

## ANTHOCYANIDINS AND RELATED COMPOUNDS—XI

### CATECHIN-FLAVYLIUM SALT CONDENSATION REACTIONS

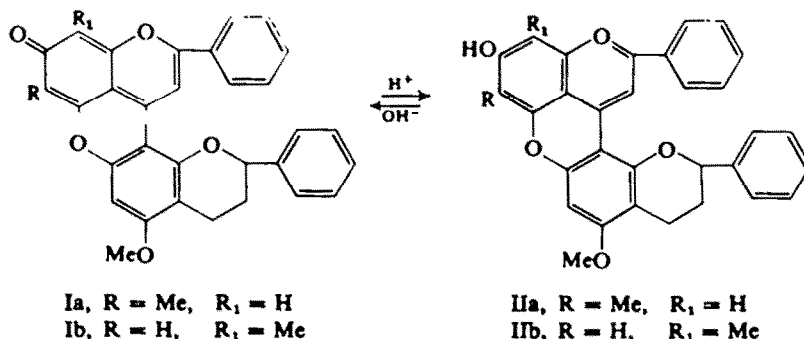
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**Abstract**—Flavylium salts and d-catechin condense oxidatively to yield crystalline 4-flavanylflavylium salts. Aerial oxidation is not involved in these condensation reactions. A 4-flavanylflavene is first formed and then oxidized by a second molecule of the flavylium salt, which is reduced to a monomeric flav-2-ene. This conclusion is supported by studies on the oxidation of model phenolic flav-2-enes. Disproportionation of a flavene, viz. VIII, to a flavylium salt and the corresponding flavan has been demonstrated unequivocally for the first time.

DRACORUBIN, a complex anhydro base present in the resin of the palm *Dracaena draco*<sup>1,2</sup> has been assigned structure Ia or Ib.<sup>3,4</sup> With acids it forms orange-red dracorubylum salts (IIa or IIb). Until recently dracorubin was the only clearly recognized example of a natural bisflavonoid in which the flavonoid nuclei are linked



by a carbon-to-carbon bond from the 4-position of one nucleus to the 8-(or 6-) position of the other. In 1965, however, natural dimeric proanthocyanidins of type III were reported.

Dracorubin and model compounds of similar structure have not yet been successfully synthesized,<sup>5</sup> although it has been suggested<sup>6</sup> that its phytochemical formation

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<sup>1</sup> H. Brockmann and R. Haase, *Chem. Ber.* **69**, 1950 (1936).

<sup>2</sup> G. Hesse and W. Klingel, *Liebigs. Ann.* **524**, 14 (1936).

<sup>3</sup> D. A. Collins, F. Haworth, K. Isaraseana and A. Robertson, *J. Chem. Soc.* 1876 (1950).

<sup>4</sup> A. Robertson, W. B. Whalley and J. Yates, *J. Chem. Soc.* 3117 (1950).

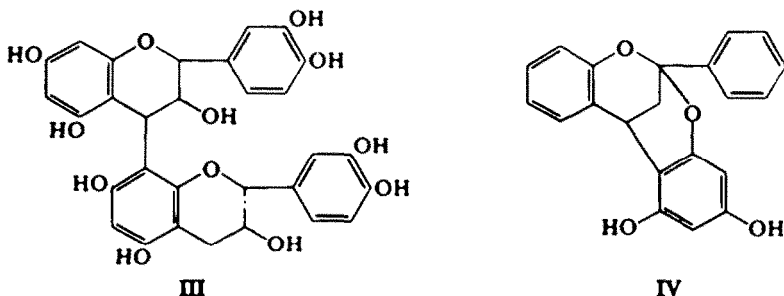
<sup>5</sup> T. A. Geissman and H. F. K. Dittmar, *Phytochemistry* **4**, 359 (1965).

<sup>6</sup> K. Weinges and K. Freudenberg, *Chem. Commun.* **11**, 220 (1965).

<sup>7</sup> L. L. Creasy and T. Swain, *Nature, Lond.* **208**, 151 (1965).

<sup>8</sup> Ch. B. Rao and V. Venkateswarlu, *Tetrahedron* **20**, 551 (1964).

