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ANTHOCYANIDINS AND RELATED COMPOUNDS—XIII
HYDROGEN PEROXIDE OXIDATION OF FLAVYLIUM SALTS

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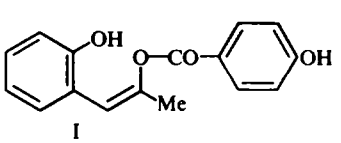
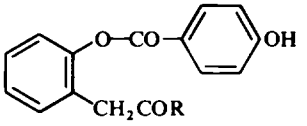
Abstract—In aqueous acetic acid solutions flavylium salts, which are unsubstituted at position 3, are oxidized by hydrogen peroxide to (±):threo keto diols of type VIa. Sodium borohydride reduction of these oxidation products yields 2,3-*trans*-3,4-*trans*-flavan-3,4-diols.

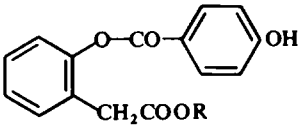
3-ALKYL- and 3-alkoxyflavylium salts undergo a Baeyer–Villiger type oxidation with hydrogen peroxide to yield benzoyl esters of types I, II and III or 3-substituted 2-phenylbenzofurans type IV.[1–4] Natural coumarino benzofurans are readily synthesized from 3-substituted flavylium salts by this method.[5,6] The nature of the



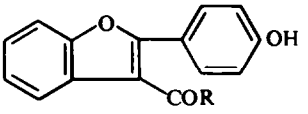
I



II; R = Me, Ph



III: R = Me, Glycosyl

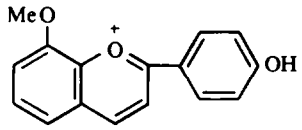


IV: R = Me, OMe

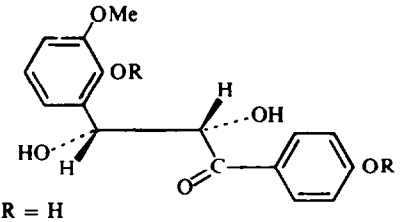
reactions involved in peroxide decompositions of flavylium salts which lack a 3-substituent, on the other hand, are obscure,* since flavylium salts of this type usually give highly colored, amorphous or oily mixtures which have not yet been successfully resolved. However, from a limited number of phenolic flavylium salts in this category we have now isolated crystalline oxidation products which retain the intact cabon skeleton of the flavylium nucleus. These oxidation products are of some interest because on reduction they yield flavan-3,4-diols.

Thus, peroxide oxidation of 8-methoxy-4′-hydroxyflavylium chloride V in aqueous acetic acid solution gives a colorless compound, $C_{16}H_{16}O_6$, considered to be the (±)-threo keto diol of structure VIa. Benzoylation of this oxidation product yields a tetrabenzoate. On alkylation, however, it forms only dialkyl derivatives. The dialkyl derivatives form dibenzoates and, therefore, the oxidation product contains two alcoholic and two phenolic OH groups. One of these phenolic OH's is present as a 4-hydroxyphenacyl grouping. This is indicated by the pronounced bathochromic

* In neutral or alkaline solutions these flavylium salts are oxidized slowly by air to the corresponding flavones.[7]

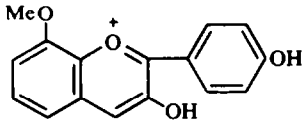


V

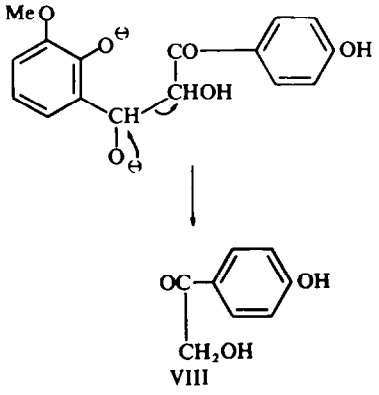


VIa: R = H
VIb: R = Me

shift (54 mμ) of its λ_{max} in alcohol (282 mμ) on addition of alkali.* Its IR spectrum shows a strong band at 1653 cm^{-1} due to a hydrogen-bonded CO group. With Gibbs reagent an immediate, intense blue color results, showing that the second phenolic OH group in the oxidation product is formed by opening of the flavylium heterocyclic ring. Warmed briefly with HCl in glacial acetic acid it undergoes facile dehydration and ring closure to 8-methoxy-3,4'-dihydroxyflavylium chloride VII. In alkaline solutions under mild conditions the oxidation product is rapidly hydrolyzed by a retro-aldol reaction to yield ω,4-dihydroxy-acetophenone VIII (isolated as its dibenzoate).

