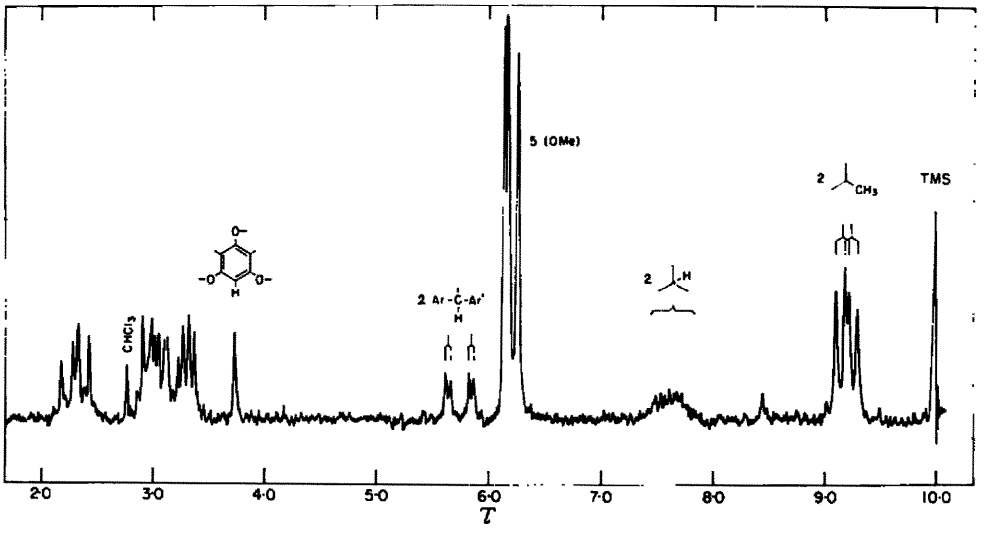


FIG. II 60 Mc NMR Spectrum of XIVb.

way, crystallized from acetone–MeOH as colourless, felted needles, m.p. 125–126°. (Found: C, 80·4; H, 6·17; MeO-, 8·85. Calc, for $C_{24}H_{22}O_8$: C, 80·4; H, 6·19; 1 MeO-, 8·66%.)

(b) *From* Va *and* D-*catechin.* Compound Va (1·5 g) and D-catechin (1·5 g) were dissolved in warm acetic acid (15·0 ml) and water (60 ml). On cooling, the dark orange-red solution rapidly deposited cream-coloured crystals. After 24 hr these were collected (0·43 g) and recrystallized from MeOHaq to give VIa, m.p. and m.m.p. 150–152° (acetate, m.p. and m.m.p. 129°).

(c) *From* Va *and phloroglucinol.* A solution of Va (10 g) and phloroglucinol (15 g) in glacial acetic acid (100 ml) and water (500 ml) was allowed to stand for 20 hr. The crude flavene separated as an orange, crystalline mass (2·0 g). Recrystallized from MeOHaq pure VIa, m.p. 150–152°, was obtained.

(d) *By borohydride reduction of* Va. Compound Va (5·0 g) was dissolved in MeOH (50 ml) and

