Flavanoids. Part 6.[1] The Kinetics and Mechanism of Base-catalysed Isomerisation of 3-Arylideneflavanones

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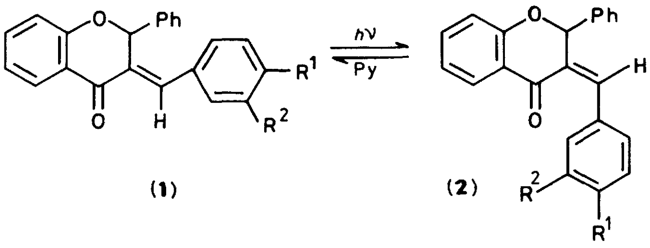
Base-catalysed $Z \longrightarrow E$ conversion of 3-arylideneflavanones provide a unique system suitable for kinetic studies by ^{1}H n.m.r. spectroscopy. Isomerisation studies of 10 enones in [$^2H_5$]pyridine showed that a first-order unimolecular reaction was taking place. The Hammett σ–ρ relationship is not adequate to accommodate the substituent effect on rate in the case of *p*- and *m*-nitro-3-benzylidene derivatives. The unusual case of the nitro substituent is discussed.

No kinetic studies are known for the $Z \longrightarrow E$ isomerisation of $\Delta^{\alpha\beta}$-enones. There are cases where $Z \longrightarrow E$ isomerisation takes place[2] but these do not cover substituent effects. Moreover, the proposed mechanism is mostly speculative without any substantiation.[3] The major difficulty is the availability of suitable *Z*,*E* pairs. (*E*)-3-Arylideneflavanones have been readily photoisomerised in high yields to *Z* isomers and the reverse isomerisation has been achieved by acid catalysis.[4a,b] Similar to the earlier reported $Z \longrightarrow E$ isomerisation of isoaurones by pyridine,[5] (*Z*)-3-arylideneflavanones are completely converted into *E* isomers on keeping in pyridine and initial qualitative time-dependent ^{1}H n.m.r. studies showed that the reaction is sufficiently slow on the ^{1}H n.m.r. time scale[6] and we now report the systematic kinetic study of this reaction to arrive at the mechanism of this isomerisation.

Results

The required 3-arylideneflavanones (**1a**—**j**) were obtained by condensation of flavanone with ten aromatic aldehydes[7] with both electron-donating and -withdrawing *para* and *meta* substituents on the 3-arylidene ring and seven of these (**1b**—**e**,**g**,**h**,**j**) are new.†



(**1**) (**2**)

	a	b	c	d	e	f	g	h	i	j
R^1	Cl	Br	F	H	H	H	CH_3	OCH_2Ph	OCH_3	NO_2
R^2	H	H	H	OCH_3	NO_2	H	H	H	H	H

Sensitised photolysis of these in benzene furnished the *Z* isomers in high yields. With added sensitisers like Methylene Blue and Rose Bengal along with a quaternary ammonium salt as a phase-transfer catalyst the isomerisation is faster. The stereochemical assignments of (**1**) and (**2**) are based on the comparison of the chemical shift of H_β in (**1**) at δ *ca.* 8.3 and in (**2**) at δ *ca.* 6.4 identified earlier for (**1f**) and (**2f**) by deuterium substitution.[4a]

Time-dependent ^{1}H *N.m.r. Studies on* $Z \longrightarrow E$ *Isomerisation of* (**2**) $\longrightarrow$ (**1**) *in* [$^2H_5$]*Pyridine*.—The (*Z*)-3-arylideneflavanone derivative was placed in the ^{1}H n.m.r. sample tube and the spectra were recorded at different time intervals. The completion of isomerisation was checked by the disappearance of the H_β signal of (**2**) at δ *ca.* 6.4, indicating 100% $Z \longrightarrow E$ conversion in every case.

Kinetic Measurements.—At time $t = 0$ the observed area under the β-proton peak in the ^{1}H n.m.r. spectrum of the sample represents the initial concentration. The decrease in the concentration of (**2**) at different time intervals was arrived at by measuring the area under the peak with a concomitant increase in the relative area of the β-proton signal of the newly formed *E* isomer. A typical ^{1}H n.m.r. trace of the isomerisation studies of (**2a**) $\longrightarrow$ (**1a**) is given in Figure 1.