<sup>9</sup> M. Blackburn, G. B. Sankey, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1573 (1957).



must involve an oxidative condensation of a flavylium salt with a flavan. On the other hand, it was recently proposed<sup>10</sup> that dracorubin-type compounds probably arise by oxidation of 5,7-dihydroxyflavans, since it was observed that 4',5,7-trimethoxyflavan darkens to a red resin in the presence of air and light.<sup>11</sup> For some time we have considered that the biosynthetic mechanism proposed<sup>9</sup> might be adapted to effect a laboratory synthesis of dracorubin-type compounds. In this connection preliminary studies<sup>12</sup> showed that phloroglucinol and flavylium salts undergo a nonoxidative condensation to form colourless 4-substituted flavans of type IV. A natural proanthocyanidin with a similar oxygen-bridged structure has just been reported.<sup>13</sup>

Reactions involved in the condensation of a model flavylium salt with *d*-catechin have now been investigated. Thus, in dilute aqueous acetic acid solutions equimolecular quantities of *d*-catechin and 8-methoxy-4'-hydroxy-3-methyl-flavylium chloride (V) rapidly deposit colorless, crystalline 8-methoxy-4'-hydroxy-3-methylflav-2-ene (VIII) and simultaneously form an orange-red pyrylium salt. Optimum yields of the pyrylium salt are obtained by reaction of *d*-catechin with two equivalents of V. The amorphous pyrylium salt crystallizes from acidified methanol-ethyl acetate solutions and can then be recrystallized easily from aqueous mineral acids. Elemental analyses on the chloride of the condensation product established the presence of one methoxyl group and a molecular formula,  $C_{32}H_{27}O_9Cl$ . Its visible and UV spectrum (Fig. 1) is almost identical with that of V in aqueous HCl solutions, except that the absorbance at the  $\lambda_{max}$  (429  $m\mu$ ) is, as expected, only about one-half that of V for solutions of the same concentration (in g/l.). In ethanolic HCl solutions the pyrylium condensation product is stable and its  $\log \epsilon$  value at  $\lambda_{max}$  439  $m\mu$  is identical with that at its  $\lambda_{max}$  in aqueous acid solutions. V, in contrast, is unstable in ethanolic HCl solutions and partially decolorizes due to formation of an equilibrium mixture with the ethyl ether of the colorless carbinol base. From these data the reaction product contains both flavylium and catechin nuclei. Since it is stable to boiling, aqueous acids and, as described below, forms a hexahydroxy reduction product, an ether linkage between the nuclei is excluded. By analogy with the phloroglucinol,<sup>12</sup> dimedone<sup>14,15</sup> and

<sup>10</sup> A. J. Birch and M. Salahuddin, *Tetrahedron Letters* No 32, 2211 (1964).

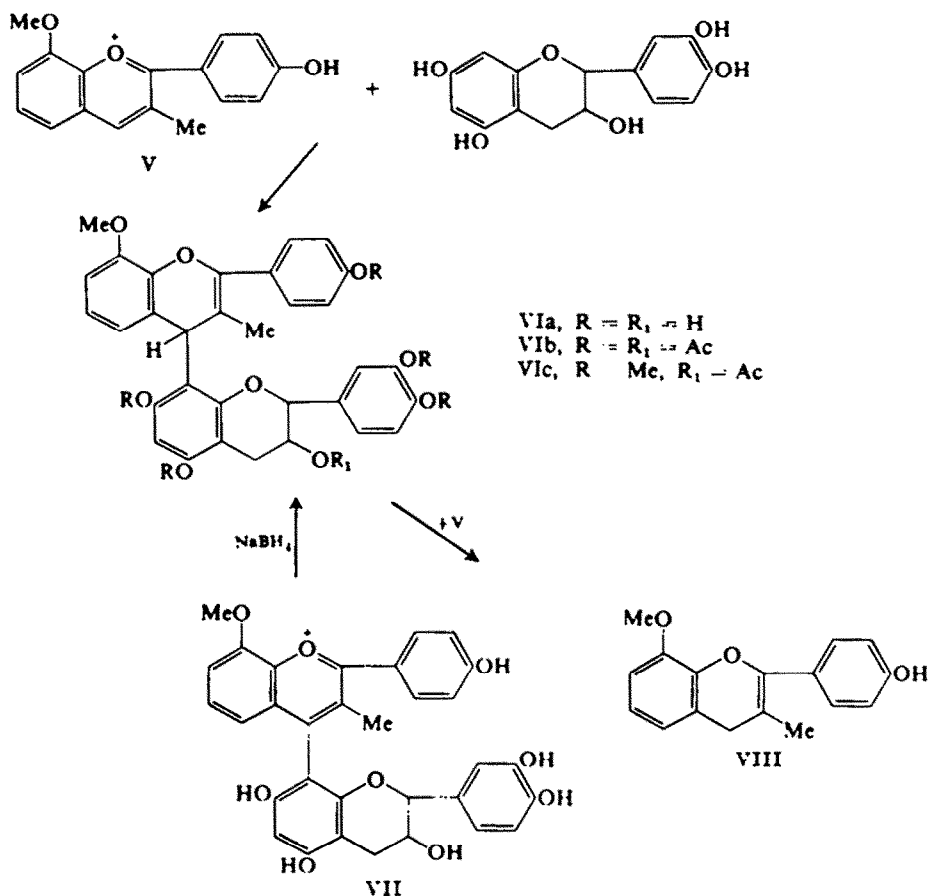
<sup>11</sup> In contrast to Birch and Salahuddin's observations we have detected no discoloration nor change in m.p. in a specimen of pure synthetic 4',5,7-trimethoxyflavan, exposed to air and light for one month (Jurd and Waiss, unpublished results).

