Isolation and characterization of tautomeric forms of 2,4-diacetyl-3-(*o*-R-aryl)-5-hydroxy-5-methylcyclohexanones

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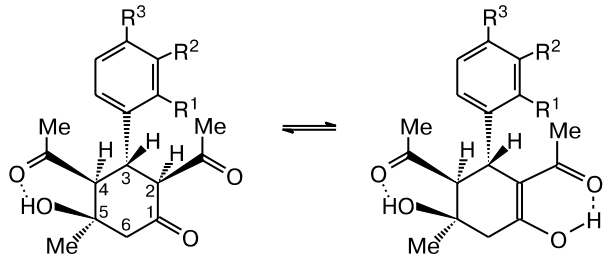
Keto-enol prototropic tautomerism of 2,4-diacetyl-3-(*o*-R-aryl)-5-hydroxy-5-methylcyclohexanones in the β-diketone fragment was studied. Individual tautomeric forms of β-diketones, *viz.*, keto and enol forms, were isolated and characterized. The latter are generated through enolization of the alicyclic carbonyl group. Enolization is facilitated by the presence of an *ortho* substituent in the benzene ring.

Key words: β-diketones, polyketones, acetylcyclohexanones, keto-enol tautomerism, tautomers, chelates, thermographic analysis.

Polycarbonyl compounds of the 2,4-diacetyl-3-aryl-5-hydroxy-5-methylcyclohexanone (acetylcyclohexanone) series can undergo keto-enol tautomerism.[1—3] Examples of isolation of ketones and enols in the pure form are few in number.[2,3] Earlier,[3] the separation of a tautomeric mixture of parent acetylcyclohexanone **1a** containing the unsubstituted phenyl group has been described, and the alicyclic carbonyl group has been found to undergo enolization giving rise to enol form **2a**. Taking into account that the presence of a substituent in the *ortho* position of the aromatic ring in compounds of different series has a substantial effect on their reactivity due to spatial proximity of the substituents and their interactions, we studied keto-enol tautomerism of *ortho*-R-aryl-substituted acetylcyclohexanones. We prepared[4] acetylcyclohexanones **1b—e** containing electron-donating and electron-withdrawing groups (F, Cl, OMe, NO_2) in the *ortho* position of the aromatic ring and examined them as the key compounds. For comparison, we also used phenyl- and *p*-methoxyphenyl-substituted acetylcyclohexanones **1a** and **1f** described in the literature[1,3] (Scheme 1). All these compounds contain four or three asymmetric centers for the diketo (**1**) or enol (**2**) forms, respectively. Nevertheless, their synthesis affords predominantly the thermodynamically most stable stereoisomers, whose diketo form has the structure of 3*r*-Ar-2*t*,4*t*-diacetyl-5*t*-hydroxy-5*c*-methylcyclohexanone and exists exclusively in a chair conformation with all substituents, except for the hydroxy group, in equatorial positions. This arrangement of the substituents is confirmed by large spin-spin coupling constants of the *trans*-diaxial protons of the cyclohexane ring (11.8—12.2 Hz for H(2)—H(3) and 9.0—12.0 Hz for H(3)—H(4)) as well as by the W-coupling between the axial H(6a) proton of the methylene fragment and the proton of the axial hydroxy group (2.3—2.5 Hz) (Table 1). Acetylcyclohexanone **1a** described earlier[3] has an analogous structure.

Scheme 1



1a—f **2a—f**

1, 2	R^1	R^2	R^3
a	H	H	H
b	F	H	H
c	Cl	H	H
d	OMe	H	H
e	NO_2	OMe	OMe
f	H	H	OMe

Thin-layer chromatograms of acetylcyclohexanones **1a—c** and **1f** have two spots, which suggests the presence of the keto form and one of the enol forms, whereas acetylcyclohexanones **1d,e** appear as one spot. All compounds **1a—f** give a positive qualitative reaction with ferric chloride for the enol form (violet color). The above results and the spectroscopic data suggest that compounds **1d,e** exist virtually completely in enol forms **2d,e**.