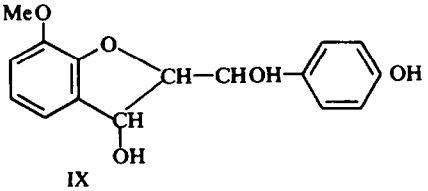


VII

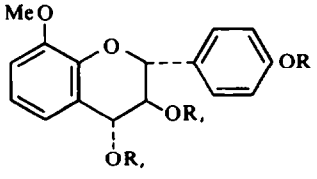


VIII

Sodium borohydride reduction of the oxidation product, followed by acid cyclization, yields a crystalline diol which could be either the 5-membered ring compound IX or a flavan-3,4-diol, e.g. Xa. Heated with alcoholic HCl this diol exhibits the typical flavan-3,4-diol property of being partially oxidized to the 3-hydroxyflavylium salt VII.



IX

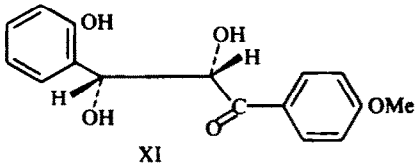


Xa: R = R_1 = H
Xb: R = R_1 = Ac
Xc: R = Me, R_1 = H
Xd: R = Me, R_1 = Ac

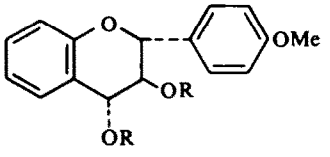
* 4-Hydroxyacetophenone (λ_{max} 278 mμ in alcohol) undergoes a 50 mμ bathochromic shift on addition of sodium ethylate.

Methylation of the phenolic group of the diol and subsequent acetylation yields a diacetate whose NMR spectrum closely coincides with those reported for diacetates of 2,3-*trans*-3,4-*trans*-flavan-3,4-diols. Thus, acetyl group absorption occurs at δ 1·80 and 2·01, and the 2H, 3H and 4H protons have chemical shifts at δ 5·15 (doublet), δ 5·49 (quartet) and δ 6·26 (doublet) respectively, $J_{2,3}$ 9·5 c/s, $J_{3,4}$ 7·3 c/s. Clark-Lewis, *et al.*[8] report chemical shifts at δ 5·18, 5·42 and 6·30 and $J_{2,3}$ 10·0 c/s, $J_{3,4}$ 7·4 c/s for the 2H, 3H and 4H respectively, of the diacetate of 2,3-*trans*-3,4-*trans*-4'-methoxyflavan-3,4-diol. For the equatorial and quasi-equatorial acetoxy groups of 3,4-*trans*-diacetoxy-4'-methoxy-6-methyl-2,3-*trans*-flavan they report δ 1·82, 2·02.

Support for structure Xa for the above reduction product has been obtained by unequivocal identification of the analogous product resulting from a similar oxidation-reduction sequence on 4'-methoxyflavylium perchlorate. Oxidation of this flavylium salt in aqueous acetic acid gave a crystalline trihydroxy compound XI which, like VIa, was readily dehydrated to the corresponding 3-hydroxy-4'-methoxyflavylium chloride. With sodium borohydride it formed a crystalline diol (m.p. 172–173°, diacetate, m.p. 93°), identical in all respects (m.m.p., TLC, NMR spectra) with a synthetic specimen[9] of authentic 2,3-*trans*-3,4-*trans*-4'-methoxyflavan-3,4-diol XIIa.

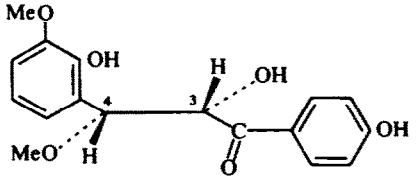


XI

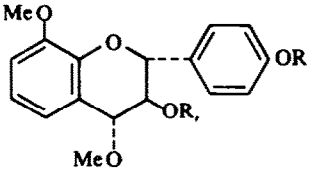


XIIa: R = H
XIIb: R = Ac

Peroxide oxidation of V in acidified aqueous methanol yields VIa and, in major amount, a monomethyl derivative of VIa. Methanolysis would be expected to occur at the benzylic position during this oxidation and the properties of the oxidation product are in accord with structure XIII. It forms a tribenzoate whose NMR spectrum



XIII



a: R = R_1 = H
b: R = R_1 = Ac
c: R = Me, R_1 = H
d: R = Me, R_1 = Ac

shows an aromatic MeO at δ 3·78 (3H, singlet), an aliphatic MeO at δ 3·22 (3H, singlet) and sharp doublets at δ 5·10 (1H) and δ 6·33 (1H). These doublets are assigned to the protons at C_4 and C_3 respectively ($J_{3,4}$ 4·0 c/s).* The oxidation product is

* VIa tetrabenzoate shows an aromatic MeO at δ 3·75 and the protons at C_3 and C_4 as doublets at δ 6·59 and 6·82 ($J_{3,4}$ 5·0 c/s).

