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β-Tricarbonyl Compounds. I. 2,4-Disubstituted 1,3-Cyclopentanediones

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Summary. Stable enolic isomers of 2-aroyl-4-aracyl-1,3-cyclopentanediones such as **3** and **4** were prepared by condensation of aryl methyl ketones and diethyl maleate using an excess of sodium ethoxide (Aryl = C_6H_5, 4-$C_6H_4CH_3$, 4-C_6H_4Br and 4-C_6H_4Cl).

Keywords. 2-Aroyl-4-aracyl-1,3-cyclopentanediones; Aryl methyl ketone; Diethyl maleate; Stable enols; β-Tricarbonyl compounds.

β-Tricarbonyl Verbindungen. I. 2,4-Disubstituierte 1,3-Cyclopentandione

Zusammenfassung. Stabile Enol-Isomere von 2-Aroyl-4-aracyl-1,3-cyclopentandionen wie **3** und **4** wurden durch Kondensation von Arylmethylketonen und Diethylmaleat mit einem Überschuß von Natriumethoxid dargestellt (Aryl = C_6H_5, 4-$C_6H_4CH_3$, 4-C_6H_4Br und 4-C_6H_4Cl).

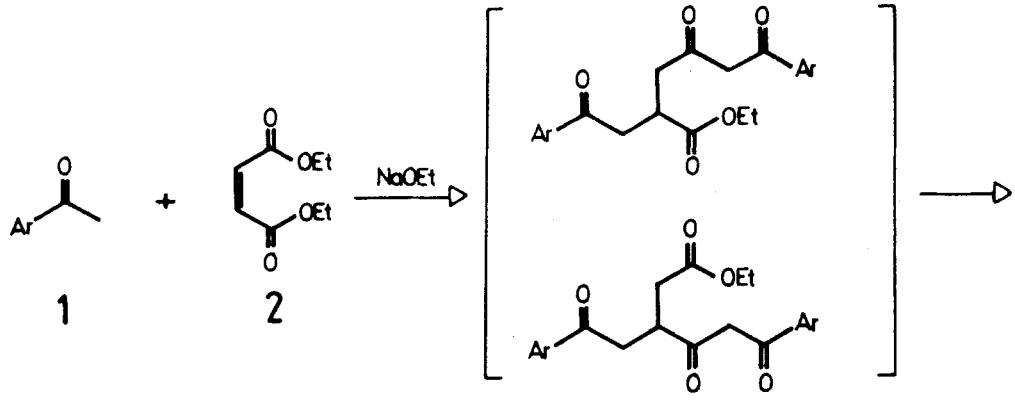
Introduction

β-Tricarbonyl derivatives of cyclopentane constitute an interesting class of compounds with potential biological activity [1]. Previously, some investigators have described the preparation of substituted cyclopentane- and cyclopentene-1,3-diones by reaction of saturated and unsaturated carboxylic acid anhydrides or chlorides with isopropenyl acetate in the presence of $AlCl_3$ [2]. 2-Isovaleryl-4,5-dimethylcyclopentane-1,3-dione (calytrone) was prepared by condensation of dimethyl dimethyl maleate with appropriate aliphatic ketone using sodium hydride as condensing agent [3]. Similar, reactions of dimethyl dimethyl maleate with acetone and acetophenone gave only the corresponding cyclopentanone derivatives [4].

In this paper, we report the preparation of several new 2,4-disubstituted 1,3-cyclopentanediones by the sodium ethoxide condensation of diethyl maleate with the appropriate aromatic ketones.

