# CHEMISTRY OF ACETALS

#### COMMUNICATION 22. CONDENSATION OF 2,4-PENTANEDIONE

#### AND 1,3-CYCLOHEXANEDIONE WITH ACETALS

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In a previous paper [1] we showed that in presence of  $BF_3$  ether complex acetoacetic ester reacts readily with acetals of various saturated and acetylenic aldehydes with formation of alkoxy derivatives of type (I):

$$\begin{array}{c} \mathrm{R'-CHOR} \\ \mathrm{I} \\ \mathrm{R'CH} \ (\mathrm{OR})_2 + \mathrm{CH}_3\mathrm{COCH}_2\mathrm{COOC}_2\mathrm{H}_5 \rightarrow \mathrm{CH}_3\mathrm{CO}-\mathrm{CH}-\mathrm{COOC}_2\mathrm{H}_5 \\ \end{array}$$
(I)

In the present work we studied the behavior of some other  $\beta$ -dicarbonyl compounds in this reaction. It was found that, as observed previously [2], malonic and cyanoacetic esters do not react with acetals even when 1 mole of BF<sub>3</sub> ether complex is added per mole of the ester. With acetaldehyde diethyl acetal 2,4-pentanedione gives a 60-70% yield of the corresponding adduct (II), which very readily loses alcohol with formation of 3-ethylidene-2,4-pentanedione (III):

Gas-liquid chromatography (GLC) showed that the latter product is identical to the product of the Knoevenagel reaction between 2,4-pentanedione and acetaldehyde. Acetals of acetylenic aldehydes react less readily with 2,4-pentanedione. Thus, propiolaldehyde diethyl acetal gives only a 37% yield of 3-(1-eth-oxy-2-propynyl)-2,4-pentanedione (IVa) contaminated with boron trifluoride 2,4-pentanedione complex [3]. This complex (crystals of m.p. 37-40°) is readily formed under the conditions of the reaction and probably removes catalyst and 2,4-pentanedione from the sphere of reaction. In the case of acetaldehyde diethyl acetal the formation of such a complex is not observed. Hence, the poor yields in this reaction when acetylenic acetals are used confirms that they are less active than saturated acetals.

$$\begin{array}{l} \mathrm{CH}_{3}\mathrm{COCH}_{2}\mathrm{COCH}_{3}+\mathrm{RC}\equiv\mathrm{C--CH}\;(\mathrm{OC}_{2}\mathrm{H}_{5})_{2}\rightarrow\mathrm{RC}\equiv\mathrm{C--CH}-\mathrm{OC}_{2}\mathrm{H}_{5}\\ & & |\\ \mathrm{CH}_{3}\mathrm{CO}-\mathrm{CH}\mathrm{COCH}_{5}\\ & & (\mathrm{IV}) \end{array}$$

$$a - R = H; \quad b - R = C_6 H_5$$

In the case of phenylpropiolal dehyde diethyl acetal we were able to isolate only the  $BF_3$  2,4-pentanedione complex, and the product (IVb) was formed in only very small amount.

With 1,3-cyclohexanedione acetals react readily, but they give the diadducts (V) and (VI), identical to the adducts obtained by the reaction of 1,3-cyclohexanedione with the corresponding aldehydes:



The reaction is accompanied by the formation of a considerable amount (40-50%) of the enol ether of 1.3-cyclohexanedione (VII). We also observed the formation of an enol ether [(VIII)] in the treatment

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of an alcoholic solution of acetoacetic ester and butyraldehyde diethyl acetal with boron trifluoride ether complex:

 $\begin{array}{c} \mathrm{CH_{8}COCH_{2}COOC_{2}H_{5}+C_{8}H_{7}CH}\left(\mathrm{OC_{2}H_{5}}\right)_{2}+C_{2}H_{5}\mathrm{OH}+\mathrm{BF_{3}}\rightarrow\\ \rightarrow \mathbf{CH_{3}-C=CHCOOC_{2}H_{5}+C_{8}H_{7}CHO}\\ \\ \downarrow\\ \mathrm{OC_{2}H_{5}}\\ (\mathrm{VIII})\end{array}$ 