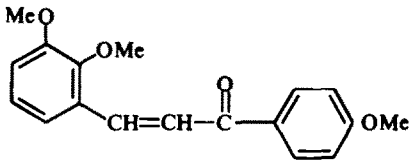
readily cyclized by acids to yield the 3-hydroxyflavylium compound VII rather than the alternate 3-methoxyflavylium salt. Reduced with sodium borohydride in methanol and subsequently cyclized by addition of warm aqueous acid it forms a monomethyl derivative of the phenolic flavan-3,4-diol Xa. This reduction product forms a diacetate (XIVb), which shows acetyl proton absorption as singlets at δ 1·88 (3H) and δ 2·25 (3H), an aromatic MeO at δ 3·83 (3H), an aliphatic MeO at δ 3·27 (3H) and the protons on C_2, C_3 and C_4 at δ 5·10 (1H, doublet), δ 5·62 (1H, quartet) and δ 4·80 (1H, doublet) respectively, $J_{2,3}$ 9·0 c/s, $J_{3,4}$ 7·8 c/s. Methylation of the reduction product forms a trimethoxy compound, which yields a monoacetate XIVd. The NMR spectrum of this monoacetate shows the presence of the acetyl, the aliphatic MeO and two aromatic MeO groups as singlets at δ 1·90, 3·31, 3·80 and 3·85 respectively, and the protons on C_2, C_3 and C_4 at δ 5·02 (1H, doublet), δ 5·65 (1H, quartet) and δ 4·83 (1H, doublet), $J_{2,3}$ 9·0 c/s, $J_{3,4}$ 7·7 c/s. Comparison of these spectra with those of Xd and XIIb establishes the 2,3-*trans*-3,4-*trans* structure XIVa for the reduction product. The aliphatic MeO group causes an upfield shift of about 1·5 ppm of the proton on C_4 and this unequivocally locates the MeO at the C_4 position.

The formation of the *trans* diol derivatives Xa, XIVa and XIIa on reduction establishes the threo configuration of the flavylium oxidation products VIa, XIII and XI, *provided** that epimerization at position 4 does not occur during the acid cyclization step. Experimental evidence which strongly indicates the absence of epimerization in these reactions has been obtained by effecting the reduction and cyclization of VIa and XIII under conditions in which any separation of the original substituent at position 4 would lead to solvolysis and the formation of easily detected, different products. Thus, XIII, reduced in ethanol and cyclized in aqueous ethanolic acid, gave only the previously obtained 4-O-methylflavan-diol XIVa. Similarly, VIa, reduced in anhydrous methanol and cyclized in a large excess of methanol by addition of concentrated sulfuric acid, gave Xa.

In connection with solvolytic displacement reactions of flavan-3,4-diols it is of interest that attempts to solvolyze the flavan-3,4-diols Xa and XIIa, both of which lack a 7-MeO group (cf. footnote 11), were abortive. Heated with methanol containing a trace of HCl, and even under forcing conditions with methanol containing concentrated H_2SO_4, the unchanged diols crystallized from the reaction solution.

In the course of this investigation the dimethyl derivative VIb of the flavylium oxidation product was synthesized from the chalcone XV. This was converted to

* Some flavan-3,4-diols rapidly epimerize or solvolyze under acidic conditions, e.g. melacacidin epimerizes to the more stable 3,4-*trans* diol, isomelacacidin, in HClaq; with EtOH containing 1% AcOH isomelacacidin forms its 4-O-ethyl derivative.[10] It is noteworthy, however, that, as far as the author is aware, the only flavan-4-ols and flavan-3,4-diols known to undergo *facile* epimerization and solvolytic displacement reactions are those which, like melacacidin and isomelacacidin, contain OH or MeO groups in the 7 or 5,7-positions. These electro-donating groups stabilize the intermediate benzyl carbonium ion. In the present case, however, the results so far described indicate that epimerization is most unlikely. Thus, the borohydride reductions described were effected in MeOH with subsequent acid cyclization in aqueous MeOH. Identical reaction conditions and relative concentrations of methanol and water were used in the acid cyclization of both reduced VIa and XIII. Since VIa gave a diol and XIII a 4-O-methyl derivative of the diol epimerization at position 4 is clearly improbable, because any separation of the original OH or MeO at position 4 by an S_N1 mechanism (which would yield the same intermediate benzyl carbonium ion from VIa and XIII) or solvolytic S_N2 mechanism *must* lead to the formation of an identical product(s) from VIa and XIII.



XV

the *trans** epoxide by alkaline hydrogen peroxide. Acid hydrolysis of the epoxide gave VIb in small yield. An S_N1 mechanism is probably involved in this hydrolysis, however, and, therefore, this synthesis is not considered to be of stereochemical significance with regard to the structure of VIa.

3-Methoxy-4'-hydroxyflavylium chloride and a number of 2'-hydroxyflavylium salts have been similarly oxidized to crystalline products structurally analogous to VIa. With flavylium salts containing a 7-OH or 7-MeO group, however, attempts to isolate homogeneous products have proved unsuccessful. In this oxidation it is not known whether initial attack occurs at the 2- or the 4-position of the flavylium nucleus. However, the formation of the threo diol and the observed methanolysis in aqueous methanol oxidation may be accounted for by initial formation of a hydroperoxide at position 4 and decomposition of this to an epoxide, e.g. by route A or B.