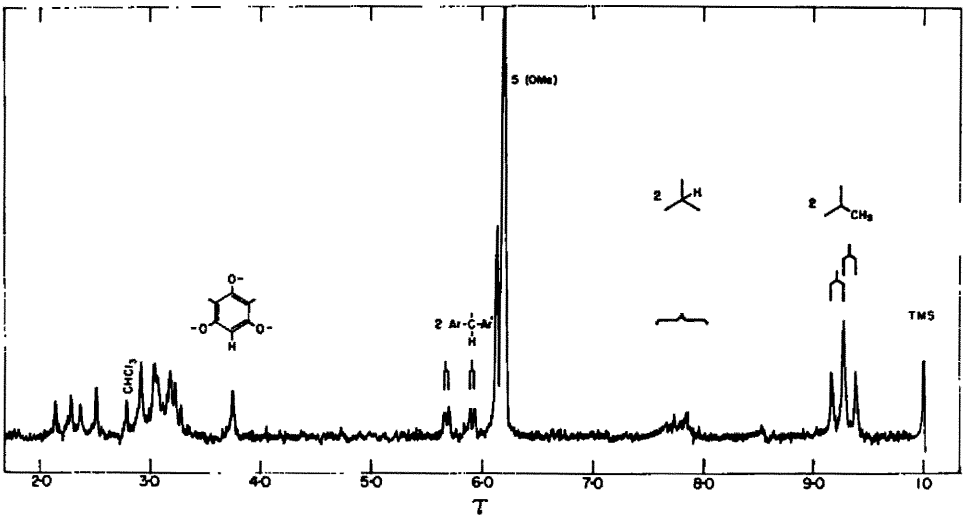


FIG. III 60 Mc NMR Spectrum of XIVe.

water (25 ml) at room temp and immediately treated with $NaBH_4$ (1·0 g) in portions during 5 mins. At the end of the addition, a colourless, crystalline mass had separated. Water (100 ml) was added and the product was collected and recrystallized from MeOHaq. Colourless needles, m.p. 138°, were obtained (3·6 g). Thin-layer chromatography of this product on silicic acid showed that the major component (R_F 0·50 (ether-Skellysolve F, 2:1), 0·39 (ethyl acetate-Skellysolve F, 1:4) was contaminated with a second component (R_F 0·47 and 0·29 in the above solvents). This second component is probably the carbonol base methyl ether (VIII). Repeated recrystallization of the crude reduction product from wet MeOH gave the pure major component as colourless needles, m.p. and m.m.p. with the above flavene, 150–152°. (Found: C, 75·8; H, 5·93; MeO-, 11·6. Calc. for $C_{17}H_{16}O_3$: C, 76·1; H, 6·01; 1 MeO-, 11·6%.)

The *acetate* of the borohydride reduction product had m.p. and m.m.p. with the flavene acetate, 128–129°. (Found: C, 73·5; H, 5·80; MeO-, 10·3. Calc. for $C_{19}H_{18}O_4$: C, 73·5; H, 5·85; 1 MeO-, 10·0%.)

Condensation of 8-*methoxy*-4′-*hydroxy*-3-*methylflavylium chloride and phloroglucinol* (*excess*)

Compound Va (20 g) and phloroglucinol (20 g) were dissolved in a mixture of MeOH (200 ml) and aqueous buffer, pH 5·8 (200 ml) at 60°. After 15 min, 30% H_2O_2 (20 ml) was added[12] and after 24 hr, the precipitated 3-acetyl-7-methoxy-2-(4-hydroxyphenyl) benzofuran[13] was collected. The filtrate, added to water (2 l.), precipitated a colourless solid which was reprecipitated from MeOHaq. Thin layer chromatography showed that this product consisted of a major component contaminated with small quantities of the benzofuran and two other substances. It was dissolved in hot MeOH (25 ml) and diluted with water (5 ml). A small quantity of the above benzofuran thereby crystallized. The filtrate, diluted with more water, gave a crystalline solid which was collected, dried and acetylated by warming with acetic anhydride (40 ml) and pyridine (2 ml) for 3 min. Addition of water gave a solid acetate. This was recrystallized 3 times from acetone–MeOH. XIIc was thus obtained as colourless, glistening prisms, m.p. 178° (8·0 g). On silicic acid it migrated as a single component, R_F 0·71 (ether), 0·31 (ether-Skellysolve F, 2:1); λ_{max} 271 (3·49) mμ (log ϵ). (Found: C, 67·3; H, 5·11; MeO-, 6·12; CH_3CO-, 24·6. Calc. for $C_{28}H_{26}O_9$: C, 67·2; H, 5·05; MeO-, 5·98; 3 CH_3CO-, 24·9%.)

