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Intermolecular Hydride Transfer Reactions. IV. Acid-induced Redox Reactions of 4-Substituted Flav-2-enes

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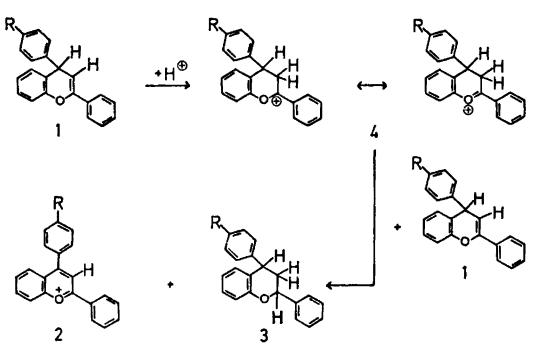
Treatment of 4-phenyl- or 4-(*p*-dimethylaminophenyl)-flav-2-ene with acid resulted in formation of the corresponding flavylium cations and flavane derivatives. The carbonium ion formed by protonation at C-3 of the flavene oxidized the unprotonated flavene through a hydride transfer reaction. The *cis*- and *trans*-4-phenyl flavanes were formed in 10:1 ratio. The stereospecificity of the hydride transfer reaction is interpreted to mean preference for a quasi axial phenyl group at C-4 of the hydride acceptor.

From treatment of 4-phenylflav-2-ene (*1*, R = H) with perchloric acid, Kröhnke and Dickoré isolated two products.[1] One of these was identified as 4-phenylflavylium perchlorate (*2*, R = H). The other compound was not identified, only melting point (141 – 142 °C) and yield were given. For this reason Kröhnke and Dickoré were unable to explain the observed reaction.

Barnes *et al.*[2] have reported that catalytic hydrogenation of 4-phenylflav-2-ene (*1*, R = H) yielded 4-phenylflavane (*3*, R = H) (m.p. 145 – 147 °C).

This work deals with the oxidation of flavenes to flavylium cations in acidic solutions. Re-examination of the work of Kröhnke and Dickoré resulted in the isolation of the flavylium salt *2* (R = H), and the unidentified compound in approximately the reported yields. Melting point, ^{1}H NMR spectrum and the mass spectrum of the latter compound were in agreement with the values of 4-phenylflavane (*3*, R = H) reported by Barnes *et al.*[2]

The acid induced intermolecular hydride transfer reaction depicted in Scheme 1 explains the formation of the flavylium salt *2* (R = H)



Scheme 1.

and the flavane derivative *3* (R = H). The yields of these products were in agreement with the equation:

$2(1) + HClO_4 = (2)\ ClO_4^- + (3)$

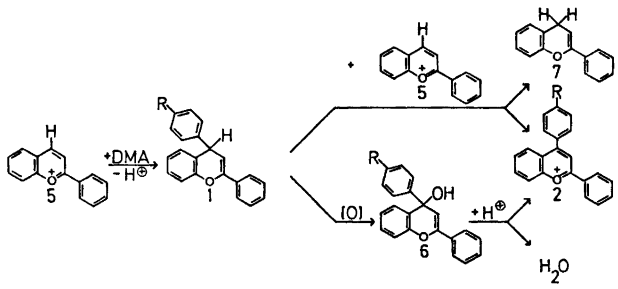
The reaction was repeated in trifluoroacetic acid (TFA) solution. The flavane derivative *3* (R = H) precipitated from the reaction mixture in 80 % yield, according to the equation above. The flavylium perchlorate (*2*, R = H) was isolated after addition of a mixture of acetic and perchloric acids to the concentrated TFA solution.