<sup>12</sup> L. Jurd and A. C. Waiss, *Tetrahedron* 21, 1471 (1965).

<sup>13</sup> W. Mayer, L. Goll, E. M. van Arndt and A. Mannschreck, *Tetrahedron Letters* No 4, 429 (1966).

<sup>14</sup> L. Jurd and B. Bergot, *Tetrahedron* 21, 3697 (1965).

<sup>15</sup> L. Jurd, *Tetrahedron* 21, 3707 (1965).



malonic acid<sup>9</sup> condensation products the flavylum nucleus is linked at its 4-position with either the 8- or 6-position of catechin. As in the case of proanthocyanidins of type III, the position of catechin substitution (i.e., 8- or 6-) has not been established. In this discussion 8-substitution is arbitrarily assumed, leading to formula VII for the pyrylium condensation product.

Compound VII is reduced by sodium borohydride to an amorphous product, which yields a colorless crystalline monomethoxy-hexaacetate,  $\text{C}_{44}\text{H}_{40}\text{O}_{15}$ . Methylation of this hexaacetate yields a crystalline hexamethoxy-monoacetate,  $\text{C}_{39}\text{H}_{40}\text{O}_{10}$ . The reduction product, therefore, contains six free OH groups and an oxygen-bridged structure of the phloroglucinol type IV is excluded. It displays typical flav-2-ene properties, e.g., ease of oxidation to a pyrylium salt in acid solutions, and is formulated as the flavenyl flavan VIa. The NMR spectrum of the hexamethoxy-monoacetate (Fig. 2), which shows the presence of eleven aromatic protons, the vinyl methyl and the bridged proton of the flavene nucleus, and the four aliphatic protons of the catechin nucleus, is in accord with structure VIc.

The flavylum-flavan reaction leading to VII is an oxidative condensation. Aerial oxidation, however, is not involved (cf. Ref. 9), since formation of the pyrylium salt VII occurs as readily in an inert atmosphere. The simultaneous formation of the

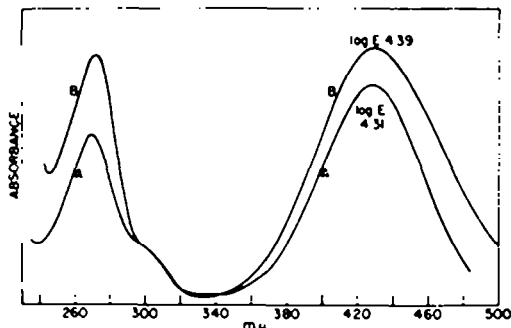


FIG. 1. Spectrum in 1% HCl aq of (A) V chloride ( $6.0 \times 10^{-3}$  g/l.) and (B) VII chloride ( $11.56 \times 10^{-3}$  g/l.).

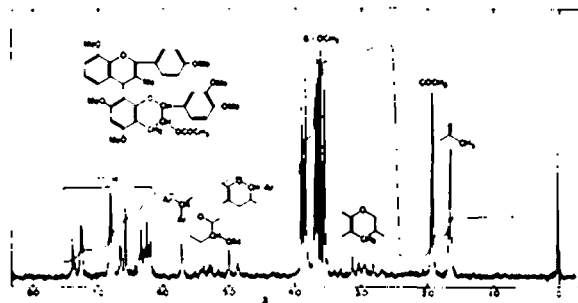
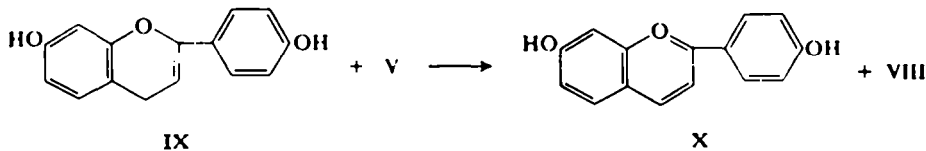


FIG. 2. 60 Mc NMR spectrum of VIc in  $\text{CDCl}_3$ ; TMS as internal reference. Assignments of structural features and proton integration are shown.

flavene VIII, a reduction product, indicates that the flavylum salt V is the oxidant and that the flavylum-flavan reaction sequence involves (a) initial condensation to yield the flavenyl-flavan VIa and (b) rapid oxidation of VIa by a second molecule of V to form VII and the monomeric flavene VIII. In agreement with this interpretation it has been determined that 4',7-dihydroxyflav-2-ene IX is rapidly oxidized by 8-methoxy-4'-hydroxy-3-methylflavylium chloride (V) in aqueous acetic acid solutions