The acetate (XIIc; 4·0 g) was deacetylated in warm acetone (15·0 ml) and 10% NaOHaq (15·0 ml). Water (50 ml) was slowly added and after 5 min the solution was cooled and acidified. The solid thus obtained was recrystallized from aqueous acetone. XIIa separated as solvent, colourless, granular crystals (3·1 g) which sinter at 164–165° and melt at 177–180°; λ_{max} 273 (3·64), inflection at 280 (3·58) mμ (log ϵ). (Found: C, 67·6; H, 5·31; MeO-, 7·65. Calc. for $C_{22}H_{20}O_6 \cdot H_2O$: C, 67·3; H, 5·40; 1 MeO-, 7·56%.)

Compound XIIc, treated with propionic anhydride and pyridine, formed a *tripropionate*. This crystallized from MeOH as colourless needles, m.p. 171°, λ_{max} 272 mμ. (Found: C, 68·7; H, 5·83; MeO-, 5·60. Calc. for $C_{34}H_{32}O_9$: C, 68·6; H, 5·75; 1 MeO-, 5·53%.)

Compound XIIc (0·3 g), methylated with dimethyl sulphate (1·5 ml), K_2CO_3 (4 g) and acetone (25 ml) in the usual way, formed a trimethyl derivative (XIIb). This separated from acetone–MeOH as glistening, colourless prisms, m.p. 177°, λ_{max} 279 (3·56), 272 (3·61) mμ (log ϵ). (Found: C, 71·8; H, 5·90; MeO-, 28·6. Calc. for $C_{26}H_{26}O_6$: C, 71·9; H, 6·03; 4 MeO-, 28·6%.)

The trimethyl derivative (XIIb; 0·1 g), dissolved in glacial acetic acid (2 ml), was treated with 4 drops of 10% HClaq and warmed for 1 min. The yellow-orange solution, diluted with water, deposited a colourless solid. Recrystallized from acetone–MeOH, unreacted XIIb, m.p. 177°, was obtained (85 mgm).

8,4′-*Dimethoxy*-3-*methylflavylium chloride* (Vb)

A mixture of *o*-vanillin (4 g) and 4-methoxypropiophenone (4 g) in ethyl acetate (30 ml) was saturated with HCl and allowed to stand overnight in the refrigerator. The chloride separated as

[12] The peroxide is not involved in the formation of the condensation product, which has also been isolated without peroxide addition. Peroxide addition destroys unreacted flavylium salt and thereby facilitates crystallization of the condensation product. Sodium borohydride has also been used in place of peroxide to facilitate isolation of a pure product.

[13] L. Jurd, *Chem. & Ind.* 1165 (1963).

orange-red crystals which were recrystallized from glacial acetic acid-ether, R_F 0·96 (water–acetic acid–conc. HCl, 80:40:5 v/v), 0·97 (formic acid–3N HCl, 1:1 v/v). The *perchlorate* of the flavylium salt crystallized from acetic acid–5% $HClO_4$aq as yellow needles, m.p. 253–255° (dec).

Condensation of 8,4′-*dimethoxy*-3-*methylflavylium chloride and phloroglucinol* (*excess*)

A solution of Vb (10 g) and phloroglucinol (20 g) in warm MeOH (100 ml) was diluted with aqueous buffer, pH 5·8 (100 ml) and allowed to stand for 30 min. The mixture was then added to 5% HClaq (300 ml). The precipitated orange solid was collected, washed with water, dissolved in MeOH (200 ml) and treated with 30% H_2O_2aq (20 ml). The solution rapidly became a pale yellow. After 5 min excess of water was added and the sticky, colourless product was collected and air-dried.

The crude product was warmed with acetic anhydride (40 ml) and pyridine (5 ml) for 5 min. Water was added and the solid acetate was collected. When warmed with MeOH the acetate crystallized. Recrystallized from acetone–MeOH the *diacetate* (XIId) separated as glistening, colourless needles, m.p. 220° (7·0 g), R_F 0·68 (ether), 0·85 (MeOH), 0·45 (ether-Skellysolve F, 2:1) on silicic acid strips. (Found: C, 68·7; H, 5·39; MeO-, 12·7; CH_3CO-, 17·3. Calc. for $C_{28}H_{20}O_8$: C, 68·6; H, 5·34; 2 MeO-, 12·65; 2 CH_3CO-, 17·5%.)

