The Formation of Dimers from Flavylium Salts

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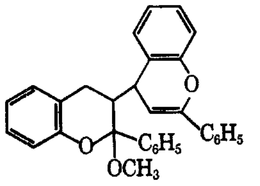
The reduction of flavylium salts and their 3-alkyl or aryl derivatives with zinc dust in acetonitrile solution gives a pair of diastereomeric dimers which have been demonstrated to be 4,4′-bis(flav-2-ene) derivatives. Reaction conditions have been found for the conversion of 3-methylflavylium perchlorate to a single dimer. This dimer is converted to its diastereomer by heat. The geometrical configuration of this latter pair of dimers indicates that the lower melting form has a *threo* configuration, whereas the higher melting form has the *erythro* configuration. Substituents in the 4 position of a flavylium salt prevent dimerization.

Flavylium salts (**1**) and sodium borohydride in alcoholic media have been recently shown[1] to yield dimers which were bonded through the 3,4 positions of the heterocyclic nuclei, as illustrated by compound **2**.

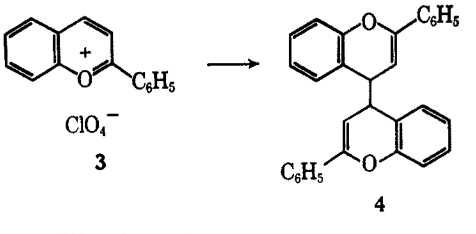


2

The reduction of **1** has been extended to include other types of reducing agents, and the present paper describes the products which were formed from **1** with zinc dust in a neutral medium.

It has been shown[2] that 2,4,6-trimethyl- and triphenyl pyrylium salts were reduced with zinc by a one-electron process, and therefore we expected **1** to react in a similar manner. Palchkov, *et al.*, have reported[3] that a red color which was formed during the reduction of 2,4,6-triphenylpyrylium perchlorate with zinc was due to a radical. We have found that many other 2,4,6-triarylpyrylium salts also gave colored solutions under these conditions, but that **1** gave either no color or a very transient coloration. The apparent discrepancy between the behavior of flavylium and pyrylium salts led us to investigate the nature of the products which were formed from **1** and zinc.

The general procedure that we used for the reduction consisted in stirring a relatively concentrated solution of **1** in acetonitrile with excess zinc dust for several hours at room temperature under a nitrogen atmosphere. The reactions were carried out at room temperature to minimize the formation of a mixture of products which were difficult to separate. The mixture is believed to be the result of heat-induced reactions of the primary reduction products.

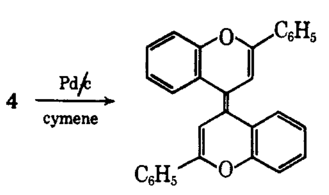


(1)

The reduction of flavylium perchlorate (**3**) (eq 1) by the general procedure described resulted, on addition of the zinc, in the immediate formation of a light orange color, accompanied by a slight temperature rise (10°), followed by complete decoloration of the mixture within a minute. The major product, which was formed in good yield, was assigned structure **4** on the basis of the nmr, infrared, ultraviolet, and mass spectra. An additional product was obtained in low yield, but it was not identified. This material could not be purified by recrystallization; it would not pass through gas chromatography columns in spite of the fact that it was relatively low melting; and it had a washed-out nmr spectrum. These data suggest that the minor product was polymeric.

Compound **4** was refluxed overnight under nitrogen in the presence of a small amount of zinc dust to yield a product which contained an isomer of **4**. A study of the nmr spectrum showed that the product was actually a mixture of diastereomers containing approximately 60% of **4** and 40% of another isomer. The mixture could not be separated by recrystallization, although the ratio of the isomers was changed slightly. A sample of compound **4** was heated in the cavity of an esr spectrometer, and a strong radical signal was obtained above 90°. The isomerization and dissociation of **2** are possible causes for the poor results which were obtained when the reduction of **3** was carried out with heating.

