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STEREOCHEMICAL STUDIES OF 2-HYDROXYCHROMANONES BY ^{1}H NMR SPECTROSCOPY

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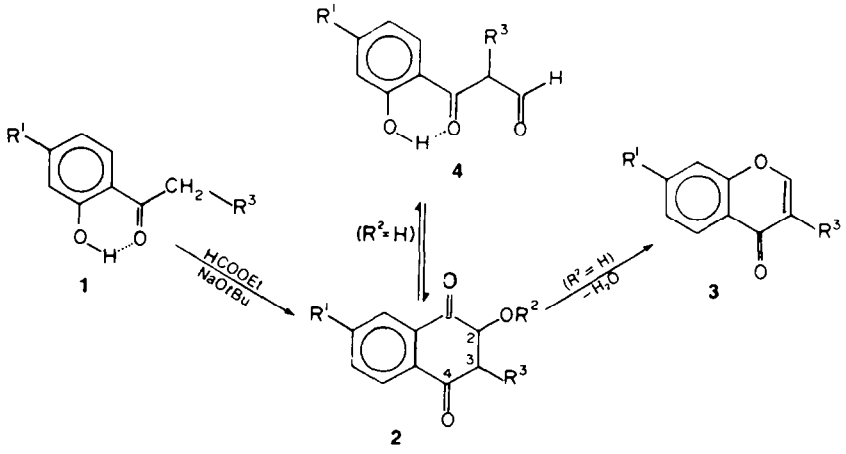
Abstract—2-Hydroxychromanones (**2a-f**) were synthesized by ring closing of 2-hydroxyacetophenones (**1a, b**) and 2-hyroxypropiophenones (**1c-f**). In the case of 2-hydroxy-3-methyl-chromanones (**2c-f**) a mixture of *cis* and *trans* isomers was obtained. The *trans* isomers are conformationally homogeneous, the *cis* isomers exist in a conformational equilibrium. At room temperature the isomers are transformed into each other via opening of the heteroring. This process becomes faster in alkaline medium and the β-diketo form **4** can also be observed.

2-Hydroxyacetophenones (**1**) can be transformed into chromones (**3**) via 2-hydroxy-chromanone derivatives (**2**) with alkali formates and alkali-alkoxides (Scheme 1).[1,2] Synthesis and investigation of these chromanones were published elsewhere[3,4]

A relatively small number of papers deal with the structure and reactivity of 2-hydroxychromanones[5]. Some authors report on a ring–chain isomerisation (**2**⇌**4**)[6], or ring opening[7] of these compounds: while others give preference to the β-diketo (**4**)[8], or to the cyclic form (**2**)[9]. There is also doubt as to the configuration of the cyclic form. Thus for 2-hydroxy-3-phenyl-chromanone either the *trans*[10] or the *cis* configuration[11] is proposed as the only form. Relevant structural data for this type compound are known for the 2-hydroxy-2-phenylchromanone[12]. The present communication reports on the stereochemical investigation of the 2-hydroxychromanone and some 2-hydroxy-3-methyl-chromanone derivatives.

Coupling constants determined from the *ABX* spin system of the heterocyclic protons of **2a** are: J_{AB} = 16,5, J_{AX} = 3,43 and J_{BX} = 4,78 Hz[9] but they do not give any information about either the **3**⇌**4** isomerism or the conformation. For this reason we studied the temperature dependence of the ^{1}H NMR spectra. On the spectrum of **2a** recorded at 30° the C_2–OH signal (Fig. 1a) is broad due to the slow exchange process: the H-2 signal triplet-like, and the H-3 signal consists of 8 lines characteristic for the *AB* part of an *ABX* system. On lowering the temperature the C_2–OH signal splits first to doublet (Fig. 1b,c) and then to a double doublet (Fig. 1d,e). The H-2 triplet transformed to quartet-like multiplet even at 0°. The lines of the *A* proton show a further split at-25°, due probably to the J(H-2, OH) coupling[13] This means that the OH group is *quasi-axial* (*a'*) because only in this case is a zig-zag (W) arrangement possible, which is favourable for the long range coupling.

After D_2O addition at -20° (Fig. 1f) the C_2–OH signal disappears and the splitting due to ^{4}J(H, OH) coupling is no longer observable: The triplet-like structure of the H-2 signal detected at room temperature (see Fig. 2a) is re-formed. The H-3 protons are partially exchanged.



	R'	R²	R³
a	H	H	H
b	OMe	H	H
c	OMe	H	Me
d	H	H	Me
e	Cl	H	Me
f	NO_2	H	Me
g	H	Ac	Me
h	NO_2	Ac	Me

Scheme 1.