The flavene derivative *1* (R = H) used in these experiments was synthesized from flavylium perchlorate and the Grignard reagent of bromobenzene.[3,4] Consequently *1* (R = H) was a racemic mixture. ^{1}H NMR analysis of the racemic reduction product *3* (R = H) showed that the phenyl substituents at C-2 and C-4 were *cis* oriented. The yield of *3* (R = H) suggested a highly stereospecific hydride

transfer reaction. The *trans*-isomers were obtained from hydrogenolysis of 4-hydroxy-4-phenylflavane, synthesized from racemic flavanone and the Grignard reagent of bromobenzene.[4] The hydrogenolysis of the carbinol yielded a mixture of *cis*- and *trans*-4-phenylflavanes (*3*, R=H), which were separated by fractional crystallisation. A reaction mixture from treatment of 4-phenylflav-2-ene (*1*, R=H) with TFA was analyzed by GLC and this showed that the *cis*- and *trans*-flavanes were formed in 10:1 ratio, respectively.

A reasonable explanation for the stereochemical control of the reaction is as follows. The initial step is formation of a resonance stabilized carbonium ion *4* by protonation (Scheme 1). A twist conformation of this heterocyclic system is expected due to the Pitzer strain of the 3,4-bond in the planar conformation. The next step is a hydride transfer from C-4 of the unprotonated flavene *1*, to the created sextet at C-2 of *4*. This transfer is almost certainly dependent on the sterical environment at the C-2 reaction center of *4*. From models the environment at C-2 will be different whether the phenyl group at C-4 is quasi equatorial or quasi axial. In the quasi equatorial conformer, the rotation of the phenyl group at C-4 will be restricted due to interaction with the hydrogen at C-5. In the quasi axial conformer there are no serious interactions of the phenyl group at C-4 with other parts of the molecule. Consequently the latter conformer is assumed to be the preferred one. Approach of the hydride donor *1* (R=H) towards C-2 of *4* at the same side as the quasi axial phenyl group will strongly be hindered. No such interaction will interfere on approach from the opposite side. From this consideration a reduction product with the phenyl group at C-4 and the transferred hydrogen at C-2 in a *trans* configuration is expected. Mutual interaction of the axial phenyl groups at C-4 and C-2 (*cis* configuration) in the product which is formed primarily, interconverts the heterocyclic ring into the more stable conformation with the phenyl groups in a quasi diequatorial position.

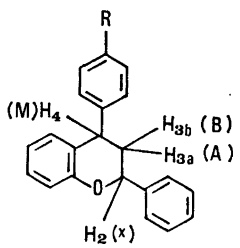
Shriner and Shotton have studied the reaction of flavylium perchlorate (*5*) with dimethylaniline in the presence of air to yield the 4-(*p*-dimethylaminophenyl)flavylium perchlorate (*2*, R=$N(CH_3)_2$).[5] The reaction was proposed to proceed through electrophilic substitution with formation of 4-(*p*-dimethylaminophenyl)flav-2-ene [*1*, R=$N(CH_3)_2$] which subsequently was oxidized by air to the 4-hydroxy-4-(*p*-dimethylaminophenyl)flav-2-ene [*6*, R=$N(CH_3)_2$]. The carbinol *6* [R=$N(CH_3)_2$] and the perchloric acid liberated in the substitution step, yielded the flavylium salt *2* [R=$N(CH_3)_2$]. Recently this reaction was reinvestigated and an alternative explanation of the formation of *2* [R=$N(CH_3)_2$] was suggested on the basis of the parent flav-2-ene (*7*) which was shown to be formed in the reaction.[6] An intermolecular hydride transfer reaction between the substitution product, [*1*, R=$N(CH_3)_2$] and unreacted flavylium cation was proposed to account for the observed products. These alternative reaction sequences are summarized in Scheme 2. The air oxidation sequence could not be excluded since Shriner and Shotton obtained the flavylium salt *2* [R=$N(CH_3)_2$] from a solution consisting of only the flavene derivative *1* [R=$N(CH_3)_2$] which had been exposed to air and then treated with strong acid.[5] However, the conditions used in the air oxidation experiment were not defined, and the postulated



Scheme 2.