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Table 1. ^{1}H NMR spectra ($CDCl_3$) of the keto (**1a—c**) and enol (**2a—e**) forms of diacetylhydroxycyclohexanones **1a—e**

Compound	δ (*J*/Hz)					
	C=C—OH (s)	O—H (br.s)	H(2) (d)	H(3)	H(4) (d)	$H(6)_{ax}$, $H(6)_{eq}$
1a [3]	—	3.96	3.80 ($J_{2,3}$ = 12.1)	3.98 (dd)	3.27 ($J_{3,4}$ = 11.8)	2.53, 2.63 ($J_{6_{ax},6_{eq}}$ = 14.3, $J_{6_{ax},OH}$ = 2.5)
2a [3]	16.12	3.54	—	4.10 (d)	2.87 ($J_{3,4}$ = 10.7)	2.52, 2.56 ($J_{6_{ax},6_{eq}}$ = 16.8)
1b	—	3.81	3.08 ($J_{2,3}$ = 12.2)	4.33 (dd)	2.93 ($J_{3,4}$ = 12.0)	2.45, 2.51 ($J_{6_{ax},6_{eq}}$ = 14.3, $J_{6_{ax},OH}$ = 2.4)
2b	16.28	3.61	—	4.45 (d)	2.56 ($J_{3,4}$ = 10.3)	2.46, 2.50 ($J_{6_{ax},6_{eq}}$ = 15.6)
1c	—	3.82	3.25 ($J_{2,3}$ = 11.8)	4.38 (dd)	3.18 ($J_{3,4}$ = 10.2)	2.42, 2.52 ($J_{6_{ax},6_{eq}}$ = 14.7, $J_{6_{ax},OH}$ = 2.3)
2c	16.11	3.37	—	4.43 (d)	2.79 ($J_{3,4}$ = 9.5)	2.40, 2.44 ($J_{6_{ax},6_{eq}}$ = 15.8)
1d	17.78	3.14	—	4.44 (d)	2.84 ($J_{3,4}$ = 9.6)	2.42, 2.46 ($J_{6_{ax},6_{eq}}$ = 15.5)
1e	16.33	3.36	—	4.84 (d)	2.64 ($J_{3,4}$ = 9.6)	2.47, 2.51 ($J_{6_{ax},6_{eq}}$ = 15.2)

In going from *ortho* isomer **1d** to its *para* isomer **1f**, the ratio sharply changes in favor of the keto tautomer. Hence, the substituent in the *ortho* position of the aromatic ring, presumably, has the major effect on the tautomer ratio regardless of its electronic effects (Table 2).

Acetylcyclohexanones were separated into the individual keto (**1a—c,f**) and enol (**2a—c,f**) forms (see Scheme 1, Table 2) by fractional crystallization from dry benzene.

In a benzene solution, acetylcyclohexanone **1a** unsubstituted in the aromatic ring exists predominantly in the keto form. The presence of the halogen atom in the phenyl substituent leads to an increase in the percentage of the enol form, which is most pronounced for chlorophenyl-substituted acetylcyclohexanone **1c**. Enol **2a** is unstable. In the crystalline state, it is subjected to ketonization at −5 °C during 12 h (TLC). Enol **2c** containing the Cl atom in the *ortho* position of the phenyl ring is more stable and remains unchanged under the above-mentioned conditions for 120 days.

The physicochemical characteristics of the keto and enol forms are sharply different from each other. The melting points of keto forms **1a—c,f** are higher than those of the corresponding enol forms **2a—c,f**, whereas the chromatographic mobilities of the enol isomers are larger than those of ketones (see Table 2). The latter phenomenon can be attributed to intramolecular hydrogen bonding between the H atom of the enol hydroxy group and the O atom of the adjacent acetyl fragment (in addition to the intramolecular hydrogen bond between the tertiary hydroxy group and the acetyl fragment at the C(4) atom, which we have described earlier[5]).