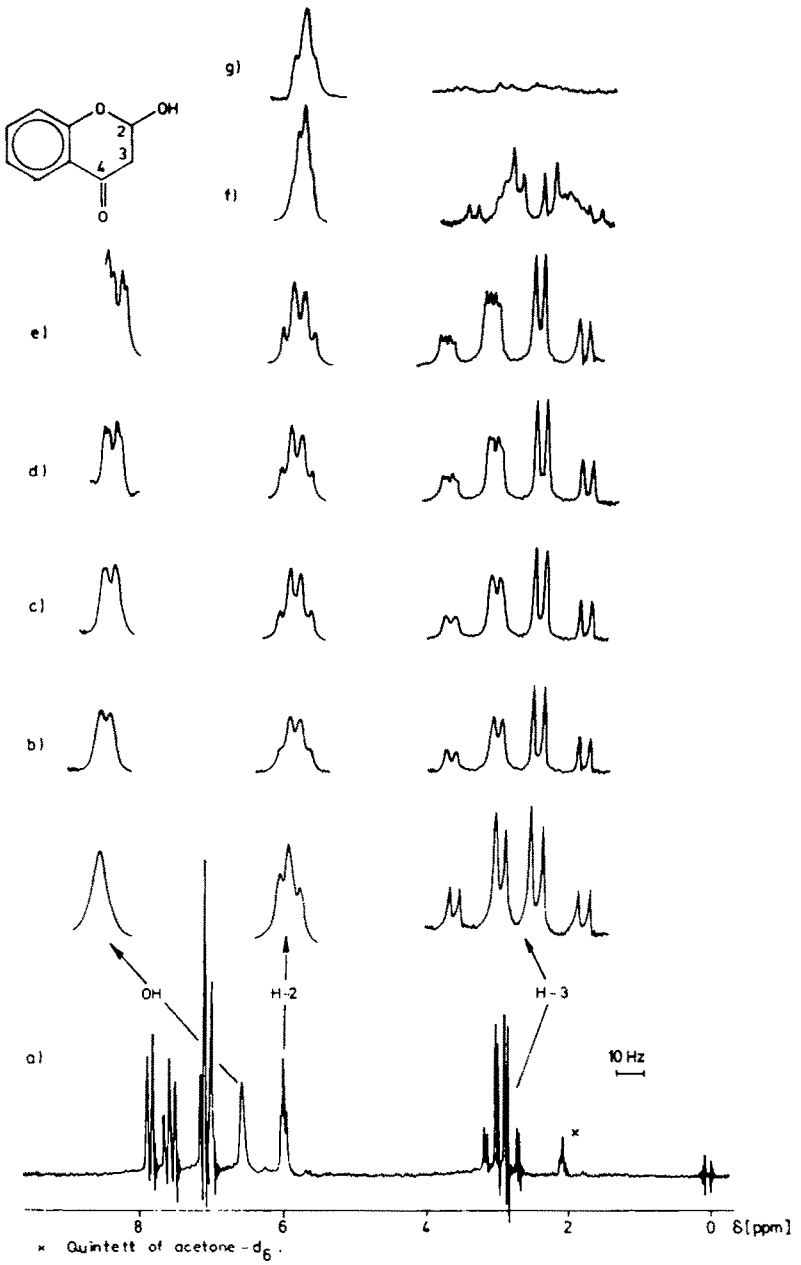


Fig. 1. ^1H NMR spectra of **2a** in acetone-d_6. a:30°:b:0°:c:-10°:d:-20°:e:-25°:f;+D_2O(-20°):g:+D_2O (after 50 hr).

and the residual H-3 signal is superimposed on the broad multiplet of the of the 3-HD group. 50 hrs later the *AB* part disappears and the *X* part becomes a broad singlet, because of the complete H→D exchange of the 3-methylene group (Fig. 1g) via ring opening or enolisation of the 4-one group.

In the synthesis of the 2-hydroxy-3-methyl-chromanones the formation of *cis-trans* isomers is possible. Our investigation was aimed at the determination of the structures of these isomers and the isomer ratio.

In the spectrum of **2d** recorded in acetone-d_6 doubled H-2, C_2–OH, H-3 and C_3-Me signals refer to a mixture of *cis* and *trans* isomers. The signals can be sorted into two sets by their intensities and coupling constants (Table 1), or by studying their temperature dependence.

At 30° (Fig. 2a) one of the H-2 signals (5.95) shows a splitting of 3,0 Hz ($J_{2,3}$) so it belongs, to the *cis* isomer which may have two chair conformers (C' and C'', Scheme 2). The other signal (5.85) having a coupling constant ($J_{2,3}$) of 6.0 Hz belongs to the *trans* isomer. The further signals can be assigned on the basis of their relative intensities.

