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ANTHOCYANIDINS AND RELATED COMPOUNDS—XIV

REDUCTIVE DIMERIZATION OF FLAVYLIUM SALTS BY METALS

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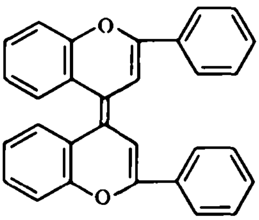
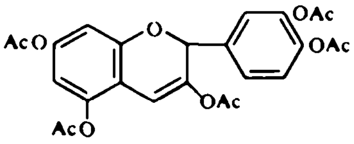
Abstract—Flavylium salts are reductively dimerized by Zn or Mg in neutral or acidic media to yield colorless, crystalline α- and β-bis-flav-2-enes of types VI and VII. The α- and β-forms undergo facile thermal interconversion.

METAL reduction is commonly used in a number of diagnostic tests for flavonoid compounds. The types of reduction products so formed are still largely obscure, although bisflavenylidenes or type I, flav-3-enes[1-3] of type II and flav-2-enes[3] of type III have recently been identified unequivocally among the zinc reductive acetylation products of flavones and flavonols. Flavylium salts have been isolated in small yields by metal reduction of flavones and flavanones in acid solutions. However, Geissman and Clinton[4] have shown that the chief pigments usually formed under these conditions distinctly differ from flavylium salts in both stability and absorption maxima. Flavylium salts, in fact, are highly susceptible to reduction by metals. Hitherto only amorphous reduction products have been isolated, e.g. from 7-hydroxyflavylium chloride,[5] and on the basis of the limited experimental evidence it was considered[6] that zinc–acid reduction of flavylium salts may yield (a) colorless monomeric flav-3-enes[7] which are rapidly reoxidized on contact with air to the original flavylium salts or (b) colorless products which are stable to air.[8] Structures have not been proposed for the stable reduction products. We have now isolated crystalline reduction products in high yields from a series of flavylium salts by reaction with metals in both acid and in neutral media. The products are dimeric bis-flav-2-enes. These flavylium salts, therefore, behave similarly to 2,4,6-trimethyl pyrylium perchlorate, which with zinc yields[9] 2,2′,4,4′,6,6′-hexamethyl-4,4′-bis-4 H-pyran.

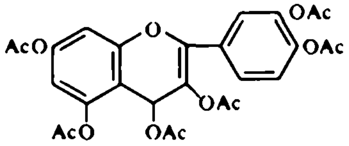
8-Methoxy-4′-hydroxy-3-methylflavylium chloride IVa, treated briefly in ethanol solution with zinc, yields approximately equal quantities of two colorless, crystalline isomeric compounds, $C_{34}H_{30}O_6$. Both of these compounds rapidly become pink on exposure to air and light and on heating they melt to deep red liquids at 188° and 159° respectively. With benzoquinone the isomers are oxidized almost quantitatively to the flavylium salt IVa. This behavior is identical with that of the known flav-2-ene[10] Va, which melts to a deep red liquid at 150–152° due to the formation[11] of the anhydrobase of IVa, and with benzoquinone quantitatively yields[12] IVa. However, the isomeric zinc reduction products form a series of well defined diacyl and dialkyl derivatives whose melting points distinctly differ from those of the corresponding acyl and alkyl derivatives of Va, so that there is no doubt that neither



I

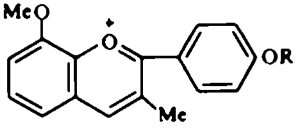


II

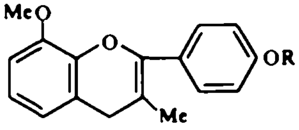


III

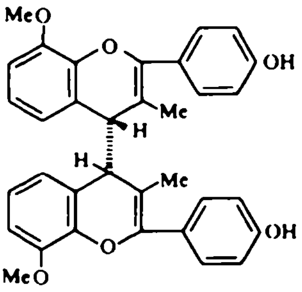
of the metal reduction products are, in fact, identical with the monomeric flav-2-ene. The UV spectra of the zinc reduction products (e.g. isomer m.p. 188°, $\lambda_{\max}$ 271, 241 mμ ($\log \varepsilon$ 4·25, 4·52); diacetate m.p. 190°, $\lambda_{\max}$ 276 mμ ($\log \varepsilon$ 4·14), inflection at 241 mμ) are closely similar in detailed shape and relative intensities of peaks to the spectra of Va derivatives (Va, $\lambda_{\max}$ 270, 243 mμ ($\log \varepsilon$ 3·90, 4·33); acetate (m.p. 129°), $\lambda_{\max}$ 275 mμ ($\log \varepsilon$ 3·82), inflection at 240 mμ). From these observations, therefore, the zinc reduction products are considered to be the isomeric α- and β-bis flav-2-enes VI and VII, although it is not known which of the isomers corresponds to the α- and to the β-form.