EXPERIMENTAL

8-Methoxy-4'-hydroxyflavylium chloride V

A cooled soln of ortho-vanillin (7·6 g) and 4-hydroxyacetophenone (6·8 g) in EtOAc (100 ml) and EtOH (10 ml) was saturated with HCl gas. After 24 hr the crystalline product was collected and dissolved in a mixture of glacial AcOH (40 ml) and 10% HClaq (40 ml). On adding 10% HClaq (100 ml) to the hot soln V chloride separated as orange needles, dec 165–168°; $\lambda_{max}^{EtOH-HCl}$ 447, 289, 273, 264 mμ.

V *Perchlorate* crystallized from glacial AcOH as yellow granules, m.p. 226–227°. (Found: C, 54·9; H, 3·81. Calc. for $C_{16}H_{13}O_7Cl$: C, 54·5; H, 3·72%).

Oxidation of V *in aqueous acetic acid*

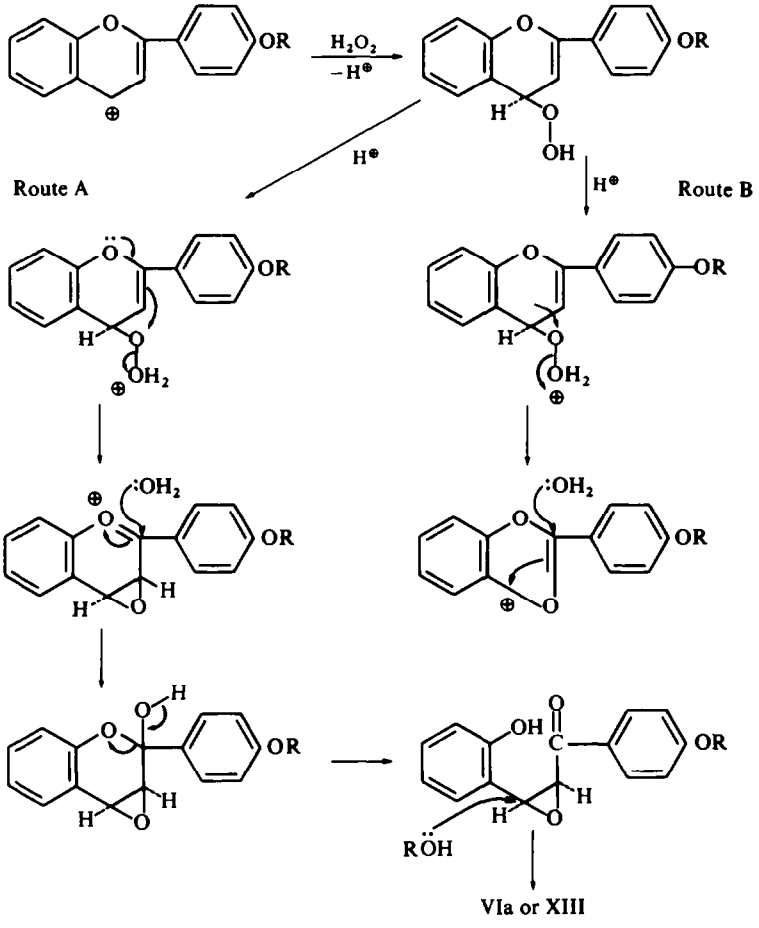
30% H_2O_2 (20 ml) and water (100 ml) were added to a soln of V chloride (10·0 g) in glacial AcOH (50 ml) and 20% H_2SO_4aq (50 ml) at 50–60°. Crystals separated within an hr. After 5 hr these were collected, washed with 50% aqueous acetone and recrystallized from acetone–MeOH. VIa separated as glistening, cream-colored needles, m.p. 202–203° (2·80–3·50 g). VIa migrates as a single species on silicic acid TLC (R_f 0·55, ether), gives a blue Gibbs test and a red color with alcoholic $FeCl_3$; λ_{max}^{EtOH} 282 (4·24), λ_{max}^{NaOEt} 336 (4·42), 240 (4·20) mμ (log ε); IR in Nujol, bands at 3488, 3365, 3250, 1653, 1605, 1582 cm^{-1}. (Found: C, 63·2; H, 5·43; MeO—, 10·9. Calc. for $C_{16}H_{16}O_6$: C, 63·15; H, 5·30; 1 MeO—, 10·2%).

VIa (0·40 g), benzoyl chloride (4·0 ml) and pyridine (4·0 ml), heated 5 min, formed VIa *tetrabenzoate*, colorless needles ex acetone–MeOH, m.p. 211–212° (1·1 g); λ_{max}^{EtOH} 233, inflection at 274 mμ. (Found: C, 73·3; H, 4·48; MeO—, 4·46. Calc. for $C_{44}H_{32}O_{10}$: C, 73·3; H, 4·48; 1 MeO—, 4·31%).