A mixture of **4**, palladium on charcoal, and *p*-cymene was refluxed to yield the known[4] dimer **5** (eq 2). The



5

(2)

reaction did not prove to be a satisfactory synthetic procedure for the preparation of **5** since it was only successful for small-scale runs that were done at high dilution with relatively large amounts of palladium on charcoal. Again, the dissociation of **4** by heat might account for the low yields of **5** which were obtained during larger runs.

When **3** was treated with zinc in hot acetonitrile solution in the presence of air, the products which were isolated were 4-flavone (**6**) and a large amount of the polymeric material. It seems probable that **6** was formed from the reaction of the radical derived from **3** with air to give an unstable peroxide which decomposed to give **6**.

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(1) G. A. Reynolds and J. A. VanAllan, *J. Org. Chem.*, **32**, 3616 (1967).

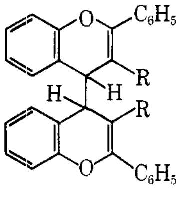
(2) A. T. Balaban, C. Bratu, and C. N. Rentea, *Tetrahedron*, **20**, 265 (1964).

(3) V. A. Palchkov, Yu. A. Zhdmov, and G. N. Dorofeemko, *J. Gen. Chem. USSR*, **35**, 1182 (1965).

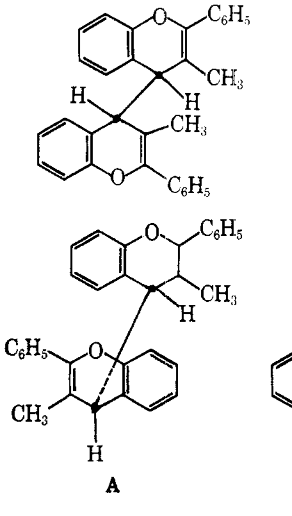
(4) E. Bayer and B. Kramer, *Chem. Ber.*, **97**, 1057 (1964).

Several 3-substituted flavylium salts were reduced with zinc under nitrogen to yield dimers which were obtained as a mixture of diastereomers. These isomers were not completely separated by crystallization in all cases. A partial separation of the isomers could be achieved by fractional cyystallization.

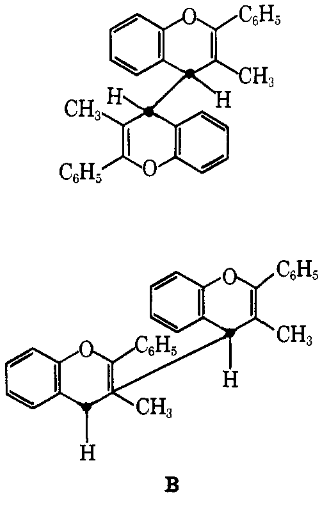
The dimers **7**, **8**, and **9** were prepared from 3-substituted flavylium salts. The diastereomers of the dimer **7** were investigated in some detail because each isomer could be obtained in a pure form The product which was obtained in this case was almost completely the low-melting, soluble isomer. In the course of determining the melting point of this material, it was noted that it melted, then solidified, and remelted at a much higher temperature. A sample of the product was heated for a short time and found to isomerize to the higher-melting isomer. Both materials showed nearly identical absorptions in both the infrared and ultraviolet regions of the spectrum. It was concluded from the data that the less stable low-melting dimer was formed by the reaction of zinc with the flavylium salt, and that this dimer dissociated on heating to a radical which recombined to give the more stable dimer. The fact that an esr signal was observed when a sample of the low-melting isomer was heated substantiates this conclusion. The nmr spectrum of **7** (low-melting isomer) was obtained in *o*-dichlorobenzene as a solvent at several temperatures, with the following results. At ambient temperature (38°), the methyl singlet fell at τ 8.27 (hexamethyldisiloxane as internal reference) and the tertiary proton fell at 6.45. The spectrum remained unchanged at 75°, but at 125° the methyl region appeared as two singlets of equal intensity at τ 8.27 and 8.19. The two methyl singlets remained constant both in intensity and in chemical shift on raising the temperature to 160° and then cooling the solution to ambient temperature. The tertiary proton remained unchanged at the different temperatures. The following explanation accounts for the difference in the absorptions of the methyl groups of the isomers. In the *threo* isomer **A**, the two methyls remain in exactly equivalent environments during rotation about the 4,4′ bond, but in the *erythro* isomer **B** the two methyls are in equivalent environments only in the conformation with the 4,4′ hydrogens either *trans* or eclipsed, and in all other conformations they are nonequivalent. The 4,4′ hydrogens remain equivalent at all times in both isomers.