Results and Discussion

By condensation of acetophenone with diethyl maleate in a molar ratio of 2 : 1 and with an excess of sodium ethoxide, according to a modified method [5], two



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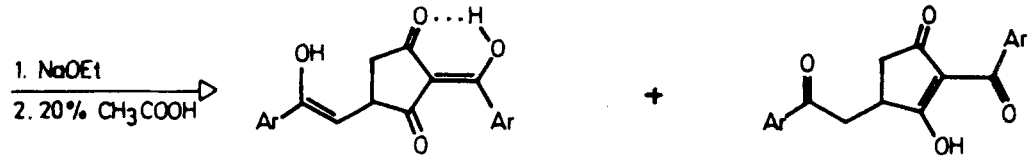

3 4

3a: Ar = C_6H_5
3b: Ar = 4-$C_6H_4CH_3$
3c: Ar = 4-C_6H_4Br
3d: Ar = 4-C_6H_4Cl

4a: Ar = C_6H_5
4b: Ar = 4-$C_6H_4CH_3$
4c: Ar = 4-C_6H_4Br
4d: Ar = 4-C_6H_4Cl

products were isolated and separated by fractional crystallization from acetone. Since the two compounds differ in all determinated physico-chemical properties including enol tests (except molecular weight) it could be concluded that they are isomers, one of which being completely enolized forming a conjugated chelate system and the other enolised preferentially in the five-membered ring.

The mechanism of their formation probably involves 1,2- and 1,4-addition followed by an intramolecular cyclization [4, 6, 7].

The structures of the compounds **3** and **4**, which are considered to be β-tricarbonyl compounds, are supported by spectral analysis. ^{1}H-NMR spectra of the compounds **3** and **4** were recorded in acetone-d_6 and $CDCl_3$, respectively. In the case of **3**, however, solution in $CDCl_3$ was accompanied by its conversion to compound **4**, being proved by identical NMR spectra. The compound **3** was con-

verted to its isomer **4** by heating as well as on longer standing of its water or dilute acid solutions at room temperature.

The ^{1}H-NMR spectrum of **3a** in acetone-d_6 showed the pattern of signals at δ 6.04, 3.82 and 2.80 attributable to the enolized methylene proton of the phenacyl moiety, methine and methylene protons of the cyclopentane ring. The IR spectrum showed a band at 1710 cm^{-1} for the cyclic non-hydrogen-bonded carbonyl group and a broad band with the centre near 1560 cm^{-1} for the hydrogen-bonded carbonyl group of the cyclopentane ring, while near 1620 cm^{-1} the enolic double bond occurred as a separate band [8, 9]. In the O-H region there is a very broad and weak absorption between 3150 and 2400 cm^{-1}.

The compound **3a** was converted with hydroxylamine hydrochloride in methanol to the corresponding isoxazole, 3-phenyl-5-(2-phenyl-2-methoxyethenyl)-5,6-dihydro-4*H*-cyclopenta[*c*]isoxazole-4-one (**5**).

The ^{1}H-NMR spectrum of the structure **4a** in $CDCl_3$ exhibited two doublets at 3.18 and 2.92 ppm attributable to methylene protons of the phenacyl moiety as well as of the cyclopentene ring and a multiplet for a methine proton centered at 3.5 ppm. Missing of a methine proton at position 2 suggested enolization at position 3. The presence of a hydroxyl group was proved by a broad singlet at 4.05 ppm being readily exchangable with D_2O. Its IR spectrum indicated the presence of hydroxyl (3300 – 3000 cm^{-1}), cyclic conjugated carbonyl (1729 cm^{-1}), carbonyl conjugated with aromatic ring (1680 cm^{-1}) and double conjugated carbonyl (1650 cm^{-1}) groups.

Conversion of the compound **4a** to 2-benzoyl-3-methoxy-4-phenacylcyclopent-2-ene-1-one (**6**) confirmed the assignment.

Experimental Part

Melting points were taken on a Küstner apparatus and are uncorrected. IR spectra were measured as solids in KBr discs on a Perkin-Elmer Model 783 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 NMR spectrometer (90 MHz). NMR spectra were recorded in acetone-d_6 and $CDCl_3$ and were reported in δ units with Me_4Si as internal standard. Mass spectra were obtained on a Varian mass spectrometer CH-7.