The enol ethers (VIII) and (VII) are formed in appreciable amounts only in presence of an acetal. The systematic study which we have made of the conditions of reactions of 1,3-cyclohexanedione with various acetals has shown that when no acetal is present in the mixture the formation of the enol ether of 1,3-cyclohexanedione does not occur. If, however, two acetals participate in the reaction (dimethyl and diethyl), then two enol ethers are formed (methyl and ethyl). When 1,3-cyclohexanedione is heated in alcohol in presence of a catalyst ( $BF_3$ ), the enol ether is formed only in very small amount. Hence, the acetal is an active carrier of alcohol residues. An analogous observation has been made in the study of the esterification of acids with alcohols. It has been found [4] that the addition of an acetal to a mixture of an acid and an alcohol greatly increases the rate of ester formation.

These facts appear to provide indirect confirmation of the view that these reactions do not go via the intermediate breakdown of the acetal with formation of a carbonium ion:

$$R_1R_2C(OR)_2 \rightleftharpoons R_1R_2C^{\oplus}OR + RO^{\ominus}$$

The formation of only diadducts in the reactions of 1,3-cyclohexanedione with acetals suggests that this reaction does not go through the preliminary stage of the formation of product of type (IX) with subsequent addition of a second 1,3-cyclohexanedione molecule. Since 1,3-cyclohexanedione probably exists in the form of dimer molecules, it is more probable that in this case the elimination of alcohol from the intermediate product and a second molecule of 1,3-cyclohexanedione occurs immediately:



It should be noted that the acidity of 1,3-cyclohexanedione is sufficiently high ( $K_a = 0.55 \cdot 10^{-5}$ ) for its reactions with acetals to go even in absence of catalyst.

In a previous paper [1] we suggested three possible schemes for the reaction of acetoacetic ester with acetals under the action of boron trifluoride leading to 2-(1-ethoxyalkyl)acetoacetic esters (I) [or to (II) in the case of 2,4-pentanedione]. If we take account of the character of the polarization of the two tautomeric forms of acetoacetic ester, we can imagine at least three more reaction schemes:



Schemes (1) and (2) are analogous to the schemes examined earlier [1] which take account of the character of the ionization of the keto and enol forms of acetoacetic ester. Scheme (3) supposes the direct replacement of hydroxyl by alkoxyl, and it requires activation of the C—O bond in the enol of aceto-acetic ester to an extent which is scarcely possible. Simple transacetalization (possibly through the stage of symmetrization) also leads to the product (VIII). All these considerations naturally apply to an equal extent also to 2,4-pentanedione and 1,3-cyclohexanedione.



Under the usual reaction conditions we have never succeeded in observing the formation of products of type  $(\Sigma)$ . However, 2,4-pentanedione with ethyl vinyl ether in presence of acidic agents gives a mixture of products in which an acetal of type (XI) appears to be present.



When this mixture is treated with 2 N ethereal HCl in the cold, the peak corresponding to (XI) on the chromatogram disappears, and the peak of 2,4-pentanedione appears (Fig. 1). Under these conditions the elimination of alcohol does not occur. We must mention that the report in [5] on the formation of the acetal (X) was not confirmed. In checking this work we showed that the fraction which in the opinion of the authors corresponded to the symmetrized acetal (XII) was actually acetoacetic ester in admixture with 2-ethylideneacetoacetic ester and 2-(1-ethoxyethyl)acetoacetic ester (I), as we showed previously [6].



It must therefore be admitted that, although schemes (1) and (2) can apply, the products of type (X) will not be stable under the conditions of the reaction. Scheme (4) probably best explains the fact of the formation of the enol ethers (VII) and (VIII). It is known that 1,3-cyclohexanedione comparatively readily gives ketals which, under acid conditions, lose alcohol with formation of (VII). We showed that the same applies for the ketal of acetoacetic ester [1]. However, under equilibrium conditions in presence of alcohol the content of the ethers (VII) and (VIII) is small. If, however, the supplier of alcohol residues in an acetal, reaction goes to the extent of 50%.