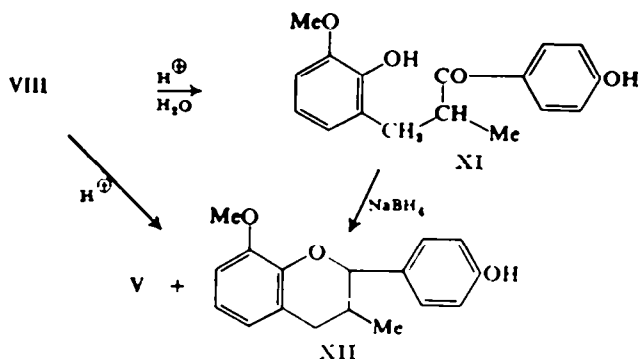
to yield the 4',7-dihydroxy-flavylium salt (X) and 8-methoxy-4'-hydroxy-3-methylflav-2-ene (VIII). This model oxidation-reduction reaction, therefore supports the proposed condensation sequence.

Although flav-2-enes are chiefly hydrolyzed to dihydrochalcones in aqueous acid solutions, in nonaqueous media they are oxidized to flavylium salts. It has not been established whether this oxidation is due to molecular oxygen or to disproportionation.<sup>16,17</sup> Since a flavan or other reduction product has not hitherto been identified

<sup>16</sup> K. Freudenberg and M. Harder, *Liebigs Ann.* **451**, 213 (1927).

<sup>17</sup> J. W. Gramshaw, A. W. Johnson and T. J. King, *J. Chem. Soc.* 4040 (1958), and references therein.

in any of the reactions studied, it has been assumed that aerial oxidation is involved.<sup>18,19</sup> Unequivocal evidence of facile disproportionation of the flavene VIII has now been obtained. Thus, VIII was almost quantitatively hydrolyzed in aqueous acid solutions to the dihydrochalcone XI, which was then reduced (sodium borohydride) and cyclized to yield authentic 8-methoxy-4'-hydroxy-3-methylflavan (XII). In benzene solutions with HCl gas, or in glacial acetic acid solutions with a drop of sulfuric or perchloric acids, VIII rapidly disproportionated to yield the flavylum salt V (50%) and the flavan XII (31%, recrystallized).



4',7-Dihydroxy- and 4',7-dimethoxy-flav-2-ene were hydrolyzed to the corresponding dihydrochalcones and the dimethoxydihydrochalcone was reduced to 4',7-dimethoxyflavan. These aqueous acid reaction solutions assumed strong yellow-orange colors, indicating at least some oxidation or disproportionation of the flavenes. In nonaqueous media 4',7-dihydroxy- and 4',7-dimethoxy-flavylium salts were formed. Flavans, however, were not isolated and it appeared that both colored and colorless polymeric materials were formed. Disproportionation of these flavenes, therefore, is still questionable. It is noteworthy, however, that 4',7-dihydroxyflavan is known to undergo rapid self-condensation to dimeric and polymeric compounds in acid media<sup>20,21</sup> and it has also been reported<sup>19</sup> that 5,7,3',4'-tetramethoxyisoflav-2-ene may demethylate and form phlobaphenes in acids. It may also be significant in connection with possible disproportionation that in the literature cited the yields of flavylum salts from flavenes were usually about 40–50%, but did not exceed 50%.

Phenolic flavenes do not appear to have been synthesized and described previously. The flavenes VIII and IX and other 7-hydroxyflav-2-enes, e.g. 7-hydroxy-4'-methoxyflav-2-ene, are almost colorless when first obtained. In moist air or in acid fumes they rapidly become yellow or red. At temperatures above 100° VIII rapidly becomes red and finally melts to a deep red liquid. The red color in this instance is due to the formation of small quantities of the *anhydro base* of V. When acidified, the yellow flavylum salt V is immediately obtained. 4',7-Dihydroxyflav-2-ene, on the other hand, does not appear to melt. At about 175° it forms a highly colored solid, the  $\lambda_{max}$  of which (475 m $\mu$  in ethanolic HCl) is identical with that of X. However chromatography shows the presence of only traces of X in this solid. The major

<sup>18</sup> F. E. King, J. W. Clark-Lewis and W. F. Forbes, *J. Chem. Soc.* 2948 (1955).

<sup>19</sup> W. Baker, *J. Chem. Soc.* 1593 (1929).

<sup>20</sup> K. Freudenberg and K. Wcings, *Tetrahedron Letters* No 23, 1073 (1962).

<sup>21</sup> B. R. Brown and G. A. Somerfield, *Tetrahedron Letters* No 14, 905 (1963).

portion of the orange pigment remains at or near the origin (streaking), indicating that at higher temperatures IX may oxidatively self-condense (possibly via disproportionation) to dimeric and polymeric flavylum salts. These observations provide experimental support for the theory recently proposed<sup>23</sup> that development of red colors in condensed tannins is due to dehydration of flavan-3,4-diols to flavenes, which are oxidized to anhydro bases of flavylum salts.