General Procedure

An etheral solution of **1** (220 mmol) was slowly added to a stirred and cooled (below 0°C) suspension of sodium ethoxide (250 mmol) in anhydrous ether (100 ml) followed by addition of **2** (110 mmol) in a few portions. After some hours the sodium salt precipitated and the mixture was left at room temperature for a week. The sodium salt was filtered off, thoroughly washed with ether and hydrolysed with cold 20% acetic acid under an ether layer. Ether was evaporated and the soluble byproducts removed by treating the residue with glacial acetic acid. The crude product was dissolved in acetone and the enol-form precipitated by adding water (yellow to yellow-green crystals). Evaporation of acetone and cooling the water solution afforded the other isomer (white crystals).

2-(1-Hydroxy-1-phenylmethylene-4-(2-hydroxy-2-phenylethenyl)cyclopentane-1,3-dione (**3a**)

Yield: 5.5 g (50%), m.p. 147 – 150°C from methanol. IR (KBr): 3150 – 2400, 1710, 1620, 1605, 1590, 1560 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ 2.80 (d, J = 6.9 Hz, 2H), 3.82 (m, $J_{4,5}$ = 6.9 Hz, $J_{5,5'}$ = 5.4 Hz, 1H), 6.04 (d, J = 5.4 Hz, 1H), 6.8 – 7.6 (m, 10H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 251 (4.22), 275 sh (4.14), 360 (3.58). MS (EI): m/z (%) = 320 (M^+, 33), 319 (11), 275 (7), 247 (7), 220 (12), 141 (7), 115 (12)), 105 (100), 77 (67), 51 (14), 28 (4). $C_{20}H_{16}O_4$ (320.33): calcd. C 74.98, H 5.03; found C 75.16, H 4.89.

2-Benzoyl-3-hydroxy-4-phenacylcyclopent-2-ene-1-one (**4a**)

Yield: 4.5 g (41%), m. p. 183–185°C from methanol. IR (KBr): 3300–3000, 1729, 1680, 1650, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 2.92 (d, J = 6.1 Hz, 2H), 3.18 (d, J = 5.0 Hz, 2H), 3.5 (m, 1H), 4.05 (bs, 1H), 7.2–7.8 (m, 10H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 253 (4.35), 275 sh (4.21). MS (EI): m/z (%) = 320 (M^+, 31), 319 (10), 275 (7), 247 (8), 220 (13), 115 (14), 105 (100), 77 (76), 51 (15), 28 (5). $C_{20}H_{16}O_4$ (320.33): calcd. C 74.98, H 5.03; found C 75.07, H 5.29.

2-(1-Hydroxy-1-p-tolylmethylene)-4-(2-hydroxy-2-p-tolylethenyl)cyclopentane-1,3-dione (**3b**)

Yield: 3.5 g (44%), m. p. 128–131°C from methanol. IR (KBr): 3200–2400, 1710, 1620, 1608, 1590, 1555 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.16 and 2.23 (two s, 6H), 2.83 (d, J = 7.03 Hz, 2H), 3.75 (m, $J_{4,5}$ = 7.03 Hz, $J_{5,5'}$ = 5.57 Hz, 1H), 6.02 (d, J = 5.57 Hz, 1H), 6.72–8.07 (m, 8H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 220 (4.22), 252 (4.25), 372 (3.77). MS (EI): m/z (%) = 348 (M^+, 50), 347 (17), 334 (5), 333 (23), 303 (8), 275 (9), 248 (12), 211 (7), 128 (6), 119 (100), 115 (5), 91 (52), 65 (16), 39 (5). $C_{22}H_{20}O_4$ (348.33): calcd. C 75.84, H 5.79; found C 75.69, H 5.87.