7, R = CH_3
8, R = C_2H_5
9, R = C_6H_5

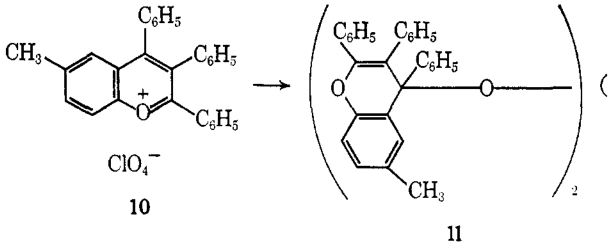


A



B

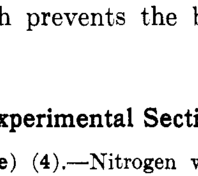
Substituents in the 4 position of the flavylium molecule affect dimer formation adversely, since 4-phenylflavylium perchlorate failed to react with zinc under the standard reaction conditions. The treatment of 6-methyl-3,4-diphenylflavylium perchlorate (**10**) with zinc also gave mostly starting material, along with a small amount of product which analyzed for the peroxide **11** (eq 3). The failure of these salts to form dimers does not appear to be due to steric hindrance because the dimer of **10** has been prepared in a different manner.[5]



(3)

10 **11**

The fact that **1** and zinc dust gave dimeric products indicates that these salts are similar in their behavior to 2,4,6-triphenylpyrylium perchlorate, which has been shown[2] to yield the dimer **12** under similar reaction conditions. The failure of **1** to give colored solutions in the presence of zinc could be due to a high rate of dimerization which prevents the buildup of flavenyl radicals.



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Experimental Section

4,4′-Bis(flav-2-ene) (**4**).—Nitrogen was passed through a solution of 25 g of flavylium perchlorate (**3**) in 700 ml of acetonitrile for 1 hr and then 40 g of zinc dust was added, with stirring. The color of the reaction mixture changed from light yellow to orange to colorless within about 1 min, and the temperature rose to 35°. The mixture was stirred at room temperature under nitrogen for 3 hr and then quickly heated to boiling and filtered to remove the unreacted zinc. The filtrate was concentrated to 300 ml *in vacuo* and allowed to stand overnight. The white solid was collected and recrystallized from acetonitrile to yield 14 g (85%) of **4**, mp 167–168°, with progressive yellowing above 120°.

Anal. Calcd for $C_{30}H_{22}O_2$: C, 87.8; H, 5.4. Found: C, 87.6; H, 5.6.

The product did not show a molecular ion in the mass spectrom-

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(5) K. Ziegler, F. A. Fries, and F. Salzer, *Ann.*, **249**, 259 (1926).

eter (heated inlet at 235°) but did give a fragmentation pattern which was identical with that of 4H-flavene. The molecular weight of **4** by the vapor pressure osmometry method was 410 (calculated 414). The ultraviolet absorption spectrum (in acetonitrile) showed peaks at 238 (ϵ 42.2 × 10^3) and 285 mμ (ϵ 11.2 × 10^3), and there was a sharp absorption at 6 μ in the infrared which is typical for 4H-flavene derivatives. The nmr spectrum[6] had the following absorptions: two mirror-image multiplets centered at τ 4.91 and 6.05 (2 H each) and a complex multiplet centered at 2.7 (18 H). The multiplets at 4.91 and 6.05 comprised an AA'XX' spectrum with $J_{AX} + J_{AX'} = 4.0$ Hz (this separation did not change at 100 MHz).