A mixture of VIa (0·40 g), benzyl chloride (3·0 ml), KI (1·0 g), K_2CO_3 (5·0 g) and dry acetone (50 ml) was refluxed for 2 hr. The filtered acetone soln was evaporated and the oily residue was suspended in warm Skellysolve F* (20 ml). The *dibenzyl ether* of VIa thereby crystallized. Recrystallized from MeOH it formed glistening, colorless plates, m.p. 128° (0·29 g). (Found: C, 74·4; H, 5·80. Calc. for $C_{30}H_{28}O_6$: C, 74·4; H, 5·83%).

* The *trans* configuration of the crude epoxide was established by its NMR spectrum, the C_3 and C_4 protons appearing as sharp doublets at δ 4·22, 4·36, $J_{3,4}$ 2·0 c/s. For *cis* epoxides J = 4–5 c/s. The *trans* configuration is in accord with the findings of Zimmerman *et al.*[11]

* Reference to a company or product name does not imply approval or recommendation of the product by the U.S. Department of Agriculture to the exclusion of others that may be suitable.



Warmed with pyridine (1·0 ml) and benzoyl chloride (1·0 ml) the above dibenzyl ether gave a *dibenzoate*, colorless needles ex acetone–methanol, m.p. 145°. (Found: C, 76·3; H, 5·29. Calc. for $C_{44}H_{36}O_8$: C, 76·3; H, 5·24%).

Acid cyclization of VIa

10% HCl aq (15·0 ml) was added to a boiling soln of VIa (0·20 g) in glacial AcOH (2·0 ml) and conc HCl (4 drops). Orange needles separated on cooling (0·14 g). Recrystallized from AcOH–10% HCl aq, the product crystallized as orange-red needles, m.p. 235–245° (dec begins at 215°), chromatographically and spectrally identical with authentic VII; $\lambda_{max}^{EtOH-HCl}$ 477 (4·44), 263 (4·33) mμ (log ε); R_f 0·72 (formic acid/3N HCl, 1:1), 0·73 (water/AcOH/conc HCl, 80:40:5), 0·58 (water/AcOH/conc HCl, 80:20:5); V (λ_{max} 447 mμ) has R_f 0·89, 0·88 and 0·74 respectively in these solvents.

Alkaline hydrolysis of VIa

Compound VIa (0·40 g) was dissolved in 10% NaOH aq (10·0 ml) at room temp. After 5 min benzoyl chloride (3·0 ml) was added with shaking for 10 min. Saturated $NaHCO_3$ aq (20 ml) was added, the oily benzoate was collected and crystallized from acetone–MeOH. The benzoate separated as colorless plates, m.p. and m.m.p. with authentic ω,4-dibenzoyloxy acetophenone, 179–180°; λ_{max}^{EtOH} 248 mμ. (Found: C, 73·3; H, 4·54. Calc. for $C_{22}H_{16}O_5$: C, 73·3; H, 4·48%).

(±)-*threo*-1-(4-*Methoxyphenyl*) 3-(2,3-*dimethoxyphenyl*) 2,3-*dihydroxy*-1-*propanone* VIb

(a) A mixture of ortho-vanillin (18·7 g) and 4-methoxyacetophenone (12·0 g) in EtOH (80 ml) and 50% KOH aq (60 ml) was kept for 24 hr, diluted with water (1·5 l) and acidified with AcOH (100 ml). The solid product, 2-*hydroxy*-3,4'-*dimethoxychalcone*, crystallized from acetone–MeOH as yellow prisms, m.p. 141–142° (19·0 g). (Found: C, 71·7; H, 5·58; MeO—, 21·7. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·67; 2 MeO—, 21·8%).

The above chalcone (5·0 g) was heated with Me_2SO_4 (5·0 ml), K_2CO_3 (10·0 g) and dry acetone (100 ml) for 2 hr. The mixture was concentrated and diluted with water. XV crystallized from acetone-MeOH as pale yellow, flat needles, m.p. 103–104° (4·7 g). (Found: C, 72·7; H, 5·97. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·08%).

2N NaOH aq (3·0 ml) and 30% H_2O_2 (3·0 ml) were added to a soln of XV (2·0 g) in acetone (20 ml) and MeOH (10 ml). After 24 hr excess of water was added and the crude, oily epoxide was collected. It was hydrolyzed by brief warming in AcOH (20 ml) and 10% H_2SO_4 aq (20 ml). After 2 days water was added. The oily ppt slowly crystallized. Recrystallized successively from aqueous MeOH and MeOH alone VIb was obtained as colorless, glistening needles, m.p. 139–140° (0·25 g). (Found: C, 65·1; H, 6·15. Calc. for $C_{18}H_{20}O_6$: C, 65·05; H, 6·07%).