3-Hydroxy-2-(4-methylbenzoyl)-4-(4-methylphenacyl)cyclopent-2-ene-1-one (**4b**)

Yield: 4 g (50%), m. p. 183–190°C from methanol. IR (KBr): 3200–2400, 1705, 1680, 1650, 1605 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.23 and 2.31 (two s, 6H), 2.85 (d, J = 6.4 Hz, 2H), 3.2 (d, J = 5.3 Hz, 2H), 3.56 (m, 1H), 7.01–7.74 (m, 8H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 236 (4.36), 285 sh (4.26). MS (EI): m/z (%) = 348 (M^+, 44), 347 (14), 333 (21), 303 (7), 275 (8), 248 (11), 211 (6), 129 (9), 128 (6), 120 (9), 119 (100), 115 (6), 91 (51), 73 (12), 65 (15), 60 (12), 57 (10), 43 (15), 41 (13), 39 (6). $C_{22}H_{20}O_4$ (348.33): calcd. C 75.84, H 5.79; found C 75.78, H 5.82.

2-(1-p-Bromophenyl-1-hydroxymethylene)-4-(2-p-bromophenyl-2-hydroxyethenyl)cyclopentane-1,3-dione (**3c**)

Yield: 6 g (67%), m. p. 145–153°C from methanol. IR (KBr): 3150–2400, 1715, 1620, 1590, 1575, 1550 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.85 (d, J = 6.8 Hz, 2H), 3.83 (m, $J_{4,5}$ = 6.8 Hz, $J_{5,5'}$ = 5.35 Hz, 1H), 6.12 (d, J = 5.35 Hz, 1H), 6.96–8.13 (m, 8H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 227 (4.18), 252 (4.23), 280 sh (4.20), 365 (3.82). MS (EI): m/z (%) = 478 (M^+, 21), 476 (11), 433 (13), 431 (7), 378 (6), 218 (6), 197 (8), 185 (94), 184 (8), 183 (100), 157 (39), 155 (43), 141 (13), 140 (8), 139 (15), 128 (10), 115 (18) 114 (17), 104 (13), 100 (6), 99 (10), 89 (6), 88 (7), 77 (16), 76 (57), 75 (45), 74 (12), 63 (16), 51 (16), 50 (32), 45 (33), 39 (24). $C_{20}H_{14}Br_2O_4$ (478.144): calcd. C 50.24, H 2.95, Br 33.43; found C 50.52, H 3.11, Br 33.44.

2-(4-Bromobenzoyl)-4-(4-bromophenacyl)-3-hydroxycyclopent-2-ene-1-one (**4c**)

Yield: 1.5 g (17%), m. p. 211–218°C from glacial CH_3COOH. IR (KBr): 3200–2800, 1735, 1675, 1630, 1605 cm^{-1}. ^{1}H-NMR (actone-d_6): δ = 2.9 (d, J = 6.6 Hz, 2H), 3.23 (d, J = 5.4 Hz, 2H), 3.53 (m, 1H), 7.2–7.8 (m, 8H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 215 (4.36), 267 (4.48). MS (EI): m/z (%) = 478 (M^+, 23), 476 (15), 433 (13), 431 (9), 185 (94), 183 (100), 157 (39), 155 (41), 141 (10), 139 (13), 115 (15), 77 (14), 76 (51), 75 (43), 63 (15), 51 (30), 50 (30), 45 (32), 39 (22). $C_{20}H_{14}Br_2O_4$ (478.144): calcd. C 50.24, H 2.95, Br 33.43; found C 49.98, H 2.73, Br 33.17.

2-(1-p-Chlorophenyl-1-hydroxymethylene)-4-(2-p-chlorophenyl-2-hydroxyethenyl)cyclopentane-1,3-dione (**3d**)

Yield: 5.4 g (54%), m. p. 146–155°C from methanol. IR (KBr): 3150–2400, 1715, 1620, 1595, 1580, 1555 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.85 (d, J = 6.8 Hz, 2H), 3.81 (m, $J_{4,5}$ = 6.8 Hz,

$J_{5,5'}$ = 5.35 Hz, 1 H), 6.12 (d, J = 5.35 Hz, 1 H), 6.9 – 7.4 (m, 8 H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 246 (4.21), 270 sh (4.16), 363 (3.78). MS (EI): m/z (%) = 389 (M^+, 7), 388 (21), 345 (8), 343 (12), 149 (4), 140 (9), 139 (100), 113 (13), 111 (32), 75 (12). $C_{20}H_{14}Cl_2O_4$ (389.23): calcd. C 61.71, H 3.63, Cl 18.22; found C 61.42, H 3.43, Cl 18.15.