The structures of the keto and enol forms were confirmed by ^{1}H and ^{13}C NMR, UV, and IR spectroscopy, as well as by chemical transformations.

The UV spectra of tautomeric mixtures of acetylcyclohexanones **1** + **2** (Table 3) show three most intense absorption bands at λ_{max} 217—230 (log ε 3.78—3.90), 260—288, and 282—343 nm (log ε 3.54—4.01). The first two bands can be assigned to absorption of the aromatic ring. The region at λ_{max} 282—343 nm corresponding to π—π* and n—π* transitions of the enone fragment is characteristic of the enol forms; this region has one maximum, whose intensity sharply increases in the spectra of pure enol tautomers.

The IR spectra of mixtures of acetylcyclohexanones **1** + **2** (tautomeric mixtures) show stretching absorption bands of the tertiary hydroxy group (3415—3508 cm^{-1}), the carbonyl groups (1698—1725 cm^{-1}), and the conjugated C=C—C=O system (1535—1640 cm^{-1}). In the IR spectra (see Table 3) of individual keto forms **1a—c,f**, the stretching bands of the hydroxy group and the carbonyl groups are retained, whereas the band of the conjugated C=C—C=O system disappears. The latter is observed in the IR spectra (see Table 3) of enols **2a—f** at 1535—1640 cm^{-1}.

The ^{1}H NMR spectra (see Table 1) are most informative and allow one to distinguish the alcohol (δ 3.14—3.98) and enol (δ 16.05—17.78) hydroxy groups and reveal the presence of the H(2) proton (δ 2.08—3.72) or its absence in the keto and enol forms, respectively. In the spectrum of a tautomeric equilibrium mixture of compounds **1b** + **2b** in $CDCl_3$, the intensity of the signal of the enol H atom indicates that the mixture contains 40%

Table 2. Characteristics of tautomeric mixtures (**1** ⇌ **2**) and the keto (**1**) and enol (**2**) forms of diacetylhydroxycyclohexanones **1a—f**

Compound	Yield[a] (%)	M.p./°C	R_f	Stability /days	Found / Calculated (%)		Molecular formula
					C	H	
1a + **2a**	—	167—168	0.24; 0.60	—	70.84	7.03	$C_{17}H_{20}O_4$
					70.81	6.99	
1a[b]	95	173—174	0.17	Stable	70.90	7.07	$C_{17}H_{20}O_4$
					70.81	6.99	
2a[c]	1	112—114	0.66	0.5	70.83	7.04	$C_{17}H_{20}O_4$
					70.81	6.99	
1b + **2b**	—	113—114	0.24; 0.50	—	66.82	6.50	$C_{17}H_{19}FO_4$
					66.66	6.25	
1b	50	117—118	0.17	30	66.74	6.28	$C_{17}H_{19}FO_4$
					66.66	6.25	
2b	43	89—91	0.44	45	66.71	6.26	$C_{17}H_{19}FO_4$
					66.66	6.25	
1c + **2c**	—	108—109	0.20; 0.54	—	63.54	5.87	$C_{17}H_{19}ClO_4$
					63.26	5.93	
1c	30	146—147	0.21	7	63.47	5.90	$C_{17}H_{19}ClO_4$
					63.26	5.93	
2c	65	90—91	0.45	120	63.36	5.89	$C_{17}H_{19}ClO_4$
					63.26	5.93	
2d	100	96—97	0.40	Non-enolizable	68.11	7.04	$C_{18}H_{22}O_5$
					67.91	6.97	
2e[d]	100	176—176.5	0.16	Non-enolizable	58.34	5.90	$C_{19}H_{23}NO_8$
					58.01	5.89	
1f + **2f**[e]	—	175—176	0.52; 0.72	—	68.05	7.01	$C_{18}H_{22}O_5$
					67.91	6.97	
1f	85	187—188	0.07	150	68.01	7.00	$C_{18}H_{22}O_5$
					67.91	6.97	
2f	10	101—103	0.37	7	67.96	7.02	$C_{18}H_{22}O_5$
					67.91	6.97	