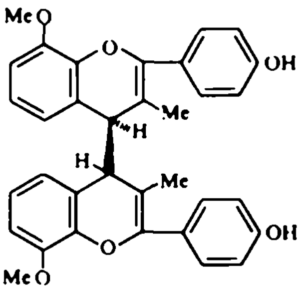
IVa: R = H
IVb: R = Me



Va: R = H
Vb: R = Me



VI



VII

The isomers, m.p. 188° and 159°, form dimethyl derivatives, m.p. 198° and m.p. 170°, respectively. Comparison of the NMR spectra of these dimethyl derivatives with that of the monomeric flav-2-ene Vb (m.p. 121°) confirms the proposed bis-flav-2-ene structures.* The NMR spectrum of monomeric flav-2-ene Vb (Fig. 1a) consists of a vinyl methyl absorption at 8·20 τ, a methylene singlet (H_4) at 6·54 τ, two aromatic O-Me singlets at 6·17 and 6·15 τ, and a typical A_2 doublet portion (2·48 τ, $J = 9{\cdot}0$ c/s; $H_{2'}$ and $H_{6'}$) of an A_2B_2 system, with the B_2 peaks overlapping with absorptions from other aromatic protons. In general appearance the NMR spectra of the two isomeric dimers (Figs 1b and 1c) are very similar to that of the monomer (Fig. 1a). Their vinyl Me (8·18 and 8·16 τ) and allylic hydrogen bands