intermediate carbinol *6* [R=N(CH$_3$)$_2$] was not reported to be identified prior to addition of acid to the solution of *1* [R=N(CH$_3$)$_2$]. As demonstrated with the 4-phenylflav-2-ene (*1*, R=H), protonated flavenes are potential oxidants in transformation of flavenes to flavylium cations. A reaction path corresponding to the one depicted in Scheme 1 was considered as an alternative explanation of the results from the oxidation experiment reported by Shriner and Shotton. The feasibility of the acid induced redox reaction of the flavene derivative *1* [R=N(CH$_3$)$_2$] was demonstrated by examining the ^{1}H NMR spectrum of this compound in TFA solution. The ^{1}H NMR spectrum showed signals due to a 1:1 mixture of the flavylium cation of *2* [R=N(CH$_3$)$_2$] and the flavane derivative *3* [R=N(CH$_3$)$_2$]. Thus acid treatment of the flavene derivative *1* [R=N(CH$_3$)$_2$] can lead directly to the corresponding flavylium cation without passing through a carbinol stage.

Table 1. ^{1}H NMR spectrum of *3* in $CDCl_3$ (δ)



Configuration	*cis*	*trans*	*cis*
Compound *3*; R	H	H	N(CH$_3$)$_2$
H$_2$(X)	5.19	5.07	5.18
H$_4$(M)	4.33	4.20	4.25
H$_{3a}$(A)	2.27	2.2–	2.0–
H$_{3b}$(B)	2.39	2.6	2.5
Arom H	6.6–	6.7–	6.5–
	7.6	7.5	7.6
R			2.90
$J_{2,3a}=J_{AX}$	10.6	13.0[a]	13.5[a]
$J_{2,3b}=J_{BX}$	1.8		
$J_{4,3a}=J_{AM}$	11.8	9.5[b]	18.5[b]
$J_{4,3b}=J_{BM}$	5.8		
$J_{3a\,3b}=J_{AB}$	−13.5		

[a] $J_{AX}+J_{BX}$. [b] $J_{AM}+J_{BM}$.

^{1}H NMR analysis of the 4-substituted flavanes *3*[7]

cis-4-Phenylflavane (m.p. 145 °C). The protons H$_2$, H$_3$a, H$_3$b, and H$_4$ form an ABMX pattern which on irradiation at either ν_M (δ 4.33) or at ν_X (δ 5.19) collapses to an ABX pattern. Calculation of the spectral parameters gave the results quoted in Table 1. The large coupling constants $J_{AX}=10.6$ Hz and $J_{AM}=11.8$ Hz reveal the quasi axial orientation of the protons X (H$_2$) and M (H$_4$). Consequently the two phenyl groups at C-2 and C-4 must be quasi equatorially and *cis* oriented.

trans-*4-Phenylflavane (m.p. 71 °C).* Protons H$_2$, H$_3$a, H$_3$b, and H$_4$ again form an ABMX pattern. A full analysis including spin decoupling was not carried out. However, $J_{AM}+J_{BM}$ is 9.5 Hz and much smaller than the corresponding value of the *cis*-isomers discussed above (16.6 Hz). This indicates that there is no axial-axial vicinal coupling involved and consequently M(H$_4$) must be quasi equatorially oriented and thus the phenyl group at C-4 is quasi axial. Furthermore $J_{AX}+J_{BX}$ is 13.0 Hz and compared to the value of the *cis*-isomers (12.4 Hz) this indicates that the proton X(H$_2$) is quasi axially oriented. Consequently the phenyl group at C-2 is quasi equatorial and *trans* oriented to the phenyl group at C-4.

cis-*4-(p-Dimethylaminophenyl)flavane.* The ^{1}H NMR spectrum was nearly identical to the spectrum of the *cis*-4-phenylflavane with respect to signals due to the alicyclic protons. This indicates *cis*-configuration of the C-2 and C-4 substituents.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian A-60A and on a Varian HA100 instrument with TMS as internal standard. A Perkin Elmer F11 instrument equipped with an OV-17 column was used for the GLC analysis. The mass spectra were run on a AEI MS902 instrument.