Amorphous mixtures of dimers similar to III have recently been obtained by acid condensation of *d*-catechin with flavan-3,4-diols.<sup>7,23</sup> Although 3-hydroxy-flavylum salts have not yet been condensed successfully with *d*-catechin, the model reactions described suggest that a possible alternate approach to the synthesis of bisflavans of type III might involve a cyanidin catechin condensation and disproportionation or reduction of the intermediate flavenyl-flavan. In reviewing possible modes of tannin formation, it has been suggested<sup>24</sup> that similar reactions, viz. self-condensation of anthocyanidins or anthocyanidin-leucoanthocyanidin condensations, may be involved.

## EXPERIMENTAL

### *Condensation of d-catechin and 8-methoxy-4'-hydroxy-3-methylflavylum chloride*

*d*-Catechin (3.1 g) and V<sup>19</sup> (6.0 g, 2 mole equivs) were dissolved in a mixture of glacial AcOH (20 ml) and water (80 ml) at 50°. Within 5 min cream-colored crystals of 8-methoxy-4'-hydroxy-3-methylflav-2-ene began to separate. Co-precipitation of a red pyrylium salt began after about 1 hr. The mixture was kept at room temp for 24 hr and the solid flavene-pyrylium salt mixture was filtered. The filtrate (A) was treated with 6N HCl (30 ml).

The flavene-pyrylium salt mixture was warmed with glacial AcOH (10 ml) and water (40 ml). The pyrylium salt dissolved and the crystalline flavene was collected (0.82 g). The aqueous AcOH filtrate was added to the acidified filtrate (A) and, after cooling, the crude pyrylium chloride was collected.

The flavene was recrystallized from aqueous MeOH to give VIII as colorless needles, m.p. 152° (lit.<sup>19</sup> m.p. 150–152°),  $\lambda_{\text{max}}^{\text{EtOH}}$  270 (3.90), 243 (4.30) 222 (4.33) m $\mu$  (log  $\epsilon$ ). It formed an *acetate*, m.p. and m.m.p. with authentic VIII acetate, 129°.

The crude pyrylium salt was dissolved in MeOH containing 2 drops of conc HCl, diluted with excess of AcOEt and concentrated until orange-red crystals separated from the boiling soln. These were collected and the filtrate was further concentrated to give a total yield of 3.20 g of the crystalline chloride of the condensation product. It was dissolved in a boiling mixture of glacial AcOH (50 ml) and 1% HCl<sub>aq</sub> (50 ml) and treated with 6N HCl (40 ml). The *chloride* of VII thereby separated as orange-red needles (2.80 g),  $\lambda_{\text{max}}$  439 (4.40), 273 (4.39) m $\mu$  (log  $\epsilon$ ) in EtOH containing 0.5% HCl,  $\lambda_{\text{max}}$  429 (4.39), 472 (4.38) m $\mu$  (log  $\epsilon$ ) in 1% HCl<sub>aq</sub>. The chloride becomes brown when heated, but does not melt below 320°. VII migrates as a single substance,  $R_f$  0.86 (water–AcOH–6N HCl, 80:40:5)  $R_f$  0.73 (water–AcOH–6N HCl, 80:20:5),  $R_f$  0.84 (formic acid–3N HCl, 1:1). V had  $R_f$  0.95, 0.83 and 0.95 in these respective solvents. (Found: C, 65.2; H, 4.75; MeO—, 5.22. Calc. for C<sub>23</sub>H<sub>17</sub>O<sub>4</sub>Cl: C, 65.0; H, 4.61; 1 MeO—, 5.25%.)

Recrystallized from a mixture of AcOH and 5% aqueous perchloric acid VII forms orange-red needles of a *perchlorate*, which decomposes at 208–210° and melts with frothing at 235–237°.

Sodium borohydride (0.40 g) was added during 5 min to a cooled suspension of the chloride of VII (0.75 g) in MeOH (5.0 ml). The soln was acidified with 3% AcOHaq (100 ml), cooled and filtered. The solid product was acetylated by warming for 5 min with Ac<sub>2</sub>O (10.0 ml) and pyridine (1.0 ml). A soln of the crude acetate in acetone and excess of MeOH was concentrated until colorless crystals separated. Recrystallized from acetone–MeOH, VIb separated as colorless needles (0.21 g), m.p. 198°  $\lambda_{\text{max}}^{\text{EtOH}}$  272 (3.87), shoulders at 308 m $\mu$  (log  $\epsilon$ ). VIb migrated as a single species on silicic acid

<sup>19</sup> D. G. Roux and S. E. Drewes, *Chem. & Ind.* 1442 (1965).