VIb formed a *dibenzoate*, colorless prism ex MeOH, m.p. 123–124° with prior sintering at 117°. (Found: C, 71·3; H, 5·27. Calc. for $C_{32}H_{28}O_8$: C, 71·1; H, 5·22%).

(b) A soln of the oxidation product VIa in acetone–MeOH was treated with excess of ethereal diazomethane. After 20 hr the soln was concentrated and diluted with a little water. Colorless needles separated. Recrystallized from MeOH VIb was obtained, m.p. and m.m.p. 139–140°. The two specimens of VIb prepared in (a) and (b) had identical R_f values on silicic acid TLC.

The above product formed a dibenzoate, m.p. and m.m.p. with VIb dibenzoate, 123–124°, with prior sintering at 117°.

8-*Methoxy*-4'-*hydroxy*-2,3-trans-*flavan*-3,4-*diol* Xa

(a) $NaBH_4$ (3·0 g) was added to a suspension of VIa (4·0 g) in MeOH (40 ml) during 10 min. The soln was acidified with glacial AcOH (10·0 ml) and 5% HCl aq (120 ml), heated rapidly to near-boiling and allowed to cool. Colorless crystals rapidly separated. Recrystallized from aqueous MeOH Xa was obtained as colorless needles, m.p. 224–225° (2·40 g). It did not give a color with Gibbs reagent. (Found: C, 66·7; H, 5·61. Calc. for $C_{16}H_{16}O_5$: C, 66·7; H, 5·59%).

Heated with Ac_2O and NaOAc the above diol gave the *triacetate*, Xb, colorless granular crystals ex MeOH, m.p. 129°. (Found: C, 63·8; H, 5·41. Calc. for $C_{22}H_{22}O_8$: C, 63·8; H, 5·35%).

Warmed with benzoyl chloride (1·0 ml) and pyridine (1·0 ml) Xa (50 mg) formed a *tribenzoate*, colorless prisms ex acetone–MeOH m.p. 184°. (Found: C, 74·0; H, 4·76. Calc. for $C_{37}H_{28}O_8$: C, 74·0; H, 4·70%).

(b) $NaBH_4$ (0·5 g) was added to a soln of VIa (0·50 g) in MeOH (10·0 ml). After 5 min the soln was diluted with MeOH (10·0 ml) and acidified with conc H_2SO_4 (1·0 ml). The mixture was heated on a steam-bath for 10 min and excess acid was neutralized by addition of solid $NaHCO_3$. The filtered MeOH soln was concentrated to small bulk and diluted with a mixture of ether and Skellysolve F. Colorless crystals separated. These were collected and, without purification, were acetylated by brief heating with Ac_2O and NaOAc. The acetate, crystallized successively from ether–Skellysolve F and from MeOH, separated as colorless granular crystals, m.p. 129°, identical (m.m.p. and NMR spectrum) with Xb.

8,4'-*Dimethoxy*-2,3-trans-*flavan*-3,4-trans-*diol* Xc

Compound (0·5 g) was heated under reflux with MeI (3·0 ml), K_2CO_3 (5 g) and dry acetone (50 ml) for 1·5 hr. The filtered acetone soln was evaporated and the product was recrystallized from MeOH. Xc separated as colorless needles, m.p. 192° (0·40 g). (Found: C, 67·7; H, 6·00. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·00%).

Xc (0·15 g), heated on a steam-bath for 20 min with Ac_2O (1·0 ml) and pyridine (1·0 ml), formed 3,4-trans-*diacetoxy*-8,4'-*dimethoxy*-2,3-trans-*flavan* Xd, colorless, fluffy needles ex MeOH, m.p. 150°. (Found: C, 65·4; H, 5·80. Calc. for $C_{21}H_{22}O_7$: C, 65·3; H, 5·74%).

Oxidation of V *in aqueous methanol*

30% H_2O_2 (20·0 ml) was added to a soln of V chloride (10·0 g) in MeOH (100 ml) and 20% H_2SO_4 aq (50 ml) at 60°. The mixture was allowed to stand at room temp for 3 hr and the crystalline product was collected (3·3 g). TLC on silicic acid showed the presence of VIa and a compound of higher R_f. The crude

mixture was dissolved in acetone, diluted with excess of MeOH and concentrated, whereupon XIII crystallized. Recrystallized from MeOH, XIII was obtained as colorless brittle prisms m.p. 209° (1·1 g). With alcoholic $FeCl_3$ it gave a red color. (Found: C, 64·2; H, 5·74; MeO— 19·5. Calc. for $C_{17}H_{18}O_6$: C, 64·1; H, 5·70; 2 MeO—, 19·5%).

Warmed with benzoyl chloride (1·0 ml) and pyridine (1·0 ml) XIII (0·1 g) formed a *tribenzoate*, colorless prisms ex acetone–MeOH, m.p. 145°. (Found: C, 72·3; H, 4·81; MeO—, 9·36. Calc. for $C_{38}H_{30}O_9$: C, 72·4; H, 4·80; 2 MeO—, 9·84%).

