Symmetrical molecules from reaction of β-cyclohexanediones with acetylenedicarboxylic acid in aqueous medium

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\textbf{ABSTRACT} In an attempt to obtain Michael adducts in aqueous medium, 1,3-cyclohexanedione (1) or dimedone (2) and acetylenedicarboxylic acid monopotassium (3) were dissolved in water and heated to reflux. Under these conditions, two products were isolated from the reaction mixture between 1 and 3: 2-[1-(2,6-dioxocyclohexyl)ethyl]-1,3-cyclohexanedione (6) and a xanthenedione (7), which corresponds to the cyclization of 6. The reaction between 2 and 3 gave only the 2-[1-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethyl-1,3-cyclohexanedione (8).

\textbf{Keywords:} xanthenediones; cyclohexanediones; symmetrical molecules; Michael addition

\section*{Introduction}

Organic reactions in aqueous medium present several potential advantages \cite{1}, since water, as a solvent, is cheap, is not detrimental to the environment, and is not toxic. Moreover, isolation of organic products from the reaction mixture can be accomplished by simple phase separation \cite{2}. Recently, various carbon-carbon bond-forming reactions in aqueous medium have been reported, e.g: (i) Diels-Alder reactions \cite{3}, (ii) Michael additions \cite{4}, (iii) Claisen rearrangements \cite{5}, (iv) Barbier-type allylations \cite{6}, and (v) aldol reactions (Mukaiyama) \cite{7}.

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Our research was focused on the synthesis of polyfunctional scaffolds (such as 4 and 5 (Scheme 1) [8], by means of the Michael addition reaction of cyclic β-dicarbonyl compounds such as 1 (1,3-cyclohexanedione) or 2 (dimedone), and acetylenedicarboxylic acid (3) in aqueous medium.

The reaction of 1,3-diketones (1 or 2) with acetylenedicarboxilic acid salt (3) in water led, unexpectedly, to the formation of symmetrical molecules by a one-pot, tandem process comprised of Michael addition, decarboxylation, cyclization and elimination.

This unexpected but interesting result prompted us to report it, along with a possible reaction mechanism, which is discussed below.

**Material and Methods**

**General**

$^1$H and $^{13}$C NMR spectra were obtained using a Bruker AVANCE DPX-300 spectrometer and were recorded at 300 and 75 MHz respectively. IR spectrum was obtained using a Perkin Elmer model 783. UV absorption spectroscopy was performed with a Hitachi U-3000 spectrophotometer. All reagents and chemicals were obtained from Acros Organic Company and were used as received unless otherwise noted.

**Typical procedure**

A mixture of β-diketone (1 or 2, 10 mmol) and salt 3 (3.5 mmol) in water (15 mL) was stirred for 3 h under reflux, and the reaction was monitored by TLC. The mixture was then extracted with CHCl$_3$ (3 x 20 mL), the combined organic layers dried over MgSO$_4$ (10 min), filtered, and evaporated. Flash chromatography (silica gel) using ethyl acetate/hexane (3:2) gave the products 6 and 7. Compound 8 was isolated in similar fashion.

2-[1-(2,6-dioxocyclohexyl)ethyl]-1,3-cyclohexanedione (6). Yield: 5%, solid. UV (chloroform): 258 nm; IR: $v_{max}$ (KBr): 3418, 2971, 1580, and 1456; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 1.42 (d, J= 7.4 Hz, 3H); 1.80 – 1.88 (m, 4H); 2.20 – 2.48 (m, 8H); 4.06 (q, J= 7.4 Hz, 1H); 12.09 (sl, 1H); 12.88 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$ (ppm):
15.9 (CH$_3$): 19.8 (CH$_2$); 23.9 (CH); 32.2 (CH$_2$); 33.3 (CH$_2$); 118.8 (C); 190.9 (C); 191.1 (C=O).

9-methyl-2,3,4,5,6,7,8,9-octahydro-1H-1,8-xanthenedione (7): Yield: 30%, solid, m.p: 53-55°C. UV (chloroform): 243 and 296 nm; IR $\nu_{\text{max}}$ (KBr): 3412; 2958, 1647, 1616, 1458, 1372 and 1177. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 1.03 (d, J= 6.5 Hz, 3H); 1.97 – 2.03 (m, 4H); 2.31 – 2.88 (m, 8H); 3.62 (q, J= 6.5 Hz, 1H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$ (ppm): 20.4 (CH$_3$); 20.8 (CH$_2$); 22.1 (CH$_2$); 27.0 (CH); 37.0 (CH$_2$); 117.9 (C); 164.3 (C); 197.3 (C=O). MS m/z (relative intensity, %) 232 [M+] (4.0); 218 (15.2); 217 (100); 175 (4.8); 105 (5.7); 91 (9.3).