The mother liquors were concentrated to dryness, and the solid residue was recrystallized five times from aqueous ethanol to give 1 g of a solid which melted from 105–125°. All attempts to purify this material were unsuccessful. This fraction from several runs was analyzed for carbon and hydrogen, but the results varied for each sample. This material was thought to be polymeric.

Mixture of Isomers of 4.—A mixture of 1 g of **4**, 1 g of zinc dust, and 25 ml of acetonitrile was refluxed overnight and then filtered to remove the zinc. The filtrate was cooled and 0.6 g of the product was collected, mp 161–166°.

Anal. Calcd for $C_{30}H_{22}O_2$: C, 87.8; H, 5.4. Found: C, 87.5; H, 5.2.

The nmr spectrum of the product showed that it contained 60% of the isomer **4** and 40% of a new isomer whose AA'XX' multiplets were centered at τ 4.49 and 6.18 ($J_{AX} + J_{AX'} = 4.5$ Hz).

Bisflavenylidene (5).—A mixture of 1 g of **4**, 0.5 g of 20% palladium on charcoal, and 25 ml of *p*-cymene was refluxed overnight and then filtered hot to remove the catalyst. The filtrate was chilled and the yellow solid was collected and washed with benzene to give 0.4 g of **5**, mp 221–222°. The product and a sample of material prepared by the published procedure[4] had identical infrared absorption curves.

Incidentally, we were able to prepare **5** by the procedure of Bargot and Jurd[7] from flavone, zinc dust, sodium acetate, and acetic anhydride, but the yield of **5** was much lower (about 15% yield) than that obtained from thioflavone and activated copper powder.[4]

Reduction of Flavylium Perchlorate (3) in the Presence of Air.—A mixture of 10 g of **3**, 20 g of zinc dust, and 25 ml of acetonitrile was refluxed for 8 hr while air was passed through the solution. The hot mixture was filtered, and the insoluble material was extracted with 250 ml of boiling acetonitrile and filtered The filtrates were allowed to stand overnight, and the white solid that separated was collected (3 g). This product was flavone **6**, as shown by comparison of the infrared absorption curve with that of an authentic sample. The mother liquors were evaporated to dryness to give 4 g of solid which could not be identified but seemed to be identical with the polymeric material which was isolated during the preparation of **4**.

4,4-Bis(3-methylflav-2-ene) (7).—A mixture of 3 g of 3-methylflavylium perchlorate, 6 g of zinc dust, and 100 ml of acetonitrile was stirred under nitrogen for 3 hr, heated to boiling, and then filtered to remove the zinc. The filtrate was diluted with water and the precipitated material was collected and recrystallized from ethanol to give 1.85 g of product, mp 156–157°, which then solidified and remelted at 247–250°.

Anal. Calcd for $C_{32}H_{26}O_2$: C, 86.9; H, 5.9. Found: C, 86.5; H, 5.9.

The nmr spectrum showed singlets at τ 8.18 (6 H) and 6.35 (2 H), and a multiplet centered at about 2.9 (18 H).

A sample of the product was heated in an oil bath at 200° for 10 min and the solid was ground and extracted with boiling ethanol. The insoluble material was collected and melted at 249–251°.

Anal. Found: C, 86.7; H, 5.9.

The nmr spectrum showed singlets at τ 8.16, 8.11 (6 H), and 6.35 (2 H), and a multiplet centered at about 2.9 (18 H). (See text for the spectrum of **7** in *o*-dichlorobenzene at various temperatures.)