XIII (0·20 g), treated with glacial AcOH and HCl aq as described for VIa, gave VII chloride as orange-red needles, $\lambda_{max}^{EtOH-HCl}$ 477, 263 mμ, m.p. and m.m.p. 235–245° (dec).

Reduction of XIII

(a) Compound XIII (1·0 g) was suspended in MeOH (10·0 ml) and reduced with $NaBH_4$ (1·0 g). After 10 min the soln was acidified with AcOH (5 ml) and 10% aq (20 ml), diluted with water (50 ml) and heated rapidly to near-boiling. On cooling, colorless crystals separated. Recrystallized from MeOH XIVa separated as colorless needles, m.p. 225°; m.m.p. with Xa, 195–200°. (Found: C, 67·6; H, 5·97; MeO—, 20·6. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·00; 2 MeO—, 20·5%).

Heated with Ac_2O and NaOAc XIVa formed a *diacetate*, colorless granular crystals ex ether Skellysolve F, m.p. 135–136°. (Found: C, 65·4; H, 5·82. Calc. for $C_{21}H_{22}O_7$: C, 65·3; H, 5·74%).

(b) Compound XIII (0·50 g) was suspended in EtOH (5·0 ml) and reduced with $NaBH_4$ (0·5 g). After 10 min the soln was acidified with AcOH (3·0 ml) and 10% HCl aq (10·0 ml). Water (25 ml) was added and the soln was heated rapidly to near boiling. On cooling colorless crystals rapidly separated (0·30 g), m.p. 222°. A portion of this crude product was acetylated with warm Ac_2O and NaOAc. Crystallized from ether–skellysolve F the diacetate XVb, m.p. and m.m.p. 136°, was obtained. In $CDCl_3$ the NMR spectrum of this diacetate showed acetyl absorption as singlets at δ 1·88 (3H), and δ 2·25 (3H), the C_4 aliphatic MeO as a singlet at δ 3·27 (3H), an aromatic MeO at δ 3·83 (3H) and the 2H, 3H and 4H protons at δ 5·10 (doublet), δ 5·62 (quartet) and δ 4·80 (doublet) respectively, $J_{2,3}$ 9·0 c/s, $J_{3,4}$ 7·8 c/s. The NMR spectrum of XVb prepared by reduction in MeOH was identical. The remaining portion of the EtOH reduction product was recrystallized from aqueous MeOH to give pure XVa, m.p. and m.m.p. 224–225°.

XVa (0·80 g) was heated under reflux with a mixture of MeI (5·0 ml), anhyd K_2CO_3 (10 g) and dry acetone (50 ml) for 2 hr. The filtered soln was evaporated and the solid product was crystallized from MeOH. XVc separated as colorless needles, m.p. 169°. (Found: C, 68·6; H, 6·38. Calc. for $C_{18}H_{20}O_5$: C, 68·3; H, 6·37%).

XVc (0·4 g) was heated on a steam-bath with Ac_2O (2·0 ml) and pyridine (2 ml) for 10 min. The solid acetate obtained on adding water was crystallized from MeOH. The monoacetate XVd was thereby obtained as colorless glistening needles, m.p. 135–136°. (Found: C, 67·1; H, 6·17. Calc. for $C_{20}H_{22}O_6$: C, 67·0; H, 6·19%).

Oxidation of 4′-methoxylflavylium perchlorate in aqueous acetic acid

30% H_2O_2 (12·0 ml), AcOH (30 ml) and water (30 ml) were added to a warm soln of 4′-methoxy-flavylium perchlorate[12] (6·0 g) in glacial AcOH (30 ml) and 20% H_2SO_4 aq (30 ml). After 20 min warm water (250 ml) was added and the soln was clarified by filtration through celite. The pale yellow filtrate was kept at room temp for 24 hr whereupon cream-colored crystals separated (1·0 g). Recrystallized from MeOH XI separated as soft, colorless needles, m.p. 157–158°, λ_{max}^{EtOH} 278 mμ. It gave a blue color with Gibbs reagent and a reddish-brown color with alcoholic $FeCl_3$. (Found: C, 66·8; H, 5·68. Calc. for $C_{16}H_{16}O_5$: C, 66·7; H, 5·59%).

XI formed a *tribenzoate*, glistening, colorless prisms ex acetone-MeOH, m.p. 151°. (Found: C, 73·9; H, 4·69. Calc. for $C_{27}H_{28}O_8$: C, 74·0; H, 4·70%).

Warmed with AcOH–HCl aq XI gave *4′-methoxy-3-hydroxyflavylium chloride*, $\lambda_{max}^{EtOH-HCl}$ 472 mμ, R_f 0·82 (water/AcOH/conc HCl, 80:40:5), R_f 0·70 (water/AcOH/conc HCl, 80:20:5).