Hence, the formation of products of type (I) can be regarded as the C-alkylation of  $\beta$ -dicarbonyl compounds, and the formation of compounds of type (VII) and (VIII) — as O-alkylation with subsequent elimination of an alcohol. The relative extents of these two reactions probably depend on the ionization constant of the  $\beta$ -dicarbonyl compound. However, our lack of knowledge about the kinetics of the reaction and how it is affected by additions of alcohol does not permit us to resolve precisely the question of the mechanism of this interesting reaction. It is quite clear, however, that the formation of an acetal or a hemiacetal is a necessary stage for the formation of the enol ether (VII) or (VIII). Study of the reactions of acetals with  $\beta$ -dicarbonyl compounds shows that they are fairly general in pattern for all compounds containing active hydrogen andnot so acidic as to bring about side processes.

#### EXPERIMENTAL

<u>Condensation of Acetaldehyde Diethyl Acetal with 2,4-Pentanedione.</u> A mixture of 11 g of 2,4-pentanedione, 21 g of acetaldehyde diethyl acetal, and 7 ml of BF<sub>3</sub> ether complex was kept at between -5 and 0° for 90 min. After neutralization of the catalyst with sodium acetate, the mixture was extracted with ether, and the extract was dried over MgSO<sub>4</sub>. On fractionation we obtained 3.2 g of unchanged 2,4-pentanedione and 12.4 g (64%) of 3-(1-ethoxyethyl)-2,4-pentanedione (II), b.p. 60-64° (3 mm);  $n_D^{20}$  1.4323. Found %: C 63.23, 63.24; H 9.23, 9.29.  $C_9H_{16}O_3$ . Calculated %: C 62.76; H 9.36.



Fig. 1. Gas-liquid chromatogram.
A) Original mixture; B) mixture
treated with ethereal HCl in the cold.
1) 2,4-Pentanedione; 2) the acetal (XI).

## Condensation of Propiolaldehyde Diethyl

A cetal with 2,4-Pentanedione. 6.4 g of propiolaldehyde diethyl acetal was added to a mixture of 7.5 g of 2,4pentanedione and 6.2 ml of BF<sub>3</sub> ether complex at 0°. After 10 min the mixture was washed with sodium acetate solution and extracted with ether. The extract was dried, and distillation gave 4.2 g of (IVa) containing some BF<sub>3</sub> 2,4-pentanedione complex as a rapidly darkening substance, b.p. 70-78° (0.1 mm);  $n_D^{20}$  1.4520. This product gave a positive test for halogen. Found %: C 64.39, 64.17; H 7.79, 7.74. C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>. Calculated %: C 65.91; H 7.74. We also obtained 1 g of a substance of b.p. 80-81° (0.1 mm), which solidified immediately; m.p. 37-40°. It was the BF<sub>3</sub> 2,4-pentanedione complex; found %: C 45.56; H 5.78.

Reaction of 2,4-Pentanedione with Ethyl Vinyl Ether. A drop of concentrated  $H_2SO_4$  was added to a mixture of 10 g of 2,4-pentanedione and 7.2 g of ethyl vinyl ether. The mixture became warm and turned black. After 4 h the mixture was neutralized with solid NaHCO<sub>3</sub>. The reaction mixture then became lighter in color. The precipitate was filtered off and washed with ether. After distillation we obtained 8.4 g of unchanged 2,4-pentanedione, 0.6 g of a mixture of b.p. 58-85° (3 mm), 1.5 g of a higher-boiling product [about 140° (3 mm) with decomposition], and 2.8 g of residue. The 58-85° fraction was investigated by means of GLC (see Fig. 1).

After treatment of this fraction with dilute ethereal HCl at room temperature the main peak disappeared almost completely, and the 2,4-pentanedione peak increased markedly. Since under these conditions alcohol is not eliminated and 3-(1-ethoxyethyl)-2,4-pentanedione (II) does not break down, the ready hydrolysis of this substance indicates the present of an acetal link of type (XI) in its molecule.