[a] The yield after the preparative separation of the tautomeric mixture.
[b] Lit. data[3]: m.p. 173—174 °C, the major isomer.
[c] Lit. data[3]: m.p. 112—114 °C, the yield was ~1%.
[d] Found (%): N, 3.65. Calculated (%): N, 3.56.
[e] Lit. data[1]: m.p. 176 °C.

of the enol form, which is close to the ratio obtained after fractional crystallization from benzene.

The assignment of the signals in the ^{13}C NMR spectra (Table 4) of the keto forms based on the data published in the literature[3] and experimental results obtained in the present study, which allowed us to unambiguously distinguish the signals for the C(1) atom of the alicyclic carbonyl group (δ 197.07—196.96), the C(7) atom of the carbonyl group of the acetyl substituent (δ 204.29—204.62), and the C(2) atom (δ 66.75—67.93). Correspondingly, the positions of the signals for the C(7) atoms in the enol forms remain virtually unchanged (δ 205.65—205.70), but changes are observed in the chemical shifts of C(1) (δ 182.40—182.92) and particularly of C(2) (δ 109.67—109.76), which confirms regioselective enolization involving the carbonyl group of the alicyclic moiety.

Due to the presence of the β-dicarbonyl fragment, acetylcyclohexanones **1a—f** can form chelate salts. We synthesized chelate copper(II) bis-2,4-diacetyl-5-hydroxy-5-methyl-3-(2-R-phenyl)cyclohexen-1-olates **3a,c** from tautomeric mixtures of **1a** + **2a** and **1c** + **2c** and copper diacetate (Scheme 2).

In the UV spectra of salts **3a,c** (see Table 3), the absorption band of the enecarbonyl fragment (λ_{max} 308—306 nm, log ε 4.04—4.08) is bathochromically shifted compared to that in the spectrum of pure enol forms **2a** (λ_{max} 286 nm, log ε 3.68) and **2c** (λ_{max} 288—289 nm, log ε 4.01—4.05). In their IR spectra (see Table 3), the narrow highly intense band of the C=C—C=O fragment is bathochromically shifted by 43—24 cm^{-1} compared to the analogous bands in the spectra of the corresponding enols.

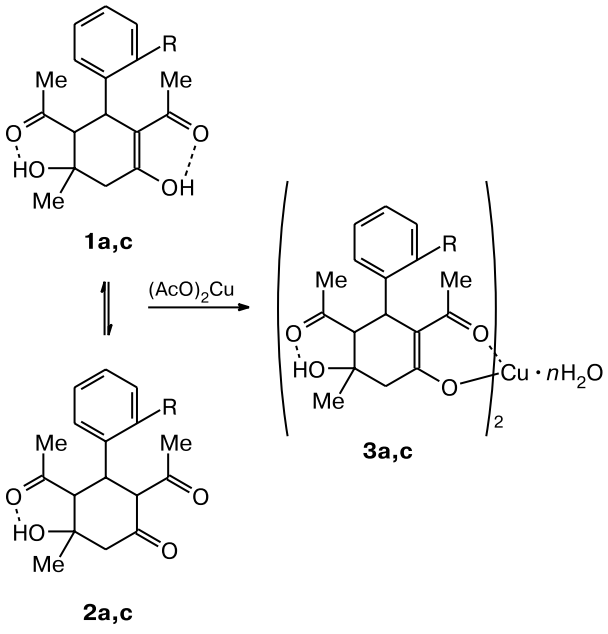
Table 3. IR spectra (Nujol mulls and hexachlorobenzene) and UV spectra (MeCN) of tautomeric mixtures (**1** ⇌ **2**), the keto (**1**) and enol (**2**) forms, and copper(II) complexes **3** of diacetylhydroxycyclohexanones **1a—f**