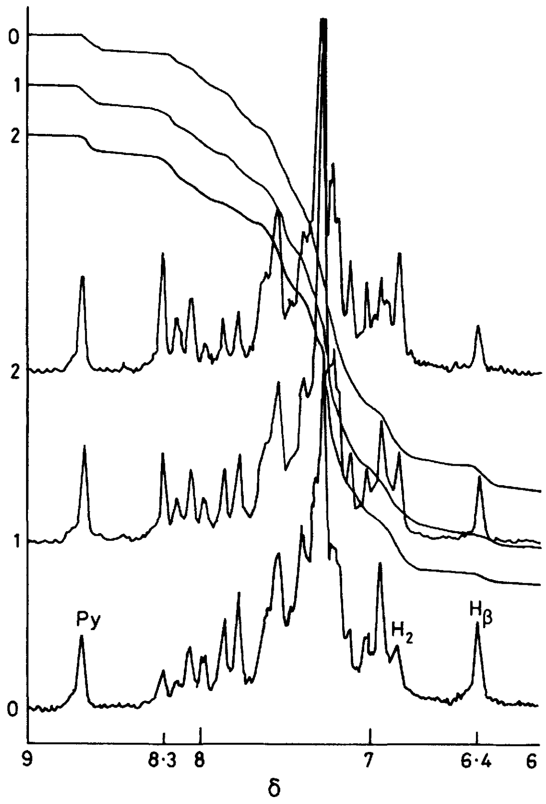


Figure 1. Time-dependent ^{1}H n.m.r. spectrum of isomerisation (**2a**) $\longrightarrow$ (**1a**)

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† Satisfactory analysis has been obtained for all these compounds.

Table 1. First-order rate constants and half-life for $Z \longrightarrow E$ isomerisation of 3-arylideneflavanones

Substituents	$10^{-2}\,k/\mathrm{h}^{-1}$*	$t_{\frac{1}{2}}$/h
4″-Cl	39.47	1.75
4″-Br	36.85	1.88
4″-F	32.24	2.15
3″-OCH_3	30.62	2.26
3″-NO_2	23.60	2.93
H	22.57	3.07
4″-CH_3	15.50	4.47
4″-OCH_2Ph	10.65	6.50
4″-OCH_3	8.86	7.82
4″-NO_2	5.26	13.16

* Subject to experimental error

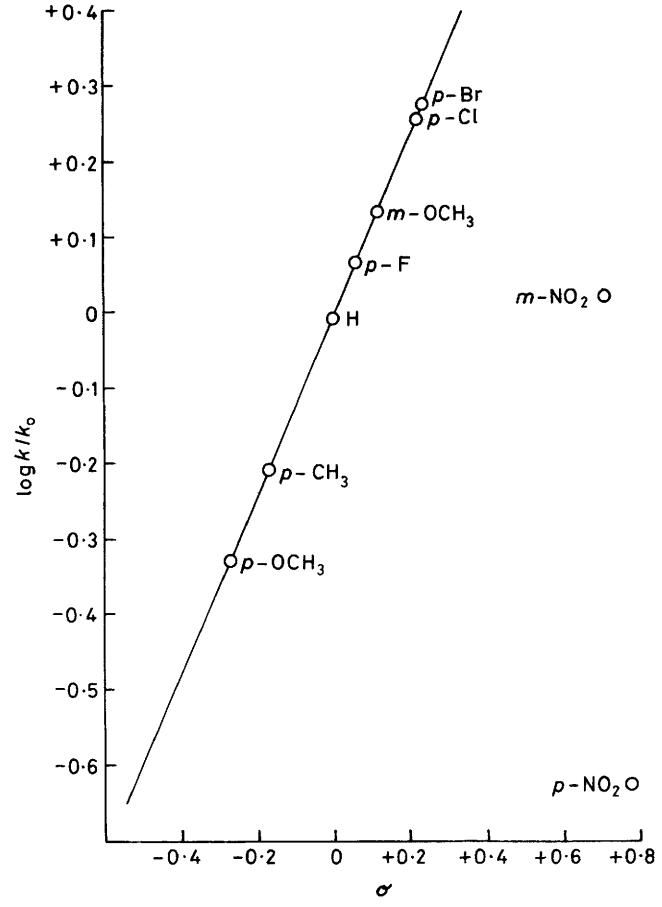

Figure 2. Hammett plot of log k/k_0 *versus* σ. The line is from least-squares analysis