<sup>23</sup> T. A. Geissman, *Tetrahedron Letters* (in press) cf. B. R. Brown, W. Cummings and J. Newbould, *J. Chem. Soc.* 3677 (1961).

<sup>24</sup> F. M. Dean, *Naturally Occurring Oxygen Ring Compounds* p. 446. Butterworths, London (1963).

TLC ( $R_f$  0.32 (ether); 0.75 (MeOH)). (Found: C, 65.3; H, 4.98; MeO—, 3.93;  $\text{CH}_2\text{CO}$ —, 33.9. Calc. for  $\text{C}_{24}\text{H}_{26}\text{O}_{13}$ : C, 65.3; H, 4.99; 1 MeO—, 3.84; 6  $\text{CH}_2\text{CO}$ —, 31.9.)

Vib (0.50 g) was heated under reflux with  $\text{Me}_2\text{SO}_4$  (5.0 ml), acetone (45 ml), MeOH (15 ml) and  $\text{K}_2\text{CO}_3$  (10 g) for 2 hr. The mixture was concentrated and diluted with water. The solid product was repeatedly recrystallized from acetone–MeOH, and was thus obtained as glistening, colorless prisms, m.p. 203–204°,  $\lambda_{\text{max}}^{\text{EtOH}}$  274 (4.15), shoulder at 281 (4.13)  $m\mu$  (log  $\epsilon$ );  $R_f$  0.54 (ether), 0.41 (ether–Skellysolve F, 2:1) on silicic acid TLC. (Found: C, 69.9; H, 6.06; MeO—, 27.2;  $\text{CH}_2\text{CO}$ —, 6.44. Calc. for  $\text{C}_{29}\text{H}_{34}\text{O}_{16}$ : C, 70.0; H, 6.03; MeO—, 27.8; 1  $\text{CH}_2\text{CO}$ —, 6.43.)

#### 4',7-Dihydroxyflav-2-ene

4',7-Dihydroxyflavylium chloride<sup>24</sup> was recrystallized from 5% aqueous perchloric acid. 4',7-dihydroxyflavylium perchlorate separated as orange needles, m.p. 244–247° (dec)  $\lambda_{\text{max}}$  475 (4.76), 2.82 (3.91), 260 (4.01), 243 (4.07)  $m\mu$  (log  $\epsilon$ ) in EtOH –0.5% HCl.

Sodium borohydride (5.0 g) was added in portions during 10 min to a cooled soln of 4',7-dihydroxyflavylium perchlorate (10.0 g) in MeOH (50 ml). 1%  $\text{NaHSO}_3\text{aq}$  (500 ml) was then added and the pink colored solid was collected. Recrystallized from very dilute aqueous MeOH 4',7-dihydroxyflav-2-ene IX was obtained as orange-red needles which decompose to deep red solid at 175–178° (5.0 g),  $\lambda_{\text{max}}^{\text{EtOH}}$  274 (3.99), 244 (4.26),  $\lambda_{\text{max}}^{\text{MeOH}}$  288  $m\mu$  (log  $\epsilon$ ). (Found: C, 74.6; H, 5.12. Calc. for  $\text{C}_{15}\text{H}_{13}\text{O}_5$ : C, 75.0; H, 5.03%.)

Warmed with  $\text{Ac}_2\text{O}$  and pyridine IX formed a diacetate, colorless needles ex MeOH, m.p. 115°. (Found: C, 70.5; H, 5.06. Calc. for  $\text{C}_{15}\text{H}_{11}\text{O}_6$ : C, 70.4; H, 4.98%.)

Heated with  $\text{Me}_2\text{SO}_4$  (5.0 ml),  $\text{K}_2\text{CO}_3$  (10.0 g) and acetone (30.0 ml) for 2 hr IX (1.0 g) gave 4',7-dimethoxyflav-2-ene. This crystallized from acetone–MeOH as colorless prisms, m.p. 137–138°,  $\lambda_{\text{max}}^{\text{EtOH}}$  272 (4.03), 244 (4.35)  $m\mu$  (log  $\epsilon$ ). In air or in acid fumes it rapidly became yellow. (Found: C, 76.2; H, 5.98; 2 MeO—, 22.5. Calc. for  $\text{C}_{17}\text{H}_{15}\text{O}_5$ : C, 76.1; H, 6.01; 2 MeO—, 23.1%.)

#### Oxidation of 4',7-dihydroxyflav-2-ene (IX) with 8-methoxy-4'-hydroxy-3-methylflavylium chloride (V)

An equimolecular mixture of IX (0.24 g) and V (0.30 g) was dissolved in glacial AcOH (3.0 g) and water (1.0 ml) at 50°. Water (10.0 ml) was then added. Within 1 min cream-colored crystals separated. After 20 min these were collected and recrystallized from aqueous MeOH. VIII was thus obtained as colorless needles (0.07 g), m.p. and m.m.p. 152°.  $\lambda_{\text{max}}^{\text{EtOH}}$  270, 242  $m\mu$ ; acetate, m.p. and m.m.p. 129°.