At lower temperature (Fig. 2b) the H-2 triplet of the *cis* isomer in split to a doublet. The coupling constants ^3J(H,H) and ^4J(H, OH) refer to interactions with H-3 and C_2–OH protons. The C_2–OH signal is also split to double doublet due to the ^3J(H,OH) and ^4J(H,OH) couplings. The multiplicity of the H-3 signal containing 16 lines is the result of the ^3J(H,CH_3) ^3J(H,H) and ^4J(H,OH) couplings, respectively.

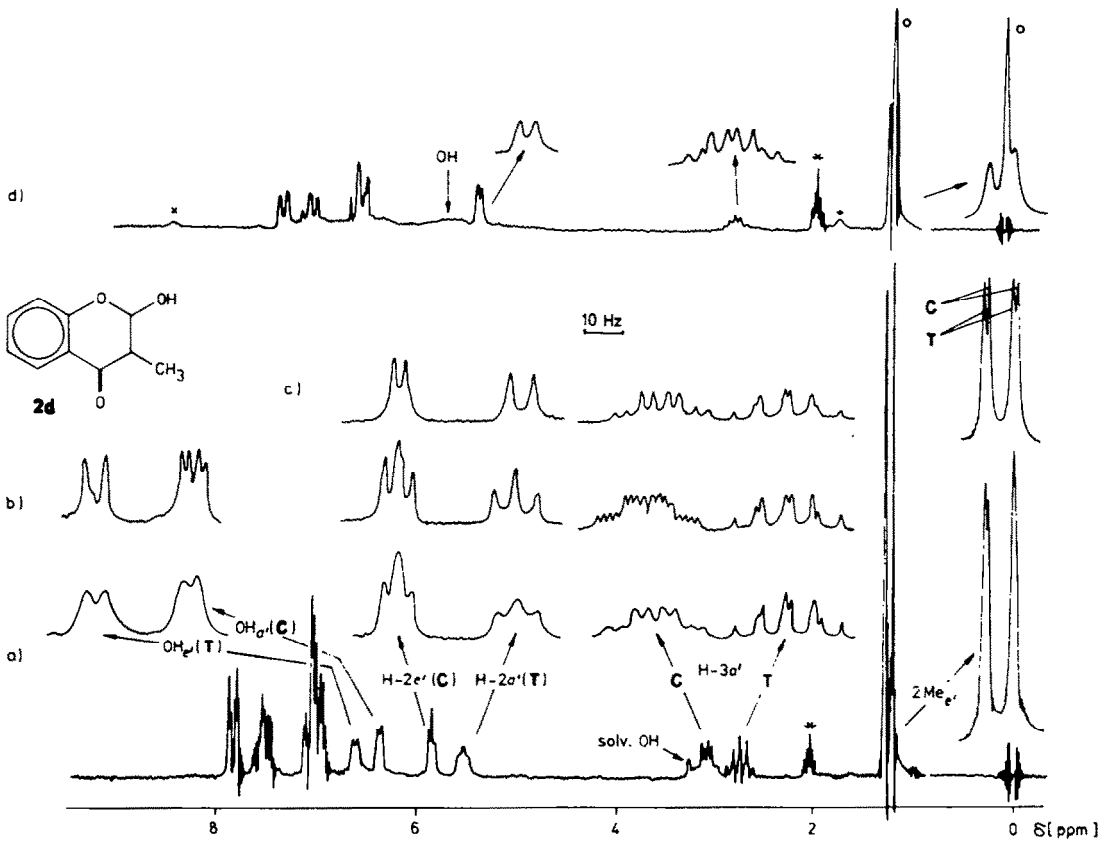
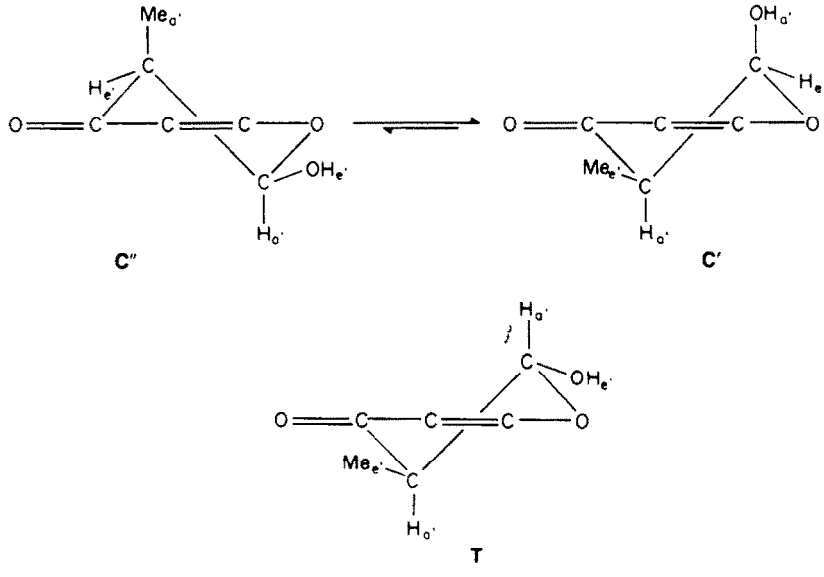