2-[1-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethyl-1,3-cyclohexanedione (8): Yield: 15%, solid, m.p: 139-141°C UV (chloroform): 260 nm. IR $\nu_{\text{max}}$ (KBr): 3303, 3263, 2963, 1671, 1489, 1170. $^1$H-NMR: (CDCl$_3$, 300 MHz) $\delta$ (ppm): 1.03 (s, 12H); 1.45 (d, J= 7.4 Hz, 3H); 1.98 – 2.67 (m, 8H); 4.07 (q, J= 7.4 Hz,1H); 12.45 (s,1H). $^{13}$C-NMR: (CDCl$_3$, 75 MHz) $\delta$ (ppm): 15.6 (CH$_3$); 23.5 (CH); 26.4 (C); 29.6 (CH$_2$); 31.1 (CH$_2$); 46.9 (CH$_2$); 117.6 (C); 189.4 (C); 189.6 (C=O).

**Results and Discussion**

Upon heating to reflux temperature, various polar products were formed (TLC); two major products were isolated by flash chromatography, and their structure determined by $^1$H- and $^{13}$C- NMR. The less polar material was identified as being compound (6) the more polar, was identified as the xanthenedione (7), which corresponds to the cyclization of 6 followed by dehydration (Figure 1). The preparation of these compounds has been reported in the literature, but they were obtained by different methods [9].

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Structures of the symmetrical molecules.

Dimedone (2) was also subjected to the same reaction conditions with 3, but, in this case, only compound 8 was observed. Compound 1 is very soluble in the reaction medium and decomposes quite extensively under these conditions, leading to lower yields. Compound 2 is partially soluble in the reaction medium and reacts with 3 giving poor yields of 8; however, a large amount of unreacted starting material is recovered. Also, no cyclization product derived from 8 was detected, as observed in the reaction of
1. Horning and Horning [9] report that the cyclization of 8 is achieved by treatment with an 8:2 mixture of methanol and water, under reflux, in the presence of dilute HCl. We propose the following mechanism to explain our observations (Scheme 2).

Enols are notoriously soft nucleophiles (neutral), which react with $\alpha,\beta$-unsaturated carbonyl compounds preferentially via conjugate addition. Since the enol form is favored in 1,3-dicarbonyl compounds, the conjugate addition may take place in neutral or slightly acidic environment [10]. It is plausible that the reaction is initiated by Michael addition followed by fast proton exchange and decarboxylation. Thus, the enol tautomerizes and undergoes a new Michael addition with 1,3-diketone, leading to a tetrahedral intermediate that collapses with loss of CO$_2$ to give compounds 6 or 8. Cyclization followed by dehydration leads to the formation of 7.

![Scheme 2.](image)

**Scheme 2.** Mechanism proposed to formation of the compounds 6-8.

Conversion of 6 $\rightarrow$ 7 (Scheme 3) occurs under mild conditions and can be observed by repeatedly taking NMR measurements of a solution of 6 in CDCl$_3$ on the course of a few days, where one can observe the gradual disappearance of signals attributed to 6, concurrent with the appearance of peaks related to 7. Due to the slight acidic character of CDCl$_3$ [11], we believe this conversion can be rationalized by the
mechanism below.

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\begin{align*}
\text{Scheme 3. Mechanism proposed to formation of compound 7 in CDCl}_3.
\end{align*}
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The difference in reactivity between 6 and 8 (Scheme 4) was rationalized based on the fact that, in the transition state that leads to intermediate 9, an adverse 1,3-diaxial interaction between the developing tertiary alcohol (formed prior to the elimination reaction) and one of the methyl groups of dimedone considerably raises the activation energy required to convert 8 into the corresponding cyclized product. The cartoon structures A and B (Scheme 4) illustrate our proposal [12]. Although in both cases it is possible to recognize that there is some steric blocking between the tertiary hydroxyl and the methyl group at the linker, it is seen that the extra steric interference in B plays a role in the rate of this reaction. It is then tempting to predict that deletion of the methyl group at the linker would lead to a faster rate of cyclization than that observed for compound 6.

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\begin{align*}
\text{Scheme 4. 1,3-diaxial interactions between the budding tertiary alcohol (formed prior to the elimination reaction) and one of the methyl groups of dimedone (cartoon B).}
\end{align*}
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Conclusion
We have presented an unexpected sequence of reactions in aqueous medium that led to formation of compounds possessing a symmetrical framework. Acetylenedicarboxylic acid has played the role of a synthetic equivalent of acetaldehyde towards reaction with a dicarbonyl compound. These results illustrate an unusual mechanistic pathway.

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**References and Notes**


[12] Models were generated using the Chem3D implementation of MM2 (CambridgeSoft; SN 251657); whenever possible, transition state geometries were calculated using the Chem3D implementation of MOPAC, at the PM3 level of theory. The structures of charged intermediates were built using MM2, followed by energy minimization using MOPAC, at the PM3 level of theory; charges were simulated using the Mulliken model.