4,4-Bis(3-ethylflav-2-ene) (8).—The procedure used for the preparation of **7** was applied to 5 g of 3-ethylflavylium perchlorate. The crude reaction product (3 g) was recrystallized twice from ethanol to yield 2 g of product, mp 145–147°. The combined alcohol solutions from the recrystallizations were concentrated to a small volume to yield a solid which was recrystallized twice from ethanol to give 0.6 g of another product, mp 123–125°. These products were a mixture of isomers, as shown by nmr.

Anal. Calcd for $C_{34}H_{30}O_2$: C, 86.6; H, 6.4. Found for high-melting isomer: C, 86.9; H, 6.6. Found for low-melting isomer: C, 86.6; H, 6.3.

The nmr spectra showed that each fraction was a mixture of isomers of different relative concentrations. The higher melting fraction showed a methyl triplet at τ 8.97 ($J = 7$ Hz) and a less intense triplet ($\sim{}^1/_2$) at 9.07. The methylene absorption centered at 7.73 was a complex, nonassignable multiplet, presumably because of nonequivalent methylenes in one of the isomers analogous to the methyls of **7**. The tertiary protons fell at 6.19 and 6.21. The lower melting isomer had an exactly analogous spectrum except that the relative intensities were reversed.

4,4-Bis(3-phenylflav-2-ene) (9).—This dimer was prepared by the same procedure that was used for the preparation of **7** and **8**, and from 3 g of 3-phenylflavylium perchlorate there was obtained 0.8 g of isomer **9A**, mp 175–176° (from ethanol), and 0.3 g of isomer **9B**, mp 108–110° (from ethanol).

Anal. Calcd for $C_{42}H_{30}O_2$: C, 88.9; H, 5.3. Found for **A**: C, 89.0; H, 5.6. Found for **B**: C, 88.9; H, 5.6.

The nmr spectrum for **A** showed a singlet at τ 5.72 (2 H) and a multiplet at about 2.95 (28 H); for **B**, the singlet was at 5.92.

Treatment of 6-Methyl-3,4-diphenylflavylium Perchlorate (10) with Zinc.—A solution of 3 g of **10** in 100 ml of acetonitrile was stirred under nitrogen and 5 g of zinc dust was added. The solution became strongly fluorescent (green), but within a minute the fluorescence faded. After the mixture has been stirred for 4 hr under nitrogen, it was heated to boiling and filtered hot. The solution became light green when it was heated. The zinc was extracted with boiling benzene and filtered. The benzene extract was concentrated to 50 ml and diluted with 10 ml of ethanol and, after it had been chilled, 0.3 g of white solid was collected. The solid was recrystallized from ethanol to give 0.2 g of the peroxide **11**; 2 g of the starting material **10** was recovered.

Anal. Calcd for $C_{56}H_{42}O_4$: C, 86.2; H, 5.4. Found: C, 85.8; H, 5.8.

The molecular weight of **11**, by the ebullioscopic method was 762 (calculated 779). The infrared absorption spectrum showed that hydroxyl and carbonyl groups were absent. There was an absorption at 6.05 μ which seems to be typical of the chromene nucleus. A peroxide similar to **11** has been reported previously.[8]

Registry No.—**4,** 14233-66-0; **7A,** 14233-67-1; **7B,** 14233-68-2; **8,** 14233-69-3; **9,** 14233-70-6; **11,** 14233-71-7.

Acknowledgment.—We wish to acknowledge the assistance of R. L. Young, for determining the nmr spectra, and that of D. P. Maier and G. P. Happ, for determining and interpreting the mass spectra.

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(6) The nmr spectra were measured in deuteriochloroform at 60 MHz on a Varian A-60 Spectrometer with tetramethylsilane as an internal standard.

(7) B. J. Bargot and L. Jurd, *Tetrahedron*, **21**, 657 (1965).

(8) A. Lowenbeim and B. Rosenbaum, *Ann.*, **448**, 223 (1926).