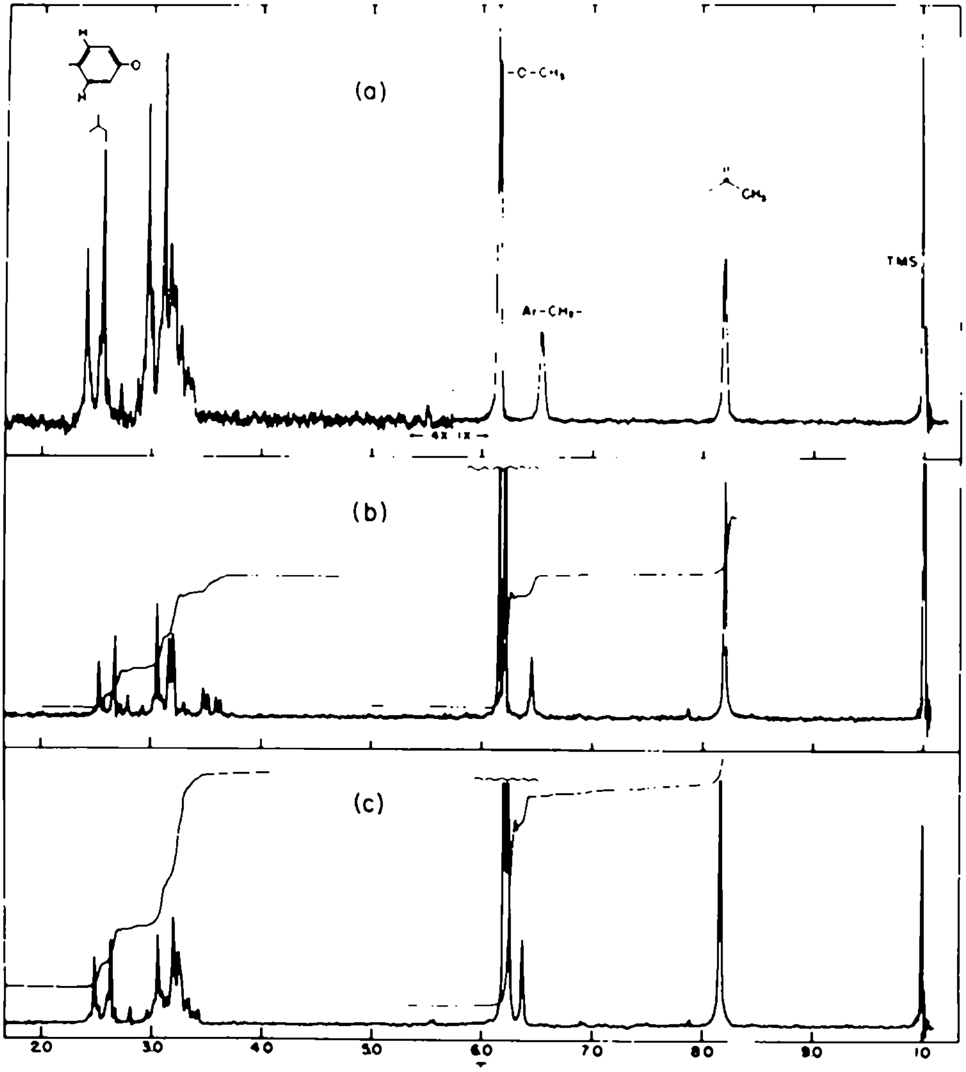


FIG. 1 60 Mc NMR spectrum of (a) VIb, (b) dimethyl derivative, m.p. 198°, of isomer A, (c) dimethyl derivative, m.p. 159°, of isomer B in $CDCl_3$.

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* The dimeric nature of the methyl ether, m.p. 170°, has been confirmed by its mass spectrum (m/e 562)

(6·46 and 6·36 τ) are only slightly shifted from their parent compound. The presence of the *ortho* coupled doublets from $H_{2'}$ and $H_{6'}$ (2·60 and 2·55 τ) clearly indicates the persistence of deshielding effect by the double bonds at C_2. Since the number of C-Me, O-Me, and particularly H_4 absorptions bands of both dimers are same, and not twice, that of the monomer it is reasonable to assume that they are quite symmetric at the point of dimerization.

Ethers of the isomeric reduction products are easily interconverted. Thus, the dimethyl (m.p. 170°) and diethyl (m.p. 154°) derivatives of the isomer m.p. 159°, heated just above their melting points and recrystallized, yield the dimethyl (m.p. 198°) and diethyl (m.p. 195°) derivatives of the isomer, m.p. 188°. NMR spectra show that on melting either the higher or the lower melting methyl ethers form an equilibrium mixture of both forms (Fig. 2). A similar equilibrium mixture is obtained by heating either of the methyl ethers in solution in DMSO at 200°. The ease of this isomerization suggests that the bis-flav-2-enes readily undergo homolytic fission to monoflav-2-ene radicals, which on recombination form both the α- and β-isomers.

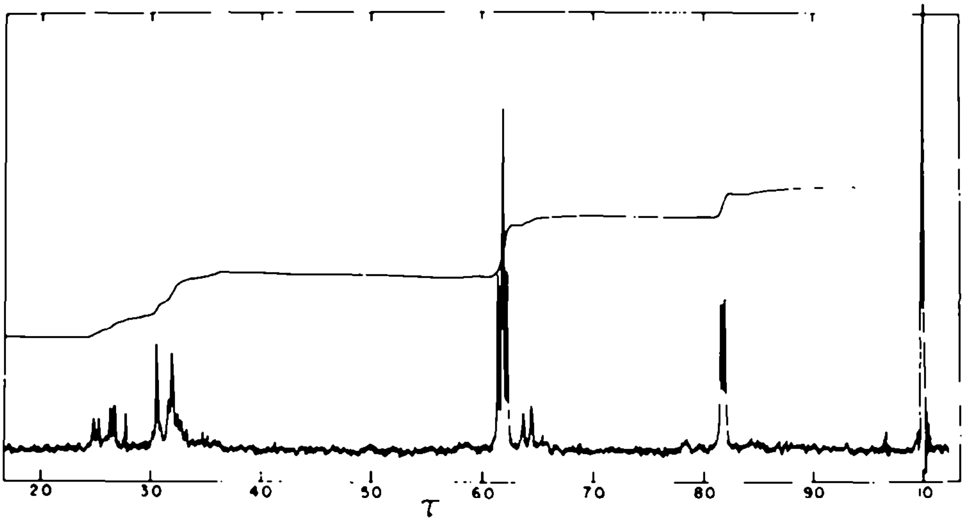

FIG 2 60 Mc NMR spectrum of melted dimethyl derivative, m.p. 198°, of isomer A in $CDCl_3$.

The above reduction products are quite unstable in acid solutions. and in these media they are easily oxidized or hydrolyzed. Thus, as previously indicated, Me derivatives are almost quantitatively oxidized to the flavylium salts IVa and IVb when briefly warmed with benzoquinone in aqueous acetic acid. With perchloric or sulfuric acid in glacial acetic acid the product (m.p. 188°) rapidly yields (15%) IVa while in aqueous acetic acid–HCl it is hydrolyzed to an unidentified, crystalline tetrahydroxy compound, $C_{34}H_{32}O_7$. In spite of the acid instability of these reduction products, however, the isomer (m.p. 188°) has been isolated in about 20% yields by reduction of IVa with zinc in acetic acid and with magnesium in ethanolic HCl.