<u>Condensation of Acetaldehyde Diethyl Acetal with 1,3-Cyclohexanedione</u>. 4.4 g of acetaldehyde diethyl acetal was added gradually to a mixture of 3.8 g of 1,3-cyclohexanedione and 4.75 ml of BF<sub>3</sub> ether complex at room temperature. After 3.5 h the reaction mixture was diluted with 80 ml of ether and treated with 20 ml of saturated sodium acetate solution. The solution was dried and evaporated, and the residue was distilled. We obtained 2.19 g (46%, based on the cyclohexanedione taken) of 3-ethoxy-2-cyclohexen-1-one (the ethyl enol ether of 1,3-cyclohexanedione), b.p. 81-83° (2 mm);  $n_D^{24}$  1.5045.  $\lambda_{max}$  250 m $\mu$  (in C<sub>2</sub>H<sub>5</sub>OH),  $\epsilon$  15,300; identical in R<sub>f</sub> and according to GLC to a known sample. In the thin-layer chromatography of the enol ether (VII) obtained we detected the presence of an impurity which was not present in a known sample of 3-ethoxy-2-cyclohexen-1-one. In column chromatography on alumina we isolated 0.23 g of an oily substance with  $n_D^{24}$  1.4920;  $\lambda_{max}$  255 m $\mu$ , whose structure has not been elucidated.

The residue (1.95 g) remaining after the distillation of 3-ethoxy-2-cyclohexen-1-one was dissolved in benzene, and the solution was washed with 5% NaOH solution. After evaporation we obtained 1.5 g (43%) of 3,4,6,7-tetrahydro-9-methylxanthene-1,8(2H,5H)-dione (VI),  $R = CH_3$ ) as a clear thick oil  $(n_D^{21.5} 1.5495)$ , which in thin-layer chromatography ( $R_f$  0.5, alumina of activity II, 1:2 acetone-hexane) and GLC was identical to a known sample of (VI,  $R = CH_3$ ) prepared from acetaldehyde and 1,3-cyclohexanedione. After chromatography on alumina and crystallization from benzene and acetone (VI,  $R = CH_3$ ) was obtained in the crystalline state. It had m.p. 103-105°, undepressed by admixture of a known sample. The abovedescribed results were not altered substantially by using an excess of the acetal or a temperature of 50-55° (1 h) in the condensation of acetaldehyde diethyl acetal with 1,3-cyclohexanedione.

Condensation of Propiolaldehyde Diethyl Acetal with 1,3-Cyclohexanedione in Presence of Boron Trifluoride Ether Complex. 3.2 g of propiolaldehyde diethyl acetal was added to a solution of 2.8 g of 1,3-cyclohexanedione in 3.1 ml of BF<sub>3</sub> ether complex at room temperature. The mixture was heated for 25 min at 50°, cooled, and diluted with ether, and the solution was treated with sodium acetate solution, 5% NaOH solution, and water and was dried over MgSO<sub>4</sub>. After evaporation and vacuum distillation we obtained 0.9 g of the above-described 3-ethoxy-2-cyclohexen-1-one (VII); the residue, amounting to 1.6 g, solidified on cooling. Recrystallization from absolute ethanol gave (VI,  $R = CH \equiv C$ ), m.p. 160-162°, which gave one spot with  $R_f$  0.4 (1:2 acetone-hexane). Found %: C 74.65, 74.41; H 5.62, 5.77.  $C_{15}H_{14}O_3$ . Calculated %: C 74.36; H 5.83.

Condensation of Phenylpropiolaldehyde Diethyl Acetal with 1,3-Cyclohexanedione. By the above-described procedure from 5.6 g of 1,3-cyclohexanedione, 6.25 ml of BF<sub>3</sub> ether complex, and 10.2 g of phenylpropiolaldehyde diethyl acetal we obtained 6.6 g of (VI, R = PhC  $\equiv$  C), m.p. 160-161° (ethanol), R<sub>f</sub> 0.55 (alumina of activity II, 1:2 acetone-hexane). Found %: C 78.91, 78.83; H 5.78, 5.76. C<sub>21</sub>H<sub>18</sub>O<sub>3</sub>. Calculated %: C 79.22; H 5.70.

It was shown by thin-layer chromatography on alumina that after the reaction the mixture contained unchanged acetal ( $R_f$  0.63).