2-(4-Chlorobenzoyl)-4-(4-chlorophenacyl)-3-hydroxycyclopent-2-ene-1-one (**4d**)

Yield: 1.5 g (15%), m. p. 212 – 216°C from glacial CH_3COOH. IR (KBr): 3200 – 2820, 1735, 1670, 1630, 1605 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.9 (d, J = 6.6 Hz, 2 H), 3.2 (d, J = 5.4 Hz, 2 H), 3.53 (m, 1 H), 7.39 and 7.89, 7.35 (q, s, J_{AB} = 9 Hz, 8 H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 203 (4.38), 262 (4.39). MS (EI): m/z (%) = 389 (M^+, 9), 388 (25), 343 (12), 315 (6), 149 (9), 141 (33), 140 (9), 139 (100), 113 (13), 75 (9). $C_{20}H_{14}Cl_2O_4$ (389.23): calcd. C 61.71, H 3.63, Cl 18.22; found C 61.53, H 3.94, Cl 17.93.

3-Phenyl-5-(2-phenyl-2-methoxyethenyl)-5,6-dihydro-4 H-cyclopenta[c]isoxazole-4-one (**5**)

To a solution of **3a** (1.6 g, 4.99 mmol) in methanol (70 ml), hydroxylamine hydrochloride (0.695 g, 10 mmol) in water (2 ml) was added. The solution was heated under reflux for 7 h. After evaporation and recrystallization from *Et*OH pure white crystals, 0.65 g, (39%) of **5** were obtained; m. p. 105 – 109°C. IR (KBr): 3065, 2960, 1730, 1660, 1635, 1570, 1460, 1430, 1350 cm^{-1}. ^{1}H NMR (acetone-d_6): δ = 3.05 – 3.30 (m, 2 H), 3.7 (s, 3 H), 3.6 – 3.9 (m, 1 H), 6.15 (d, J = 4.5 Hz, 1 H), 7.0 – 7.3, (m, 10 H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 235 (4.0), 275 (4.2). MS (EI): m/z (%) 331 (M^+, 46), 291 (3), 272 (97), 254 (14), 244 (7), 215 (3), 202 (4), 167 (6), 166 (6), 141 (8), 139 (7), 115 (7), 105 (100), 91 (5), 77 (97), 59 (12), 51 (20), 29 (14). $C_{21}H_{17}NO_3$ (331.35): calcd. C 76.12, H 5.17, N 4.23; found C 75.98, H 5.39, N 4.48.

2-Benzoyl-3-methoxy-4-phenacylcyclopent-2-ene-1-one (**6**)

A solution of **4a** (1.922 g, 6 mmol) in conc. H_2SO_4 (20 ml) was stirred at 0°C for 15 min and poured into ice water (200 ml). The white amorphous precipitate was filtered off and recrystallized from *Me*OH affording 1.36 g (68%) of **6** as white plates; m. p. 104 – 106°C. IR (KBr): 1727, 1678, 1647, 1613, 1205 cm^{-1}. ^{1}H-NMR (acetone-d_6): δ = 2.83 (d, J = 6.15 Hz, 2 H), 3.14 (d, J = 5.37 Hz, 2 H), 3.52 (m, 1 H), 3.73 (s, 3 H), 7.25 – 7.75 (m, 10 H). UV/VIS (dioxane): λ_{max} [nm] (lg ε) = 256 (4.24), 280 sh (4.14). MS (EI): m/z (%) = 334 (M^+, 34), 333 (7), 303 (3), 275 (22), 247 (8), 220 (13), 105 (100), 77 (49), 59 (3), 51 (8). $C_{21}H_{18}O_4$ (334.35): calcd. C 75.44, H 5.42; found C 75.39, H 5.55.

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