Crystalline reduction products corresponding to the above isomers have been prepared from the flavylium salts listed in Table 1. The properties of these products

TABLE 1. BIS-FLAV-2-ENES FROM 3-METHYLFLAVYLIUM SALTS

3-Methylflavylium	Product	m.p.	Formula	Found %				Calc. %			
				C	H	MeO	MeCO	C	H	MeO	MeCO
7-Hydroxy-	Isomer "A"	244–245°	$C_{32}H_{26}O_4$	80·7	5·63			81·0	5·52		
	Diacetate	162–163°	$C_{36}H_{30}O_6$	77·5	5·45		15·3	77·4	5·41		15·4
	Dimethyl ether	136–137°	$C_{34}H_{30}O_4$	81·1	6·01	12·2		81·2	6·02	12·3	
	Dibenzyl ether	180°	$C_{46}H_{38}O_4$	84·4	5·85			84·4	5·85		
	Isomer "B"	197–200°									
	Diacetate	179–180°	$C_{36}H_{30}O_6$	77·5	5·44		15·1	77·4	5·41		15·4
	Dimethyl ether	151°	$C_{34}H_{30}O_4$	81·4	6·03	12·2		81·2	6·02	12·3	
	Dibenzyl ether	182°	$C_{46}H_{38}O_4$	84·4	5·84			84·4	5·85		
4',7-Dihydroxy-	Isomer "A"										
	Tetra-acetate	164–165°	$C_{40}H_{34}O_{10}$	70·8	5·49		24·2	71·2	5·08		25·5
	Isomer "B"										
	Tetraacetate	183–184°	$C_{40}H_{34}O_{10}$	71·1	5·18		24·4	71·2	·08		25·5
	Tetramethyl ether	159–160°	$C_{36}H_{34}O_6$	76·9	6·09		21·9	76·8	6·09		22·0
7-Hydroxy-4'-	Isomer "A"										
	Diacetate	150°	$C_{38}H_{34}O_8$	73·8	5·47			73·8	5·54	10·0	13·9
	Isomer "B"										
	Diacetate	219°	$C_{38}H_{34}O_8$	73·8	5·57	10·4	13·1	73·8	5·54	10·0	13·9
	Isomer "B"										
	Dimethyl ether	159–160°									

generally agree with those described above so that they are considered to be analogous bis-flav-2-enes. It is noteworthy, however, that the reduction products* of 7-hydroxy-3-methylflavylium chloride differ from those of IVa in being more stable to acid hydrolysis. For this reason very high yields of these products are obtained by reduction of 7-hydroxy-3-methylflavylium chloride with Mg in ethanolic HCl solution.

EXPERIMENTAL

Reduction of 8-methoxy-4′-hydroxy-3-methylflavylium chloride IVa *in ethanol.* A mixture of IVa (20 g), Zn dust (30 g) and EtOH (80 ml) was heated on a steam-bath for 10 min and filtered. The Zn was washed with EtOH (40 ml) and the combined filtrate and washings were seeded with a specimen of previously obtained product (m.p. 188°). Colorless crystals of this crude product thereby separated (6·0 g). Recrystallized from acetone–MeOH the pure isomer separated as colorless needles, m.p. 188° (A). (Found: C, 76·5; H, 5·69; MeO—, 11·5. Calc. for $C_{34}H_{30}O_6$: C, 76·4; H, 5·66; 2 MeO—, 11·6%).

The alcoholic filtrate from (A) was heated to boiling and slowly diluted with water (100 ml). On cooling, colorless glistening prisms separated (5·0 g). Recrystallized from acetone–MeOH the pure isomer separated as colorless prisms which rapidly turn pink in air, m.p. 158–159° (B). (Found: C, 76·3; H, 6·02. Calc. for $C_{34}H_{30}O_6$: C, 76·4; H, 5·66%).

The aqueous alcoholic filtrate from (B), treated with excess of water, gave a mixture of both isomers (3·5 g).