4-Phenylflavane (3, R=H) and 4-phenylflavylium perchlorate (2, R=H). From treatment of 4-phenylflav-2-ene (*1*, R=H);[4]

(a) *with perchloric acid/acetic acid.* The results of Kröhnke and Dickoré were obtained.[1]

(b) *with trifluoroacetic acid.* 4-Phenylflav-2-ene (*1*, R=H) (2.84 g, 0.01 mol) was added to trifluoroacetic acid (25 ml) with stirring. The solution was left at 20 °C overnight and the

precipitated *cis*-4-phenylflavane was collected by filtration in 80 % (1.23 g) yield with m.p. 143 – 145 °C.[2] ^{1}H NMR spectrum see Table 1. The remaining solution after removal of *3* (R = H) was concentrated and the residual oil was redissolved in a mixture of acetic acid (10 ml) and 70 % perchloric acid (2 ml). Addition of ether precipitated the 4-phenyl-flavylium perchlorate (*2*, R = H) in 80 % (1.5 g) yield with m.p. 218 °C (AcOH).[1]

The ^{1}H NMR spectrum of a solution prepared from addition of *1* (R = H) to TFA with subsequent removal of the precipitated *3* (R = H), confirmed that the flavylium cation was formed prior to the work up with the perchloric and acetic acid mixture.

cis- *and* trans-*4-Phenylflavanes (3, R = H) from treatment of 4-phenylflav-2-ene (1, R = H) with TFA*. The conditions of experiment (b) were used. However, instead of removing the precipitated *cis*-4-phenylflavane, the solvent was evaporated. The residual oil was completely dissolved in chloroform. The homogeneous solution was analyzed by GLC and the *cis*:*trans* ratio was determined to 10:1.

trans-*4-Phenylflavane (3, R = H)*. 4-Hydroxy-4-phenylflavane (1.0 g), prepared from flavanon and phenylmagnesium bromide,[4] was hydrogenated over Pd/C (10 %) (1.0 g) catalyst in ethyl acetate (100 ml) in a Parr apparatus with an initial pressure of 250 kPa for 24 h at 20 °C. The hydrogenolysis was quantitative as shown by the ^{1}H NMR spectrum of the concentrated solution after removal of the catalyst, and furthermore the *cis*- and *trans*-4-phenylflavanes were formed in approximately 1:1 ratio. The separation of the diastereomers was achieved by fractional crystallization. The *cis*-isomers were less soluble in ethanol than the *trans*-isomers. *trans*-4-Phenylflavane: m.p. 70 – 71 °C (EtOH). (Found: C 88.27; H 6.42. Calc. for $C_{21}H_{18}O$: C 88.10; H 6.29). ^{1}H NMR spectrum, see Table 1.

A solution of the *trans*-isomers in chloroform was mixed with TFA and left standing for 24 h at 20 °C. Isomerization to the *cis*-isomers could not be detected as shown by GLC analysis of the solution.

4-(p-Dimethylaminophenyl)flavane [*3*, *R* = *N*(CH_3)$_2$]. 4-(*p*-Dimethylaminophenyl)flav-2-ene [*1*, R = N(CH_3)$_2$][5,6] (1.63 g, 0.005 mol) was dissolved in trifluoroacetic acid (10 ml) with stirring. After 2 h at 20 °C the solvent was evaporated and the residual oil was dissolved in dimethyl sulfoxide (25 ml). A saturated solution of sodium bicarbonate (25 ml) was added with stirring and after 1 h the mixture was diluted with water.

The precipitated material was collected by filtration, washed with water and crystallized from dilute ethanol. M.p. 137 °C. Molecular weight by mass spectrometry: Found: 329.1779. Calc. for $C_{23}H_{23}NO$: 329.1780. ^{1}H NMR spectrum, see Table 1.

The ^{1}H NMR spectrum of a solution prepared from addition of 4-(*p*-dimethylaminophenyl)-flav-2-ene [*1*, R = N(CH_3)$_2$] to TFA showed signals due to the flavylium cation of *2* [R = N(CH_3)$_2$][6] and the flavane derivative *3* [R = N(CH_3)$_2$] in 1:1 ratio.

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