<u>Condensation of Phenylpropiolaldehyde Diethyl Acetal with 1,3-Cyclo-hexanedione in Absence of Catalyst.</u> 5.1 g of phenylpropiolaldehyde diethyl acetal was added to a solution of 2.8 g of 1,3-cyclohexanedione in 7 ml of absolute alcohol. The mixture was heated for 1.5 h at the boiling point of alcohol. Solvent was evaporated, and the residue (7.5 g) was washed with water to remove 1,3-cyclohexanedione. Ether was then added, and the solution was washed with sodium carbonate solution. From the alkaline solution after acidification we obtained 0.65 g of (V, R = PhC  $\equiv$  C), m.p. 179-182° (ethanol), undepressed by admixture of a sample prepared from phenylpropiolaldehyde and 1,3-cyclo-hexanedione. From the neutral part we obtained 4.3 g of a mixture with  $n_D^{20}$  1.5220, which contained the original acetal, phenylpropiolaldehyde, 3-ethoxy-2-cyclohexen-1-one (VII), and (VI, R = PhC  $\equiv$  C).

<u>Condensation of Propiolaldehyde with 1,3-Cyclohexanedione.</u> A mixture of 1.1 g of propiolaldehyde and 4.5 g of 1,3-cyclohexanedione in 10 ml of absolute ethanol was heated for 45 min at 50°. On the next day 4.3 g of crystalline reaction product was filtered off. After several crystallizations from absolute ethanol we isolated (VI,  $R = CH \equiv C$ ), m.p. 159-161°, which melted without depression in admixture with the above-described sample. From this experiment we also isolated (V,  $R = CH \equiv C$ ), m.p. 144-146°. Found %: C 69.11, 69.16; H 6.34, 6.30.  $C_{15}H_{16}O_4$ . Calculated %: C 69.21; H 6.20.

<u>Condensation of Phenylpropiolaldehyde with 1,3-Cyclohexanedione in Presence of Piperidine.</u> A mixture of 2.6 g of 1,3-cyclohexanedione, 6 ml of absolute methanol, 1.5 g of phenylpropiolaldehyde, and 1 drop of piperidine was boiled for 2 h and then distilled. We obtained 1.3 g of 3-methoxy-2-cyclohexen-1-one; b.p. 62-65° (0.4 mm);  $n_D^{20}$  1.5225; m.p. 30-31° (hexane),  $R_f$  0.7 (alumina of activity II, 1:2 acetone-hexane); identical with a known sample. We also obtained 1 g of residue, which was dissolved in chloroform; the solution was treated with 5% KOH, washed with water, and dried. After evaporation we obtained (VI, R = PhC  $\equiv$  C), m.p. 162-164° (ethanol), identical with the sample described above. From the alkaline sample after acidification we obtained (V, R = PhC  $\equiv$  C) with m.p. 178-180° (ethanol). Found %: C 74.50, 74.51; H 6.30, 6.05. C<sub>21</sub>H<sub>20</sub>O<sub>4</sub>. Calculated %: C 74.98; H 5.99.

<u>Condensation of Acetaldehyde with 1,3-Cyclohexanedione</u>. A mixture of 2.24 g of 1,3-cyclohexanedione, 0.88 g of acetaldehyde, 5 ml of methanol, and 1 drop of piperidine was boiled for 1 h. After the usual treatment we obtained the crystalline diol (V,  $R = CH_3$ ), m.p. 153-155° (ethanol). Found %: C 67.06, 67.07; H 6.88, 7.07.  $C_{14}H_{18}O_4$ . Calculated %: C 67.18; H 7.25.

When an alcoholic solution of the diol (V,  $R = CH_3$ ) was heated with 1 N HCl we obtained (VI,  $R = CH_3$ ), which after chromatography on alumina and recrystallization from benzene had m.p. 103-105°. Found %: C 72.16, 72.19; H 6.96, 6.78.  $C_{14}H_{16}O_3$ . Calculated %: C 72.39; H 6.94.

### CONCLUSIONS

1. The condensation of the acetals of some saturated and acetylenic aldehydes with 2,4-pentanedione and 1,3-cyclohexanedione was studied.

2. Views are expressed concerning the possible mechanism of the formation of enol ethers of  $\beta$ -carbonyl compounds in the condensation of compounds containing a mobile hydrogen atom with acetals.

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