Methylation of A *and* B. Compound A (1·0 g) was heated under reflux with Me_2SO_4 (3·0 ml), K_2CO_3 (5·0 g) and acetone (50 ml). The mixture was concentrated, diluted with water and the solid product was collected. Recrystallized from acetone–MeOH the *dimethyl derivative* of A separated as colorless, glistening prisms, m.p. 198° (0·90 g). (Found: C, 76·9; H, 6·04; MeO—, 21·3. Calc. for $C_{36}H_{34}O_6$: C, 76·85; H, 6·09; 4 MeO—, 22·0%).

Compound B (1·5 g), methylated as described above, gave the *dimethyl derivative*, colorless, brittle prisms ex acetone–MeOH, m.p. 170°. (Found: C, 77·0; H, 6·12. Calc. for $C_{36}H_{34}O_6$: C, 76·85; H, 6·09%).

Ethylation of A *and* B. Compound A (1·0 g), treated with Et_2SO_4 (3·0 ml), K_2CO_3 and acetone as described above, formed the *diethyl derivative*, colorless, glistening plates ex THF–MeOH, m.p. 195°. (Found: C, 77·4; H, 6·47. Calc. for $C_{38}H_{38}O_6$: C, 77·3; H, 6·48%).

Compound B (1·0 g), ethylated as above, formed the *diethyl derivative*, cream-colored prisms ex acetone–MeOH, m.p. 154°.

Benzylation of A *and* B. Compound A (0·5 g) was heated under reflux with benzyl chloride (2·0 ml), KI (0·5 g), K_2CO_3 (5·0 g) and dry acetone (30 ml), for 2 hr. The *dibenzyl derivative* of A crystallized from THF–MeOH as colorless, glistening needles, m.p. 185°. (Found: C, 80·8; H, 5·94. Calc. for $C_{48}H_{42}O_6$: C, 80·7; H, 5·92%).

Compound B, benzylated as described above, gave the *dibenzyl derivative*, colorless prisms ex THF–MeOH, m.p. 183°. (Found: C, 80·6; H, 5·99. Calc. for $C_{48}H_{42}O_6$: C, 80·7; H, 5·92%).

Acetylation of A *and* B. Compound A (0·5 g) was heated on a steam-bath with Ac_2O (5 ml) and pyridine (1 ml) for 5 min. The *diacetate*, obtained on adding water, crystallized from acetone–MeOH as colorless, felted needles, m.p. 189–190°. (Found: C, 73·6; H, 5·57; MeO—, 10·1; MeCO—, 13·7. Calc for $C_{38}H_{34}O_8$: C, 73·8; H, 5·54; 2 MeO—, 10·0; 2 MeCO—, 13·9%).

Compound B formed a *diacetate*, colorless prisms ex acetone–MeOH, m.p. 193°. (Found: C, 73·9; H, 5·52. Calc. for $C_{38}H_{34}O_8$: C, 73·8; H, 5·54%).

Introconversion of dimethyl and diethyl derivatives of A *and* B. The dimethyl deriv of B (m.p. 170°; 0·20 g) was heated just above its m.p. for 10 sec, cooled and crystallized from acetone–MeOH (0·15 g; m.p. 193–195°). Recrystallized from acetone–MeOH the pure methyl deriv of A was obtained, m.p. and m.m.p. 198°.

The diethyl deriv of B (m.p. 154°; 0·24 g), heated to 180° in an oil-bath, melted and resolidified. Recrystallized from THF–MeOH the diethyl deriv of A was obtained, m.p. 195° (0·16 g).

Benzoquinone oxidation of A *and* B. Compound A (0·17 g) was heated to boiling for 30 sec with benzoquinone (0·20 g) and 50% AcOH aq (4·0 ml). 5% $HClO_4$ aq (15 ml) was added to the clear soln and the crystalline IVa perchlorate was collected, washed with EtOAc and ether, and recrystallized from AcOH–5% $HClO_4$ aq, m.p. and m.m.p. 241° (0·19 g).

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* NMR spectra of these products are in accord with the proposed bis-flav-2-ene structures. The mass spectra of the methylated products shows m/e 502.

Compound B (0·20 g), oxidized with benzoquinone similarly, gave IVa perchlorate, m.p. and m.m.p. 241° (0·23 g).

The dimethyl ether of A (0·20 g), heated with benzoquinone (0·20 g) in glacial AcOH (2 ml) containing one drop of water and treated with 5% $HClO_4$ aq, gave IVb perchlorate, m.p. and m.m.p. 267–268 (0·22 g).

The dimethyl ether of B (0·20 g), treated with benzoquinone (0·20 g) and perchloric acid as described, gave IVb, m.p. and m.m.p. 267–268° (0·20 g).

