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Transformation of Cyclopentane-1,3-diones into Cyclohexane-1,4-diones - A Novel Ring Enlargement Process

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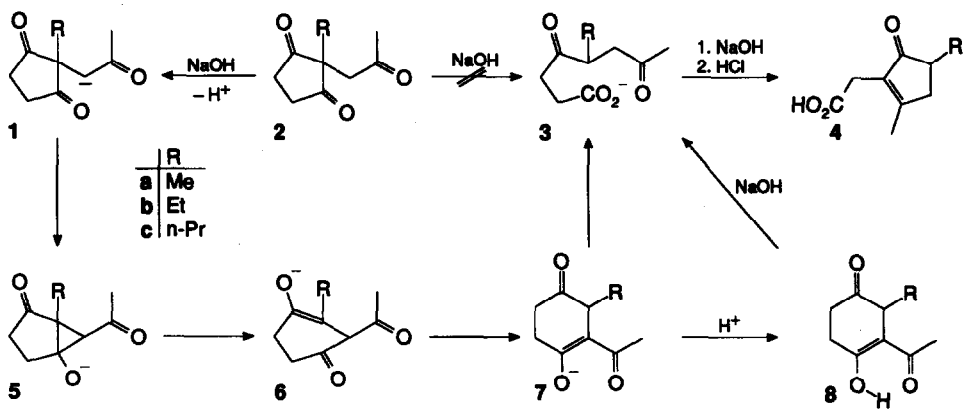
Abstract: 2-Alkyl-2-(2-oxopropyl)cyclopentane-1,3-diones are smoothly converted into 2-acetyl-3-alkylcyclohexane-1,4-diones (3-acetyl-2-alkylcyclohex-3-en-4-olones) by treatment with an equimolar amount of sodium hydroxide in water or sodium methoxide in methanol. This ring enlargement can be considered as the result of an intramolecular aldol reaction followed by a ring opening of the formed bicyclo[3.1.0]hexane system.

2,2-Dialkylated cyclopentane-1,3-diones are easily cleaved by aqueous alkali under formation of 5-substituted 4-oxoalkanoic acids.[1-4] Therefore it has been assumed that the earlier described transformation of 2-alkyl-2-(2-oxopropyl)cyclopentane-1,3-diones **2** into 2-(2,4-dialkyl-5-oxocyclopent-1-enyl)acetic acids **4** proceeds via an intramolecular aldolization of the corresponding 5-alkyl-4,7-dioxoalkanoates **3**.[5] In connection with our recent interest in the intramolecular aldolization of 2,2-dialkylated cyclopentane-1,3-diones with an additional carbonyl group in one of the two side-chains[6] the formation of **4** from **2** was investigated in more detail. As a result, we now can report on an unexpected ring enlargement process.



Scheme 1. Conversion of the cyclopentane-1,3-diones **2** into the cyclohex-3-en-4-olones **8**

When a solution of the triketone **2b** in water was treated at 22°C for 2 min with 1 equivalent of sodium hydroxide and thereafter acidified by an excess of diluted sulfuric acid, the cyclohexenolone **8b** could be isolated as a crystalline substance in a yield of about 50 %. The structure of this compound was unambiguously elucidated by ^{1}H NMR, ^{13}C NMR, and mass spectrometry, as well as by elemental analysis. Under the same conditions **2a** and **2c** were converted into the homologues **8a** and **8c**.

The unexpected formation of the cyclohexenolones **8** may be explained as depicted in Scheme 1. In the first step the hydroxide ion does not cleave the cyclopentane-1,3-dione system of **2** under formation of the expected carboxylate **3** but deprotonates the active methylene group of the side chain under formation of the carbanion **1**. Intramolecular nucleophilic attack on one of the ring carbonyl groups gives rise to the bicyclic alkoxide **5**, which can be rearranged by a ring opening via **6** into the more stable enolate **7**. Protonation, finally, yields the completely enolized triketone **8**.

That the enolate **7** has to be regarded as the first isolable intermediate in the alkali-mediated conversion of the triketone **2** into the acid **4** can be demonstrated by the fact that the treatment of **8** with an excess of sodium hydroxide provides **4** in good yield. In this step the open-chain carboxylate **3**, accessible by cleavage of the 1,3-dicarbonyl system of **7** with alkali, reacts as intermediate.

In order to optimize the yield of the conversion of the triketones **2** into the cyclohexenolones **8**, the ring enlargement reaction was performed in methanol with sodium methoxide as base. Under these conditions in all cases yields in the order of 70 % could be obtained.[7]

In conclusion, the described transformation of 2-alkyl-2-(2-oxopropyl)cyclopentane-1,3-diones into 2-acetyl-3-alkylcyclohexane-1,4-diones represents a novel ring enlargement. This unique process seems to be closely connected with the special functionalization of the triketones **2**. Their analogues with a 3-oxobutyl side-chain instead of the 2-oxopropyl side-chain form tetrahydroindane-1,5-diones, known as versatile intermediates for the total syntheses of 19-norsteroids.[8] The analogues without a second carbonyl group in the five-membered ring are not reported to give a comparable ring enlargement reaction.[9,10]

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7. Typical procedure: The triketone **2c**[11] (588 mg, 3 mmol) was added to a 1N solution of sodium methoxide in methanol (3 mL, 3 mmol). The reaction mixture was stirred at 22°C for 15 min, acidified with 2N sulfuric acid (3 mL, 6 mmol), and extracted with diethyl ether (4 x 10 mL). The combined extracts were dried with magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with hexane/ethyl acetate (7:3) as eluent afforded **8c** (412 mg, 70 %) as colourless crystals: mp. 62-64°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J* 7.5 Hz, 3 H, CH_2CH_3), 1.18-1.36 (m, 2 H, CH_2Me), 1.60 (q, *J* 7.5 Hz, 2 H, $CHCH_2$), 2.07 (s, 3 H, $COCH_3$), 2.42-2.92 (m, 4 H, 5-H_2 and 6-H_2), 3.13 (t, *J* 7.5 Hz, 1 H, $CHCH_2$), 16.10 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.89 (CH_2CH_3), 20.23 ($COCH_3$), 22.66, 30.90, 34.81, 36.81 (4 x CH_2), 48.72 (C-2), 108.28 (C-3), 188.08 (C-4), 192.39 (COMe), 210.05 (CO); Anal. calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.55; H, 8.30.
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