The k values and $t_{\frac{1}{2}}$ are the average of a minimum of three measurements in each case and are given in Table 1. The values of k_{obs} have been fitted to the Hammett equation. The aid of computer-assisted least-squares analysis allowed the determination of the isomerisation rate–σ profile based on the Hammett equation which fitted very closely to the experimental data, providing support for its validity.

In Figure 2 the points are experimental and the line is that of best fit. Least-squares analysis gave a ρ value of 1.2 [correlation coefficient (r) 0.9697 and standard deviation (s) 0.063] which agrees well with that (ρ 1.199) obtained from analysis of the kinetic data.

The bimolecular nature of the reaction was ascertained by studying the reaction rate at different concentrations of (**2f**) and [$^2H_5$]pyridine in $CDCl_3$. The rate was immeasurably slow with an equimolar ratio of reactants (0.257M). With a molar ratio of 1:10.8 $t_{\frac{1}{2}}$ was 14.54 h; it was 4.54 h with a ratio of 1:20.8. The reaction followed the second-order rate law.

Discussion

In contrast with the failure of tertiary amines to isomerise dimethyl maleate[8] the observed $Z \longrightarrow E$ isomerisation is in accord with the suggested mechanism by Eliel[3] and provides rationalisation of our results. Addition of pyridine at the β-carbon of (**2**) leading to the pyridinium betaine (**3**), rotation of the C_3–C_β bond giving the rotamer (**4**) stabilised by intramolecular dipolar attraction through space. Subsequent elimination of pyridine results in the formation of (**1**). Alternatively, as with the base-catalysed ring opening of flavanones to chalcones,[9,*] ring opening of the betaines (**3**) or (**4**) to the chalcone betaine (**5**) and recyclisation with concomitant bond rotation and elimination of pyridine will yield (**1**). However, because of intramolecular dipolar attraction, (**5**) is most likely to exist in the *s-cis* conformation (**6**), the stable conformation of chalcones.[9a] In this case attack of the 2′-oxyanion on the sp^3-β carbon with the expulsion of pyridine would lead to the rearranged 3-arylideneflavanone (**7**). Moreover, a similar rearrangement of 3-arylidenechromanone (**8**) to 3-methylflavone (**10**) also involves 3-methyleneflavanone (**9**) as an intermediate, but the reaction conditions are drastic.[10]

In our studies under mild conditions (solution in $CDCl_3$ and/or pyridine at 35 °C, the ^1H n.m.r. probe temperature) no compounds other than (**1**) and (**2**) could be detected in the ^1H n.m.r. spectra of all the compounds studied and rule out the possibility of ring opening to betaines (**5**) or (**6**) and (**3**) or (**4**) fail to appear in spectroscopically detectable concentration. The rate-determining step could be (a) the attack of pyridine at C_β, (b) rotation of the C_3–C_β bond *i.e.* conversion of (**3**) into (**4**), or (c) elimination of pyridine. A study of the influence of substitution in pyridine nucleus on the rate can give an indication. However, as pyridine in quaternisation reactions is a good deal less polarisable, *i.e.* reluctant to either donate or accept electronic charge,[11] the expected difference in the rate of isomerisation with substituted pyridines will be relatively small and the substituted deuteriated pyridines are not readily available. Our studies are therefore limited to the isomerisations in [$^2H_5$]pyridine with different substituents in the 3-arylidene group.

The enone (**2**) is a vinylogous carbonyl system and, similar to well studied ester hydrolysis,[12] the rate of isomerisation would be dependent on the substituent on the C-3-arylidene group and would follow the Hammett correlation. A Hammett plot of log k/k_0 *versus* σ showed a neat free energy relationship for eight (**1a**—**d**,**f**—**i**) out of the ten compounds studied and the observed second-order rate law indicated the bimolecular nature of the reaction. The results clearly show that addition of pyridine at C-β (step a) is the slow rate-determining step and the rate varies with the electron density of C-β. All other steps are fast and irreversible.