The diacetate (6·0 g) was dissolved in acetone (50 ml) and 10% NaOHaq (50 ml), warmed and diluted with water (150 ml). After 5 min the solution was acidified. The oil which separated rapidly crystallized. Recrystallized from MeOHaq (norite) the phenol (XII, R = R_2 = Me, R_1 = OMe, R_3 = R_4 = OH) separated, colourless needles, m.p. 149–150° after sintering at 142–144° (4·5 g). The phenol gave a blue colour with Gibbs reagent. (Found: C, 70·9; H, 5·64; MeO-, 15·0. Calc. for $C_{24}H_{22}O_8$: C, 70·6; H, 5·92; 2 MeO-, 15·2%.)

Methylation of the above phenol gave XIIb, m.p. 177°, undepressed on admixture with the trimethyl derivative of the previously described C_{23} condensation product.

Reaction of Va *and* 0·5 mole *phloroglucinol*

A mixture of Va (10 g) and phloroglucinol (2·5 g) was dissolved in MeOH (100 ml) and water (50 ml), warmed briefly and allowed to stand overnight. Cream coloured crystals separated. Recrystallized from acetone–MeOH XIVa was obtained as colourless needles (0·55 g) m.p. 333–334° (dec), λ_{max} 274 (3·88), inflection at 280 (3·83) mμ (log ϵ). (Found: C, 72·4; H, 5·20; MeO-, 9·63. Calc. for $C_{40}H_{34}O_9$: C, 72·9; H, 5·20; 2 MeO-, 9·42%.)

Compound XIVa was best prepared by reaction of XIIa (0·80 g) and Va (0·60 g) in 50% MeOHaq (20 ml). The crystalline mass which separated on adding more MeOH (5 ml) was recrystallized from acetone–MeOH, m.p. and m.m.p with above product, 333–334° (0·34 g).

Treated with acetic anhydride and pyridine XIVa formed a triacetate, (XIVc), which crystallized from acetone–MeOH as glistening, colourless prisms, m.p. 258–259°, λ_{max} 273 (3·64), inflection at 280 (3·59) mμ (log ϵ). (Found: C, 70·0; H, 5·31; MeO-, 7·82; CH_3CO-, 16·4. Calc. for $C_{46}H_{40}O_{12}$: C, 70·4; H, 5·14; 2 MeO-, 7·91; 3 CH_3CO-, 16·5%.)

The *tripropionate* of XIVa crystallized from acetone–MeOH as colourless prisms, m.p. 271–272°. (Found: C, 70·9; H, 5·62; MeO-, 7·46. Calc. for $C_{49}H_{46}O_{12}$: C, 71·1; H, 5·61; 2 MeO-, 7·51%.)

Compound XIVa was methylated with MeI, K_2CO_3 and acetone in the usual way. The trimethyl derivative (XIVb) crystallized from MeOH as colourless prisms, m.p. 289°, λ_{max} 279 (3·70), 272 (3·73) mμ (log ϵ). (Found: C, 73·6; H, 5·66; MeO-, 22·5; mol. wt.[14] 700 ± 2. Calc. for $C_{43}H_{40}O_9$: C, 73·7; H, 5·76; 5 MeO-, 22·1%; mol. wt. 700·3.)

Reaction of Vb *and* 0·5 mole *phloroglucinol*

A solution of Vb (6·0 g) and phloroglucinol (1·5 g) in MeOH (90 ml) and water (12·0 ml) was heated on a steam bath for 10 min. A heavy, crystalline solid separated. After standing 1 hr, the crystalline solid was collected (A). The reaction filtrate from (A) was diluted with water and the red precipitate (2·2 g) was collected (B).