Compound	IR, ν/cm^{-1}			UV, λ_{max}/nm (logε)
	OH	C=O at C(2) and C(4)	Alicyclic C=O	
1a + **2a**	3415	1695; 1700	1722	223 (3.84), 265 (3.56), 286 (3.48)
1a	3432	1696; 1706	1720	—
2a	3520	1615; 1705	—	—
1b + **2b**	3456	1690; 1710	1725	224 (3.77), 260 (4.00), 288 (3.46)
1b	3452	1688; 1710	1720	220 (3.96), 258 (4.02), 300 (3.45)
2b	3452	1616; 1702	—	220 (3.96), 308 (4.06)
1c + **2c**	3508	1698; 1705	1725	226 (3.83), 260 (4.00), 284 (3.63)
1c	3472	1700; 1710	1725	228 (3.90), 268 (3.85), 288 (3.56)
2c	3508	1590; 1712	—	222 (3.78), 288 (4.05)
2d	3496	1596; 1700	—	224 (3.85), 282 (4.05)
2e	3492	1578; 1700	—	228 (3.94), 248 (3.97), 288 (3.80), 343 (3.54)
1f + **2f**	3408	1706; 1690	1718	230 (4.00), 279 (3.65)
1f	3412	1694; 1706	1720	—
2f	3436	1612; 1698	—	—
3a	3524; 3364—3056	1572; 1700	—	224 (3.80), 308 (4.04)
3c	3424	1566; 1700	—	227 (3.93), 306 (4.08)

At 140 °C, the DTA curve of salt **3a** shows a sharp endothermic peak with the 5% weight change, which is indicative of the presence of two water molecules of crystallization. Further heating of complexes **3a** and **3c** gives endothermic peaks at 196 and 223 °C, which corresponds to their melting points.

Hence, the presence and the nature of a substituent in the aryl moiety of 3*r*-Ar-2*t*,4*t*-diacetyl-5*t*-hydroxy-5*c*-methylcyclohexanones has a decisive effect on their ability to undergo enolization.

Scheme 2



R = H, *n* = 2 (**1a—3a**); R = Cl, *n* = 0 (**1c—3c**)

Experimental

The IR spectra were recorded on a Specord M-80 instrument in Nujol mulls and hexachlorobenzene. The UV spectra were measured on a Flyuorat-02 Panorama instrument in MeCN. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ or DMSO-d_6 with Me_4Si as the internal standard immediately after dissolution of the samples.

Thermogravimetric analysis was carried out on a Paulik—Paulik—Erdey OD-103 MOM derivatograph (Hungary) in a temperature range of 20—1000 °C with a heating rate of 10 °C min^{-1}. The temperature was recorded using a Pt—Pt/Rh thermocouple; calcined Al_2O_3 was used as the standard; the weight of the sample was 200 mg; all measurements were carried out on air.

The course of the reactions and purity of the compounds were monitored by TLC on Silufol UV-254 plates (a 2 : 2 : 1 hexane—ethyl acetate—chloroform system, visualization with iodine vapor).

2*t*,4*t*-Diacetyl-5*t*-hydroxy-5*c*-methyl-3*r*-phenylcyclohexanone (**1a**)[3], 2*t*,4*t*-diacetyl-3*r*-(2-fluorophenyl)-5*t*-hydroxy-5*c*-methylcyclohexanone (**1b**)[4], 2*t*,4*t*-diacetyl-3*r*-(2-chlorophenyl)-5*t*-hydroxy-5*c*-methylcyclohexanone (**1c**),[4] and 2,4-diacetyl-5-

Table 4. ^{13}C NMR spectra (DMSO-d_6) of the keto (**1b,c**) and enol (**2b,c**) forms