Thus this work establishes for the first time the mechanism of base-catalysed enone isomerisation and the applicability of the Hammett correlation adds one more new reaction amenable to the study of substituent effects. With the availability of the ρ value for this reaction a new substitution constant σ_p for p-OCH_2Ph (−0.26) is available. Apart from a recent report,[13]

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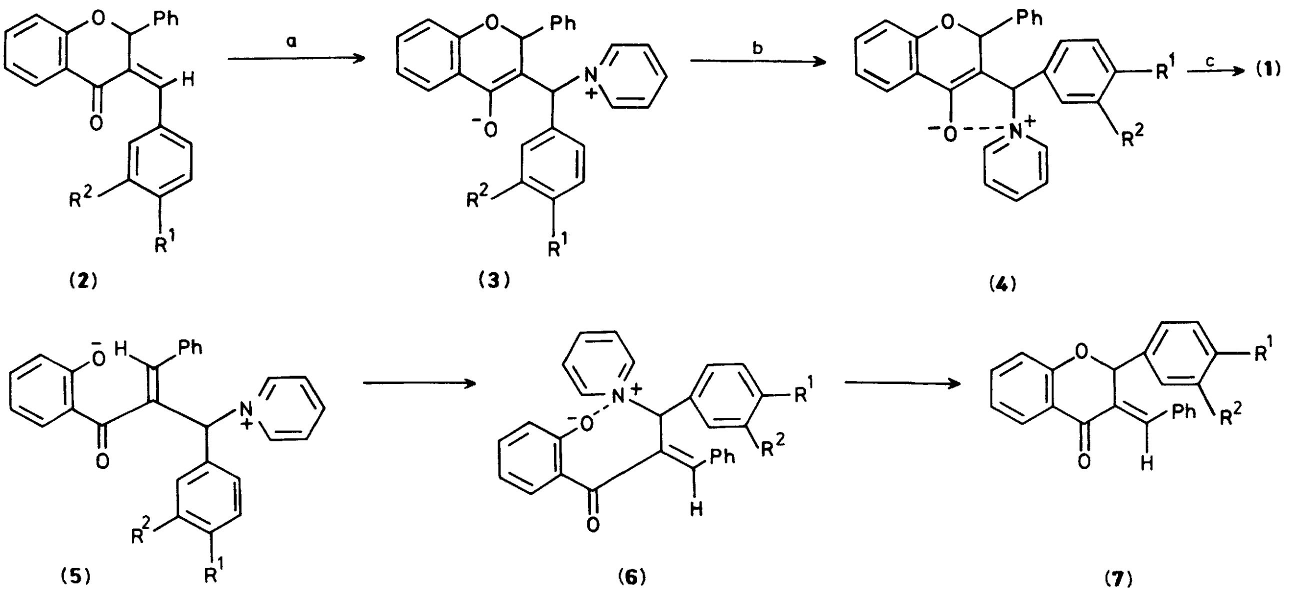
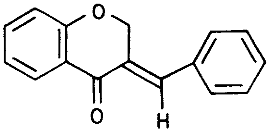
* We thank a referee for proposing the possibility of this mechanism.





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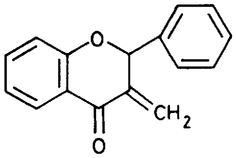

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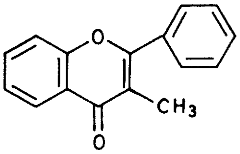