Fig. 2. ^{1}H NMR spectra of **2d** in acetone-d_6. a:30°:b:0°:c:after adding D_2O (0°) and d:after adding NaOtBu. °:t-Bu group *: quintet of aceton-d_6, + and ×: methyl and formyl signals of **4**.



Scheme 2.

The spectral change is similar to that of observed in the case of **2a**, so the C' conformer of **2d** with a *quasi-axial* C_2–OH group is more stable at lower temperature. The higher stability of this conformer is probably due to the anomer effect[14]. It should be noted that in DMSO-d_6 the long range coupling ^{4}J(H,OH) can be observed even at 30°. The signals of the *trans* isomer are temperature-independent (to-60°), so it can be regarded as conformationally homogeneous and the substituents (C_2-OH and C_3-Me) are *diequatorial*, as expected.

At -50° the spectrum of **2f** is analogous to the spectra of **2d** and **2e** recorded at 0° and 30°, respectively, only the ratio of the isomers is different (Table 1).

In the case of **2f** at higher temperature H-2, H-3 and

Table 1. ^{1}H NMR data of compounds **2a-2h** in aceton-d_6 (chemical shifts are given in δ ppm: $\delta_{TMS} = 0$ ppm, coupling constants in Hz)

Compound	Temp. [°C]	Isomer	Cis–trans ratio	δ CH_3	δ H – 2	δ H – 3	δ OH	$^2J_{3,3}$(H, H) or ^3J(CH_3, H)	$^3J_{2,3a}$(H, H) and $^3J_{2,3e}$(H, H)	^3J(H, OH)	^4J(H, OH)
2a	30			-	5.85 m	3.08 (a) m 2.70 (e) m	6.52 bs	16.0	4.1 2.9	-	-
	–25			-	6.00 m*	3.10 (a) m* 2.80 (e) m*	6.82 dd+	16.5	3.5 3.0	5.0	1.8
2b	30			-	5.82 m*	2.90 (a) m* 2.65 (e) m*	7.40 bs+	16.2	5.2 2.8	-	-
2c	30	cis	11:10	1.20 d*	5.80 br*	2.98 dq*	7.20 bs+	7.0	2.9	-	-
	30	trans		1.22 d*	5.45 br*	2.63 dq*	7.40 bs+	7.2	6.0	-	-
2d	30	cis	6:5	1.22 d*	5.95 br*	3.10 dq*	6.38 bs+	6.8	3.0	-	-
	0			1.20 d*	5.85 dd^x	3.03 ddq•	7.18 dd+	6.8	3.0	3.2	1.9
	30	trans		1.25 d*	5.58 br*	2.75 dq*	6.63 bs+	7.2	6.0	-	-
	0			1.23 d*	5.55 dd^x	2.72 dq*	7.42 d+	7.2	6.0	4.8	-
2e	30	cis	5:7	1.23 d*	5.92 dd^x	3.15 ddq•	6.72 dd+	6.9	3.1	4.2	1.9
	30	trans		1.25 d*	5.62 dd^x	2.78 dq*	6.95 d+	7.2	5.5	5.5	-
	30	cis+trans		1.25 d°	5.90 br*	3.15 bs+	6.85 bs+	6.8	-	-	-
2f	–50	cis	1:3	1.25 d	6.08 dd	3.25 ddq	7.40 dd	6.8	3.0	4.3	2.9
	–50	trans		1.25 d	5.85 dd	2.95 dq	7.65 d	6.8	5.2	4.8	-
2g	60								4.1	-	-
	30	trans		1.30 d	6.45 d	2.82 dq	2.00 s▽	7.3	3.9	-	-
	–60								2.8	-	-
2h	30	trans		1.35 d	6.70 d	3.10 dq	2.15 s▽	7.3	4.0	-	-
2d + base	30			1.22 d	5.68 d	2.90 dq	6.15 bs	7.0	4.5	-	-

s: singulet, bs: broad singulet, d: doublet, dd: double doublet, dq: double quartet, ddq: doubled double quartet (four lines of which are collapsed to two doublets), m: multiplet, br: broad signal (triplet-like dd),

Multiplicity after adding D_2O: *: no change, +: the signal dissappear, x: d, °: bs, •: dq,

▽: δCH_3 singulet of the acetyl group in case of compounds 2g and 2h.