The aqueous AcOH reaction filtrate was warmed and treated with 6N HCl (2.0 ml). 4',7-Dihydroxyflavylium chloride separated as orange needles (0.18 g). Recrystallized from aqueous perchloric acid X perchlorate was obtained as orange needles, m.p. 244–245°,  $\lambda_{\text{max}}$  475, 280, 260  $m\mu$  (EtOH–0.5% HCl), chromatographically identical with authentic X.

#### 8-Methoxy-4'-hydroxy-3-methylflavan (XII)

Water (20.0 ml) was added to a warm solution of VIII (1.1 g) in glacial AcOH (15.0 ml) and 10% HClaq (5.0 ml). The soln was heated on a steam-bath for 5 min and allowed to cool. The crystalline product was recrystallized from aqueous MeOH to give the dihydrochalcone (XI) as colorless, glistening needles, m.p. 143°,  $\lambda_{\text{max}}^{\text{EtOH}}$  279  $m\mu$  (log  $\epsilon$  4.22),  $\lambda_{\text{max}}^{\text{MeOH}}$  328  $m\mu$  (1.0 g). It gave an immediate intense blue color with Gibbs reagent. (Found: C, 71.4; H, 6.31; MeO—, 10.5. Calc. for  $\text{C}_{17}\text{H}_{16}\text{O}_4$ : C, 71.3; H, 6.34; 1 MeO—, 10.8%.)

A suspension of XI (1.0 g) in MeOH (10.0 ml) was treated with  $\text{NaBH}_4$  (0.50 g). After 10 min the soln was warmed and acidified with 10% HClaq (10.0 ml). The colorless crystals which separated were recrystallized from aqueous MeOH. XII separated as colorless, felted needles, m.p. 190°,  $\lambda_{\text{max}}^{\text{EtOH}}$  281 (3.55), 274 (3.58), 223 (4.30)  $m\mu$  (log  $\epsilon$ ),  $\lambda_{\text{max}}^{\text{MeOH}}$  282 (3.92), 245 (4.44)  $m\mu$  (log  $\epsilon$ ) (0.80 g). XII did not give a color with Gibbs reagent. (Found: C, 75.6; H, 6.65; MeO—, 11.4. Calc. for  $\text{C}_{17}\text{H}_{16}\text{O}_5$ : C, 75.5; H, 6.71; 1 MeO—, 11.5%.)

Compound XII formed a monoacetate, which crystallized from acetone–MeOH as colorless needles, m.p. 172°,  $\lambda_{\text{max}}^{\text{EtOH}}$  282 (3.32), 273 (3.34)  $m\mu$  (log  $\epsilon$ ). (Found: C, 73.2; H, 6.36; MeO—, 9.75;  $\text{CH}_2\text{CO}$ —, 13.5. Calc. for  $\text{C}_{19}\text{H}_{18}\text{O}_6$ : C, 73.1; H, 6.45; 1 MeO—, 9.81; 1  $\text{CH}_2\text{CO}$ —, 13.8%.)

<sup>24</sup> K. Freudenberg and K. Weinges, *Liebigs. Ann.* 590, 140 (1954).

*8,4'-Dimethoxy-3-methylflavan*

8,4'-Dimethoxy-3-methyl-flav-2-ene<sup>13</sup> (1.0 g) was dissolved in warm glacial AcOH (15 ml) and 5% HClaq (10.0 ml). Colorless needles separated on cooling. Recrystallized from aqueous MeOH the methyl ether of XI was obtained as colorless needles, m.p. 93–94°,  $\lambda_{\text{max}}^{\text{EtOH}}$  274, 219 m $\mu$  (1.0 g). (Found: C, 72.0; H, 6.64; MeO—, 20.5. Calc. for C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>: C, 72.0; H, 6.71; 2 MeO—, 20.6%.)

Reduced with NaBH<sub>4</sub> (0.4 g) and acidified as previously described the above dihydrochalcone (1.0 g) gave 8,4'-dimethoxy-3-methylflavan (0.86 g), colorless needles ex acetone–MeOH, m.p. 154°,  $\lambda_{\text{max}}^{\text{EtOH}}$  281 (3.50), 273 (3.53), 225 (4.35) m $\mu$  (log  $\epsilon$ ). (Found: C, 76.0; H, 7.01; MeO—, 21.7. Calc. for C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>: C, 76.0; H, 7.09; 2 MeO—, 21.8%.)