Compound	δ								
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	Me
1b	197.07	66.75	46.16	64.59	67.93	55.29	204.62	209.05	28.02; 27.31; 25.22
2b	182.40	109.67	46.16	63.22	72.36	55.29	205.65	209.38	34.84; 29.89
1c	196.96	67.93	45.79	63.83	68.13	55.08	204.29	209.00	27.47; 27.12; 25.89
2c	182.92	109.76	45.79	67.93	72.31	55.08	205.70	209.16	31.12; 30.38

hydroxy-3-(4-methoxyphenyl)-5-methylcyclohexanone (**1f**)[1] have been described earlier. 2,4*t*-Diacetyl-3*r*-(2-methoxyphenyl)-5*c*-methylcyclohex-1-ene-1,5*t*-diol (**2d**) and 2,4*t*-diacetyl-3*r*-(3,4-dimethoxy-2-nitrophenyl)-5*c*-methylcyclohex-1-ene-1,5*t*-diol (**2e**) were synthesized according to a known procedure.[4]

2*t*,4*t*-Diacetyl-5*t*-hydroxy-5*c*-methyl-3*r*-phenylcyclohexanone (**1a**),[3] 2*t*,4*t*-diacetyl-3*r*-(2-fluorophenyl)-5*t*-hydroxy-5*c*-methylcyclohexanone (**1b**), 2*t*,4*t*-diacetyl-3*r*-(2-chlorophenyl)-5*t*-hydroxy-5*c*-methylcyclohexanone (**1c**), 2*t*,4*t*-diacetyl-5*t*-hydroxy-3*r*-(4-methoxyphenyl)-5*c*-methylcyclohexanone (**1f**), 2,4*t*-diacetyl-5*c*-methyl-3*r*-phenylcyclohex-1-ene-1,5*t*-diol (**2a**),[3] 2,4*t*-diacetyl-3*r*-(2-fluorophenyl)-5*c*-methylcyclohex-1-ene-1,5*t*-diol (**2b**), 2,4*t*-diacetyl-3*r*-(2-chlorophenyl)-5*c*-methylcyclohex-1-ene-1,5*t*-diol (**2c**), and 2,4*t*-diacetyl-3*r*-(4-methoxyphenyl)-5*c*-methylcyclohex-1-ene-1,5*t*-diol (**2f**) were isolated by separation of tautomeric mixtures using recrystallization from dry benzene as described earlier.[3]

Copper(II) bis-2,4-diacetyl-5-hydroxy-5-methyl-3-phenylcyclohexen-1-olate (3a). A 5% alcoholic solution of ketol **1a** (40 mL, 6.94 mmol) was mixed with a 5% aqueous solution of copper(II) diacetate (30 mL, 8.33 mmol). The reaction mixture was kept at room temperature for 2 h. The crystals that formed were filtered off and washed with water and EtOH. Product **3a** was obtained in a yield of 2.18 g (50%) as greenish crystals, m.p. 196—197 °C (decomp.). Found (%): C, 60.56; H, 6.40. $C_{34}H_{38}CuO_8 \cdot 2H_2O$. Calculated (%): C, 60.57; H, 6.28.

Copper(II) bis-2,4-diacetyl-3-(2-chlorophenyl)-5-hydroxy-5-methylcyclohexen-1-olate (3c). Analogously, product **3c** was synthesized from a 5% alcoholic solution of ketol **1c** (40 mL, 6.21 mmol) and a 5% aqueous solution of copper(II) diacetate (30 mL, 8.33 mmol) in a yield of 3.33 g (76%) as greenish-grey crystals, m.p. 224—226 °C (decomp.). Found (%): C, 57.59; H, 5.32; Cl, 11.09. $C_{34}H_{36}Cl_2CuO_8$. Calculated (%): C, 57.75; H, 5.13; Cl, 10.03.

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