Table 2. Yields, melting points and IR data (in cm^{-1}) of compounds **2a-2h**

Compound	Yield [%]	Melting point [°C]	IR data νOH KBr	IR data νOH $CHCl_3$	IR data νC = O KBr	IR data νC = O $CHCl_3$
2a	92.3	94 - 96	3337	3595^{+} 3350	1663	1691
2b	77.5	110 - 114	3341	-	1652	-
2c	85.0	135 - 138	3380	-	1655	-
2d	91.0	101 - 102	3400	3680^{+} 3586^{+} 3350^{o}	1675	1689
2e	83.0	104 - 105	3270	-	1676	-
2f	97.0	140 - 142	3415	-	1690	-
2g	90.2	45 - 46	-	-	1700^{x} 1768^{x}	-
2h	35.2	129 - 130	-	-	1678^{x} 1760^{x}	-

$^{+}$: Monomer, ^{o}: dimer, ^{x}: acetoxy group

C_2–OH signals are broadened gradually and above 20° signals of the two isomers collapse in to overlapped broad maximums. After adding D_2O the C_2–OH proton is exchanged instantly and also the H-3 atoms exchange very fast. The H-2 signal of this deuterated compound is a broad singlet at 20°, which splits at -10° into two lines belonging to the *cis* and *trans* isomers. This fact can be explained by a *trans*⇌*cis* isomerisation simultaneous with a fast C'⇌C" inversion, which can take place via enolisation of the 4-one group or by **2**⇌**4** tautomerism.

The spectrum of **2d** recorded in abs acetone after addition of a catalytic amount of NaOtBu base (Fig. 2d) gives experimental evidences for the **2**⇌**4** tautomerism. In this spectrum namely the formly and methyl signal of **4** appear at 9.00, and 1.80 ppm, respectively, with 1:3 intensity. The signals of the *cis* and *trans* isomers of **2d** collapse at average values (Fig. 2d) indicating a fast isomerisation. The $J_{2,3}$ coupling constant is an averaged value (4.5 Hz) of that of the *cis* and *trans* isomers (3.0 and 6.0 Hz).

Further evidence for the isomerism is the acylation of **2d**. When this was carried out at -10° in pyridine, using acetic anhydride, **2g** was obtained as the stereohomogeneous *trans*-isomer with approximately 90% yield ($J_{2,3}$ = 4,0 Hz). The *-I* effect of the acetoxy group may be the reason of the relative small coupling constant. Since **2d** is a 1:1 mixture of *cis* and *trans* forms (Fig. 2a and Table 1) the formation of stereohomogeneous *trans* acetoxy derivative of 90% yield confirms unambiguously the *cis*⇌*trans* isomerisation. The faster acylation of the *trans* isomer refers to an effective kinetic control (otherwise the *cis* isomer is the more stable one).

Acylating **2f** in the same manner also yielded a stereohomogeneous *trans* isomer (**2h**) ($J_{2,3}$ = 4,5 Hz) but in lower yield.

It can be concluded (Table 1.) that the C'⇌C" conformational equilibrium is shifted toward C' at lower temperatures. Our experiments clearly demonstrated that the electron-attractive substituents at position 7 accelerate significantly the *cis*⇌*trans* isomerisation and increase the relative amount of the *cis* form in the mixture. In the case of **2c** and **2d** the *cis-trans* ratio is nearly 1:1 while in **2f** it is about 3:1.

EXPERIMENTAL

The IR spectra were run on a Perkin-Elmer 283 spectrometer, the ^1H NMR spectra were recorded on a JEOL NM11-100, using TMS as internal reference.

Preparation of **2a-f**. Compounds **1a-f** were reacted with ethyl formate in the presence of NaOtBu as described. Compounds **2a-f** were obtained with a high yield (Table 2.)

Preparation of **2g** *and* **2h**. 2×10^{-2} M of **2d** or **2f** was dissolved in anhydr. pyridine (2 ml), and at - 10° acetic anhydride was added (2.2×10^{-3} M). After 24 hr the mixture was poured into ice-water (20 ml). The crystals were recrystallized from EtOH.

The yields, m.p.s and IR data of **2a-h** are shown in Table 2.

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