Acid hydrolysis of A. Compound A (0·60 g) was dissolved in boiling glacial AcOH (15 ml) and 10% HCl aq (15 ml) and, after 30 sec, water (15 ml) was added. Cream-colored crystals rapidly separated (0·42 g). Recrystallized from acetone–MeOH the pure hydrolysis product separated as colorless granules, m.p. 260°, which give an intense blue color with Gibbs reagent. (Found: C, 73·7; H, 5·90, MeO—, 12·0. Calc. for $C_{34}H_{32}O_7$: C, 73·9; H, 5·84; 2 MeO—, 11·23%).

Warmed with Ac_2O and pyridine the hydrolysis product formed a *tetraacetate*, colorless needles ex MeOH, m.p. 174–175°. (Found: C, 70·0; H, 5·61; MeO—, 8·57; MeCO—, 23·8. Calc. for $C_{42}H_{40}O_{11}$: C, 70·0; H, 5·60; 2 MeO—, 8·61; 4 MeCO—, 23·9%).

A soln of A (0·30 g) in glacial AcOH (2·0 ml) containing one drop of 70% $HClO_4$ aq was heated briefly to boiling and diluted with ether. Recrystallized from AcOH–5% $HClO_4$ aq the yellow product gave IVa perchlorate, m.p. and m.m.p. 241° (40 mg).

Reduction of IVa *in acetic acid*. A mixture of IVa chloride (5·0 g), Zn dust (7·0 g) and glacial AcOH (25 ml) was heated rapidly to boiling. After 1 min the Zn was filtered and washed with glacial AcOH (10 ml). The warm filtrate was slowly diluted with water (20 ml), whereupon crystals rapidly separated. Recrystallized from acetone–MeOH the isomer A was obtained as colorless needles, m.p. 188° (1·5 g). TLC on silicic acid of the AcOH aq filtrate from A showed the presence of 3 major unidentified components.

Reduction of IVa *with magnesium in ethanolic* HCl. Conc HCl (7·0 ml) was added slowly to a suspension of IVa chloride (5·0 g) and Mg turnings (5·0 g) in alcohol (50 ml). After 5 min the Mg was filtered off and washed with alcohol. The combined filtrate and washings (65 ml) were warmed and diluted with water (40 ml). The isomer A separated, m.p. 188° (ex acetone–MeOH) (1·27 g).

Reduction of 7-hydroxy-3-methylflavylium chloride in ethanol. A mixture of the flavylium salt (10 g), Zn dust (20 g) and EtOH (50 ml) was heated for 10 min, filtered and the Zn washed with alcohol (20 ml). Water (50 ml) was added to the warm filtrate, whereupon the virtually pure isomer "A" crystallized (5·2 g; m.p. 243°) Recrystallized from THF–MeOH (A) separated as colorless granules which rapidly became orange in air, m.p. 244–245°. A forms a diacetate (m.p. 162–163°) and other derivatives listed in Table 1.

The aqueous EtOH filtrate from A was treated with excess of water. The gummy orange-colored ppt was collected and acetylated in warm Ac_2O (30 ml) and pyridine (10 ml). The crude acetate was dissolved in acetone, the soln was diluted with MeOH and concentrated. The diacetate of isomer B, m.p. 179–180°, separated from the hot soln (3·6 g).

Diacetate of B was converted into the dimethyl deriv of B by heating it (3·0 g) with Me_2SO_4 (15 ml), K_2CO_3 (30 g), acetone (250 ml) and MeOH (75 ml) for 2 hr. The *dimethyl derivative* crystallized from acetone–MeOH as colorless prisms, m.p. 151° (2·5 g).

The diacetate of B (1·0 g) was deacetylated by heating its suspension in acetone (10 ml) and MeOH with 10% NaOH aq (5 ml) for 5 min. The soln was diluted with water, acidified with glacial AcOH and filtered. Isomer "B" crystallized from MeOH aq as glistening, orange-colored prisms, m.p. 197–200°.

Reduction of 7-hydroxy-3-methylflavylium chloride with magnesium in ethanolic HCl. Conc HCl (25 ml) was added to a suspension of the flavylium salt (10 g) and Mg turnings (10 g) in EtOH (100 ml). After 5 min the mixture was filtered and the hot filtrate was diluted with water (70 ml). Isomer "A", mixed with a little isomer "B" separated. The crude product was acetylated and the acetate was recrystallized twice from acetone–MeOH. The diacetate of isomer "A" was thereby obtained as colorless prisms, m.p. 162° (5·7 g).

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