*Disproportionation of 8-methoxy-4'-hydroxy-3-methylflav-2-ene (VIII)*

(a) A stream of HCl gas was passed for 5 min into a soln of VIII (1.0 g) in benzene (50.0 ml). Yellow crystals rapidly separated on scratching. After 1 hr ether (100 ml) was added and the pptd 8-methoxy-4'-hydroxy-3-methylflavylium chloride was collected (0.49 g). Recrystallized from HClaq V was obtained as yellow-orange needles, m.p. and m.m.p. 212–213° (dec),  $\lambda_{\text{max}}$  443, 272 m $\mu$  EtOH–0.5% HCl; spectrum measured immediately after mixing).

The ether–benzene filtrate was washed with 10% HClaq and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to 10 ml. Skellysolve F was added. The colorless crystals which separated (0.31 g) were recrystallized from aqueous MeOH to give XII as colorless needles, m.p. and m.m.p. 190°,  $\lambda_{\text{max}}^{\text{EtOH}}$  281, 274, 223 m $\mu$ . Co-chromatographed with authentic XII the product migrates as a single species on silicic acid TLC R<sub>F</sub> 0.50 (ether–Skellysolve F, 2:1), and 0.54 (AcOEt–Skellysolve F, 1:4). (Found: C, 75.4; H, 6.57. Calc. for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>: C, 75.5; H, 6.71%.)

The acetate of the product separated from acetone–MeOH as colorless needles, m.p. and m.m.p. with XII acetate, 172°,  $\lambda_{\text{max}}^{\text{EtOH}}$  282, 273 m $\mu$ .

(b) Compound VIII (0.40 g) was suspended in glacial AcOH (2.0 ml) and conc H<sub>2</sub>SO<sub>4</sub> (2 drops) was added. A yellow-orange crystalline mass separated. After 5 min ether (25.0 ml) was added and the yellow crystals were collected (0.20 g). These were recrystallized from HClaq to give V chloride, m.p. and m.m.p. 212–213°. The ether–AcOH filtrate was washed with water and evaporated. The product crystallized from aqueous MeOH to give XII, m.p. 190° (0.12 g).

*4',7-Dimethoxyflavan*

4',7-Dimethoxyflav-2-ene (0.40 g) was heated on a steam-bath in 50% AcOHaq (20 ml) for 1 hr. 2'-Hydroxy-4,4'-dimethoxydihydrochalcone crystallized on cooling. Recrystallized from aqueous MeOH it was obtained as colorless needles, m.p. 78°,  $\lambda_{\text{max}}^{\text{EtOH}}$  278, 218 m $\mu$  (0.31 g). (Found: C, 71.0; H, 6.39; MeO—, 21.2. Calc. for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>: C, 71.3; H, 6.34; 2 MeO—, 21.7%.)

The above dihydrochalcone (0.40 g) was suspended in MeOH (5.0 ml) and treated with NaBH<sub>4</sub> (0.40 g). Colorless crystals separated. Water was added and the product was recrystallized from aqueous MeOH. 1-(4-Methoxyphenyl)-3-(2-hydroxy-4-methoxyphenyl) propan-1-ol separated as colorless plates, m.p. 155° (0.30 g),  $\lambda_{\text{max}}^{\text{EtOH}}$  280 m $\mu$ . (Found: C, 70.9; H, 7.03. Calc. for C<sub>17</sub>H<sub>18</sub>O<sub>4</sub>: C, 70.8; H, 6.99%.)

Addition of a few drops of 6N HCl to a soln of the above carbinol in MeOH formed 4',7-dimethoxyflavan, glistening, colorless needles ex aqueous MeOH, m.p. 85° (lit.<sup>14</sup> m.p. 85°). (Found: C, 75.6; H, 6.71; MeO—, 22.9. Calc. for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>: C, 75.5; H, 6.71; 2 MeO—, 22.9%.)

*2',4,4'-Trihydroxydihydrochalcone*

Compound IX (0.40 g) was dissolved in a warm mixture of AcOH (1.0 ml) and 1% HClaq (10.0 ml) and allowed to stand overnight. Orange-colored crystals separated from the yellow-orange soln (0.37 g). Recrystallized from dilute aqueous MeOH 2',4,4'-trihydroxydihydrochalcone separated as hydrated slightly orange needles, m.p. 162–163° (dried *in vacuo* over KOH);  $\lambda_{\text{max}}^{\text{EtOH}}$  281 (4.20),  $\lambda_{\text{max}}^{\text{acetone}}$  329 (4.38) m $\mu$  (log  $\epsilon$ ). (Found: C, 69.9; H, 5.50. Calc. for C<sub>14</sub>H<sub>14</sub>O<sub>4</sub>: C, 69.75; H, 5.46%.)

Warmed with benzoyl chloride and pyridine it formed a colorless tribenzoate, m.p. 83–84° (ex MeOH). (Found: C, 75.7; H, 4.81. Calc. for C<sub>26</sub>H<sub>20</sub>O<sub>7</sub>: C, 75.8; H, 4.59%.)

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