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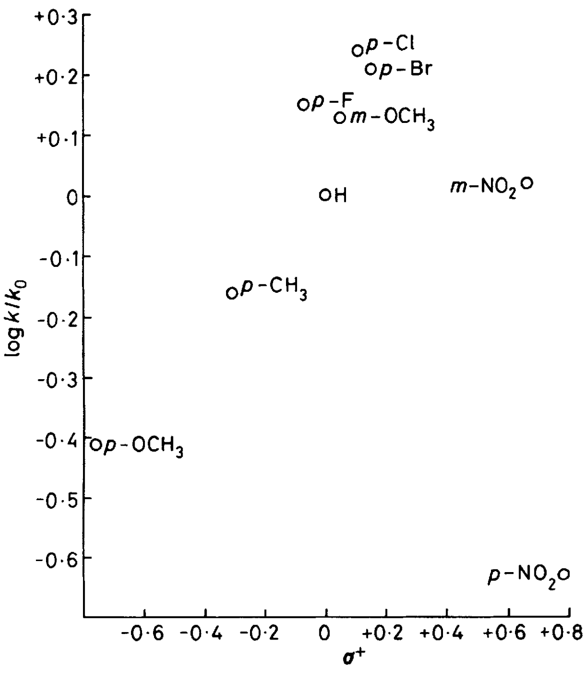

Figure 3. log k/k_0 *versus* σ^+. No line of best fit could be drawn

prior to our elementary studies[6] there are no reports of the utility of ^1H n.m.r. for time-dependent kinetic studies even though temperature-dependent studies have been reported.[14]

However, the effect of the strong electron-withdrawing NO_2 group both at $-3''$ and $-4''$, *i.e.* at the *meta*- and *para*-positions of the aryl group, at C-β appear anomalous (Figure 2), do not fit either Hammett σ or Brown σ^+ values (Figure 3), and will form the subject of a future investigation.

Experimental

General Procedure for Synthesis of (E)-3-*Arylideneflavanones*.—To a solution of flavanone (0.01M) and aromatic aldehyde (0.01M) in ethanol (20 ml) dry hydrogen chloride was passed till the solution turned red. The mixture was kept overnight at 0 °C, when the product separated out. It was filtered, washed, and recrystallised from methylene dichloride—light petroleum to yield (*E*)-3-arylideneflavanone (*ca.* 90—95%). Analytical data are shown in Table 2.

General Procedure for Photoisomerisation of (E)-3-*Arylideneflavanones*.—3-Arylideneflavanone (0.4 g) in dry benzene (10 ml) was photolysed in a Pyrex immersion system with a 125 W medium-pressure mercury arc with external cooling. Isomerisation was complete in *ca.* 10 h. The photoisomer was purified by column chromatography on silica gel with benzene and crystallised from methylene dichloride–light petroleum to yield (*Z*)-3-arylideneflavanone (*ca.* 70—75%). Analytical data are shown in Table 2.

Rate Measurements.—At time $t = 0$ the observed area under the peak of the β-proton of (**2**) at δ 6.4 in the ^1H n.m.r. spectrum represents the initial concentration and measurements were taken at equal intervals till isomerisation was complete. The complete isomerisation was checked by observing the disappearance of the signal at δ *ca.* 6.4 in the ^1H n.m.r. spectrum of (**2**) in every case.

Table 2. Analytical data of (*E*)- and (*Z*)-3-arylideneflavanones

Compound	M.p. (°C)	Found		Required		Molecular formula for isomers (1) and (2)	Compound	M.p. (°C)	Found	
		C (%)	H (%)	C (%)	H (%)				C (%)	H (%)
(1b)	171—173	67.2	3.55	67.5	3.8	$C_{22}H_{15}BrO_2$	**(2b)**	110—112	67.35	3.7
(1c)	133—135	80.1	4.6	80.0	4.6	$C_{22}H_{15}FO_2$	**(2c)**	92—92	79.85	4.5
(1d)	*	80.9	5.3	80.7	5.3	$C_{23}H_{18}O_3$	**(2d)**	*	80.6	5.0
(1e)	147—149	74.05	4.3	73.9	4.2	$C_{22}H_{15}NO_4$	**(2e)**	*	74.2	4.4
(1g)	153—154	84.7	5.6	84.6	5.6	$C_{23}H_{18}O_2$	**(2g)**	*	84.5	5.4
(1h)	172—173	83.3	5.4	83.25	5.3	$C_{29}H_{22}O_3$	**(2h)**	*	83.4	5.0
(1j)	138—140	74.4	4.4	73.9	4.2	$C_{22}H_{15}NO_4$	**(2j)**	133—134	73.8	4.2

* These are liquids purified by chromatography and spectroscopically single isomers

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