2,3-trans-3,4-trans-4′-*Methoxyflavan*-3,4-*diol* XIIa

(a) 3-Hydroxy-4′-methoxyflavanone, prepared and reduced with $NaBH_4$ as described,[9] gave XIIa, colorless needles ex methanol, m.p. 172–173°. (Found: C, 70·7; H, 5·89. Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 5·92%).

The *diacetate* XIIb crystallized from Skellysolve F as colorless prisms, m.p. 93° (lit.[9] m.p. 93°). In $CDCl_3$ acetyl absorption occurs as singlets at δ 1·84 and δ 2·04, and the 2H, 3H and 4H protons have chemical shifts at δ 5·04 (doublet), δ 5·53 (quartet), δ 6·32 (doublet), $J_{2,3}$ 9·5 c/s, $J_{3,4}$ 7·3 c/s.

(b) The 4'-methoxyflavylium oxidation product XI (0·80 g) was suspended in MeOH (10·0 ml) and treated with cooling with $NaBH_4$ (0·80 g). After 10 min the soln was acidified with 5% HCl aq (20 ml), heated briefly to boiling and allowed to cool. The colorless product (0·3 g), recrystallized from wet MeOH, separated as colorless, glistening needles, m.p. and m.m.p. with authentic XIIa, 172–173°. XIIa and the product migrates as a single species on TLC on silicic acid. (Found: C, 70·7; H, 5·93; Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 5·92%).

The product formed a *diacetate*, colorless prisms ex Skellysolve F, m.p. and m.m.p. with XIIb, 93°. R_f values and NMR spectrum of this diacetate were identical with those of XIIb.

Attempted methanolysis of flavan-3,4-diols Xa *and* XIIa

(a) A soln of XIIa (0·20 g) in anhyd MeOH (4·0 ml) containing 2 drops of 10% HCl aq was heated on a steam-bath for 20 min and allowed to cool slowly to room temp. Unreacted XIIa crystallized, m.p. and m.m.p. 173°.

(b) A soln of XIIa (0·37 g) in anhyd MeOH (15·0 ml) containing 1 drop of conc H_2SO_4 was heated on a steam-bath for 20 min, the volume of the soln thereby being reduced to about 2·0 ml. On cooling, colorless crystals separated (0·21 g). These were collected and acetylated by heating with Ac_2O and pyridine. Crystallized from ether–Skellysolve F the diacetate XIIb was obtained, m.p. and m.m.p. 92°. The NMR spectrum of this acetate showed a complete absence of aliphatic MeO protons and was identical with the spectrum of authentic XIIb.

(c) A soln of Xa (0·20 g) in MeOH (4·0 ml) containing 2 drops of 10% HCl aq was heated as described above. On cooling unreacted Xa crystallized, m.p. and m.m.p. 224° (0·12 g).

(d) A soln of Xa (0·30 g) in anhyd MeOH (15·0 ml) containing 1 drop of conc H_2SO_4 was concentrated during 20 min to about 2·0 ml. Cream crystals separated from the yellow soln on cooling (0·14 g). The crude product was benzoylated with warm benzoyl chloride and pyridine. Crystallized from acetone–MeOH Xa dibenzoate was obtained, m.p. and m.m.p. 183–184°. The NMR spectrum of this dibenzoate showed an aromatic MeO at δ 3·92 (3H), a doublet at δ 5·70 (1H), a triplet at δ 6·2 (1H) and a doublet at δ 6·62 (1H), $J_{2,3}$ 5·5 c/s, $J_{3,4}$ 5·5 c/s.

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REFERENCES

[1] L. Jurd, *Tetrahedron* **22**, 2913 (1966).
[2] W. Dilthey and W. Hoschen, *J. Prakt. Chem.* **246**, 42 (1933).
[3] P. Karrer, R. Widmer, A. Helfenstein, W. Hurliman, O. Nievergelt and P. Monsarrat-Thoms, *Helv. Chim. Acta* **10**, 729 (1927).
[4] L. Jurd, *J. Org. Chem.* **29**, 2602 (1964).
[5] L. Jurd, *Tetrahedron Letters* No. 18, 1151 (1963).
[6] R. R. Spencer, B. E. Knuckles and E. M. Bickoff, *J. Heterocyclic Chem.* **3**, 450 (1966).
[7] D. W. Hill and R. R. Melhuish, *J. Chem. Soc.* 1161 (1935).
[8] J. W. Clark-Lewis, L. M. Jackman and T. M. Spotswood, *Aust. J. Chem.* **17**, 632 (1964).
[9] M. M. Bokadia, B. R. Brown and W. Cummings, *J. Chem. Soc.* 3308 (1960).
[10] J. W. Clark-Lewis, *Rev. Pure Appl. Chem.* **12**, 96 (1966).
[11] H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.* **81**, 108 (1959).
[12] Ch. Michaelidis and R. Wizinger, *Helv. Chim. Acta* **34**, 1761 (1951).