The crude product (A) was recrystallized from acetone–MeOH giving colourless prisms, m.p. 311–312°, which migrate as a single spot on silicic acid (1·65 g) (C). Concentration of the acetone–MeOH filtrate from (C) gave a crystalline product which, recrystallized twice more from acetone–MeOH, separated as colourless needles, m.p. 241–242° (0·4 g) (D).

[14] Kindly determined mass spectrophotometrically by Dr. W. H. McFadden.

The red precipitate (B) was dissolved in MeOH (20 ml) and decolourized by addition of $NaBH_4$ (0·1 g). Water (2·0 ml) was added and the solution allowed to stand for 24 hr. Colourless crystals slowly separated (1·8 g) (E). From the methanolic filtrate the previously described C_{24} compound was isolated and purified as its diacetate XIId (m.p. 220°).

(E) consisted of a mixture of two compounds (on silicic acid, R_F 0·72, 0·47 (ether)). By repeated fractional crystallization these two compounds were separated in a chromatographically pure condition. Colourless needles, m.p. 243°, R_F 0·47 (ether) (product F) were obtained.

Purification of (C). Recrystallization of (C) gave XIV (R = Me, R_1 = H) as glistening, colourless prisms, m.p. 315° (dec). (Found: C, 73·4; H, 5·66; MeO-, 17·9. Calc. for $C_{42}H_{38}O_9$: C, 73·4; H, 5·58; 4 MeO-, 18·1%.)

Acetylation of this compound (0·3 g) in acetic anhydride (3·0 ml) and pyridine (0·5 ml), gave the *monoacetate* (XIVd). This crystallized from acetone–MeOH as colourless needles which soften at 216–218° and melt at 230°. On silicic acid it has R_F 0·55 (ether), 0·34 (ether-Skellysolve F, 2:1), 0·68 (acetone–$CHCl_3$, 1:10). (Found: C, 72·1; H, 5·51; MeO-, 16·8; CH_3CO-, 5·66. Calc. for $C_{44}H_{40}O_{10}$: C, 72·5; H, 5·54; 4 MeO-, 17·0; 1 CH_3CO-, 5·91%.)

The *propionate* of the phenol crystallized from acetone–MeOH as colourless prisms, m.p. 270–271°. (Found: C, 72·9; H, 5·63; MeO-, 16·6. Calc. for $C_{45}H_{42}O_{10}$: C, 72·8; H, 5·70; 4 MeO-, 16·7%.)

Methylation of the phenol gave a monomethyl derivative, m.p. 289°, identical with XIVb.

Purification of (D). Recrystallized from acetone–MeOH (D) gave colourless needles of an isomer of XIV (R = Me, R_1 = H) which soften and decompose at 243–245°, λ_{max} 278, 272 mμ. (Found: C, 73·4; H, 5·77; MeO-, 17·3. Calc. for $C_{42}H_{38}O_9$: C, 73·4; H, 5·58; MeO-, 18·1%.)

Acetylation of this phenol gave a *monoacetate* (XIVf) which crystallized from acetone–MeOH as colourless, glistening prisms. These crystals melt at 245°, resolidify and melt again at 263°. On silicic acid, R_F 0·63 (ether); λ_{max} 278, 272 mμ. (Found: C, 72·5; H, 5·53; MeO-, 16·8; CH_3CO-, 5·82. Calc. for $C_{44}H_{40}O_{10}$: C, 72·5; H, 5·54; 4 MeO-, 17·0; 1 CH_3CO-, 5·91%.)

Methylation of the phenol gave a *monomethyl derivative* (XIVe). This crystallized from acetone–MeOH as colourless needles, m.p. 203°, R_F 0·70 (ether) on silicic acid. (Found: C, 73·4; H, 5·82; MeO-, 21·5. Calc. for $C_{43}H_{40}O_9$: C, 73·7; H, 5·76; 5 MeO-, 22·1%.)

Purification of (F). (F) was recrystallized from acetone–MeOH to give XV as colourless needles, m.p. 263–264° (to an orange liquid). (Found: C, 73·3; H, 5·56; MeO-, 17·4. Calc. for $C_{42}H_{38}O_9$: C, 73·4; H, 5·58; 4 MeO-, 18·1%.)

The diacetate of XV crystallized from acetone–MeOH as colourless glistening prisms, m.p. 240°, R_F on silicic acid 0·61 (ether). (Found: C, 71·7; H, 5·48; MeO-, 15·9; CH_3CO-, 9·0. Calc. for $C_{46}H_{42}O_{11}$: C, 71·65; H, 5·50; 4 MeO-, 16·1; 2 CH_3CO-, 11·2%.)

Condensation of 4'-hydroxyflavylium chloride and phloroglucinol

A mixture of 4'-hydroxyflavylium chloride[15] (2·0 g) and phloroglucinol (4·0 g) in 50% MeOHaq (20 ml) was briefly warmed and allowed to stand 1 hr. $NaBH_4$ was added to reduce the colour of the mixture to a pale yellow and excess of dil. aqueous acetic acid was added. The sticky precipitate was collected, dried and acetylated. The crude acetate crystallized from wet MeOH. Recrystallized from acetone–MeOH the triacetate (XIIh) separated as colourless needles, m.p. 164–165°. (Found: C, 68·5; H, 4·70; CH_3CO-, 27·1. Calc. for $C_{27}H_{22}O_8$: C, 68·35; H, 4·67; 3 CH_3CO-, 27·2%.)

Condensation of 4'-hydroxy-3-methylflavylium chloride and phloroglucinol

4'-Hydroxy-3-methylflavylium chloride (5·0 g) and phloroglucinol (5·0 g) were allowed to react in 50% MeOHaq (50 ml) for 1 hr. The reaction product was decoloured with $NaBH_4$ and precipitated with dil. aqueous acetic acid. The crude product was acetylated with acetic anhydride (20 ml) and pyridine (1·0 ml). The triacetate crystallized from acetone–MeOH. XIIg separated as glistening, colourless prisms, m.p. 159°. On silicic acid it migrated as a single substance, R_F 0·76 (ether), 0·80 (acetone–$CHCl_3$, 1:10), 0·86 (MeOH). (Found: C, 69·0; H, 4·91; CH_3CO-, 26·1. Calc. for $C_{28}H_{24}O_8$: C, 68·8; H, 4·95; 3 CH_3CO-, 26·4 (572)%.)

The acetate (2·0 g) was deacetylated in acetone (10·0 ml) and 10% NaOHaq (10 ml). The phenol obtained on acidification separated as an oil which was not crystallized. The oily product was methylated by heating under reflux with dimethyl sulphate (3·0 ml), K_2CO_3 (5 g) and acetone (30 ml) for

[15] K. Freudenberg and K. Weinges, *Liebigs Ann.* **590**, 140 (1954).

2 hr. The trimethyl derivative (XIIf) separated from acetone–MeOH as glistening, colourless prisms, m.p. 149–150°. (Found: C, 74·3; H, 6·03; MeO-, 22·7. Calc. for $C_{25}H_{24}O_5$: C, 74·2; H, 5·98; 3 MeO-, 23·0%.)

Condensation of 8,4'-*dimethoxy*-3-*methylflavylium chloride and resorcinol*

Compound Vb (2·0 g) and resorcinol (1·0 g) were warmed in MeOH (20 ml) and water (5 ml) for 10 min, cooled and diluted with water. The orange solid was dissolved in MeOH, decolourized by addition of a little $NaBH_4$ and diluted with excess of 5% NaOHaq. The precipitate was filtered. The filtrate was acidified and the precipitated solid was collected, air dried and acetylated. Recrystallized from acetone–MeOH the monoacetate (XIIe) of the condensation product separated as glistening, colourless prisms, m.p. 196–197°. (Found: C, 72·3; H, 5·57; MeO-, 14·2; CH_3CO-, 9·84. Calc. for $C_{26}H_{24}O_6$: C, 72·2; H, 5·59; 2 MeO-, 14·4; 1 CH_3CO-, 9·95%.)

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