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Abstract

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ON SUBSTITUTION REACTIONS IN THE METHYLENE LINKAGE OF β-KETOACETALS

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β-Ketoacetals have recently been finding ever wider application in organic synthesis. The ready availability of these compounds is due to well-developed methods for their synthesis from β-chlorovinyl ketones ([1,2]) and oxymethylene ketones ([3]). The cyclic β-ketoacetals recently obtained in our laboratory ([4]) have proved especially convenient, owing to their high stability.

Up to the present, for purposes of synthesis only condensations at the keto group of acetals ([2,4–6]) or transformations of them of the type characteristic of β-dicarbonyl compounds have been used, chiefly for the synthesis of heterocyclic compounds (see, for example, ([1,7])). Of particular interest are substitution reactions in the methylene group of β-ketoacetals; these will make it possible to use them in an entirely new direction and will thus extend still further the synthetic use of β-chlorovinyl ketones ([8]), of which β-ketoacetals are analogs and derivatives.

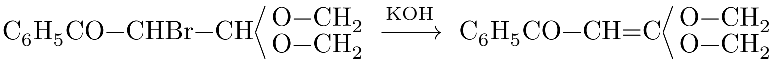
In the present article we report some preliminary data on reactions of this type. First of all, we studied the bromination of β-ketoacetals under various conditions. In aqueous medium, in the presence of barium carbonate, bromination of the methylene linkage of β-ketoacetals proceeds readily; however, the reaction is complicated by cleavage of the acetal group, as a result of which meso-substituted β-ketoaldehydes are formed, which in some cases have also been obtained in the bromination of oxymethylene ketones ([9]):

$$CH_3COCH_2CH(OCH_3)_2 \xrightarrow[H_2O]{Br_2} CH_3COCHBrC(=O)H$$

A more interesting result was obtained in the bromination of cyclic acetals in ether in the presence of barium carbonate; in this case bromination also occurs at the methylene group, but the acetal group is retained:

$$RCO-CH_2-CH\left\langle\begin{matrix}O-CH_2\\O-CH_2\end{matrix}\right. \xrightarrow{Br_2} R-CO-CHBr-CH\left\langle\begin{matrix}O-CH_2\\O-CH_2\end{matrix}\right. \qquad R = CH_3-;\ C_6H_5-$$

The bromoacetals obtained can subsequently be used in various directions; however, one of the most interesting possibilities is the dehydrobromination carried out by us under the action of caustic potash in benzene.

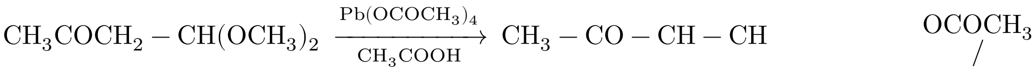


$$C_6H_5CO{-}CHBr{-}CH\left\langle\begin{matrix}O{-}CH_2\\O{-}CH_2\end{matrix}\right. \xrightarrow{KOH} C_6H_5CO{-}CH{=}C\left\langle\begin{matrix}O{-}CH_2\\O{-}CH_2\end{matrix}\right.$$

It may be hoped that this reaction opens up possibilities for obtaining a great variety of acetals of β-acyl ketones, for which at present there is no general satisfactory method of synthesis. Under the action of an excess of alcoholic alkali on mesobromo ketoacetals, an ester of a β-keto acid is obtained, formed as a result of a further transformation of the acetal of β-acetyl ketene:

$$CH_3COCHBr - CH(OCH_2)_2 \xrightarrow[CH_3OH]{KOH} CH_3COCH_2 - COOCH_3.$$

Another reaction of β-ketoaldehydes, the study of which we have now begun, is oxidation with lead tetraacetate. On heating the dimethyl acetal of acetoacetaldehyde with this reagent in benzene or acetic-acid solution, oxidation of the acetal at the methylene group occurs, the reaction being complicated by replacement of one of the alkoxyl radicals by an acetoxy group:

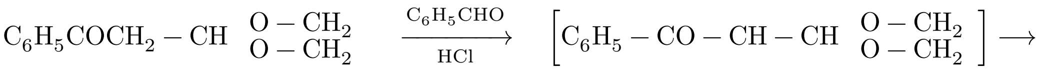


$$CH_3COCH_2 - CH(OCH_3)_2 \xrightarrow[CH_3COOH]{Pb(OCOCH_3)_4} CH_3 - CO - CH - CH \qquad \overset{OCOCH_3}{/}$$

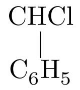
$$CH_3 - CO - CH(OCOCH_3) - CH(OCOCH_3)(OCH_3).$$

Exchange of alkoxyl radicals in acetals for an acyloxy group under analogous conditions is well known (10). During the course of this work there appeared a brief note by Pininger and Müller (11), who report results analogous to ours without indicating any experimental details or constants of the compounds obtained.

In addition to the foregoing, we studied the condensation of the cyclic acetal of benzoylacetaldehyde with benzaldehyde. When the two reagents were allowed to react in methanol in the presence of gaseous hydrogen chloride, β-chloro-β-phenylpropiophenone was isolated, the structure of which was proved by its conversion into 3,5-diphenylisoxazoline. Thus, condensation of the acetal at the methylene group with benzaldehyde is complicated by decomposition of the acetal according to the type of decomposition of β-dicarbonyl compounds, since the reaction proceeded under fairly severe conditions:



$$C_6H_5COCH_2 - CH \begin{matrix}O - CH_2\\O - CH_2\end{matrix} \xrightarrow[HCl]{C_6H_5CHO} \left[C_6H_5 - CO - CH - CH \begin{matrix}O - CH_2\\O - CH_2\end{matrix}\right] \longrightarrow$$



$$\begin{array}{c}\mathrm{CHCl} \\ | \\ \mathrm{C_6H_5}\end{array}$$

$$\longrightarrow\ \mathrm{C_6H_5COCH_2-CH(Cl)-C_6H_5}.$$

In attempting to carry out nitration and sulfurization of β-ketoacetals, we have so far been unable to obtain the desired results.

The preliminary data reported in this article show that the activity of the methylene group in β-ketoacetals can hardly be compared with the activity of the methylene unit in other β-dicarbonyl compounds; it rather resembles the activity of the α-carbon unit of ordinary ketones.

Experimental Part*

Bromination of the dimethyl acetal of acetoacetaldehyde in water.

To a mixture of 7 g of the acetal, 5.2 g of barium carbonate, and 15 ml of water, with stirring and illumination by a lamp, 2.9 ml of bromine are added dropwise, and the reaction mixture is gradually heated until the reaction begins on a water bath. After the addition of half of the total amount of bromine, the temperature of the reaction mixture should reach 55-60°, after which heating is stopped. After complete decolorization of the reaction mixture, the lower layer is separated. The aqueous layer is extracted three times with ether. The ethereal extracts are combined with the separated oil and dried over sodium sulfate. After careful removal of the ether under vacuum, a crystalline substance remains in the flask; it is pressed on a porous filter, washed once with 1-2 ml of chloroform and with petroleum ether (3 × 4 ml). The substance is dried in a vacuum desiccator. Yield 4.4 g (51%).

α-Bromo-β-ketobutyric aldehyde—slightly pinkish plates, m.p. 109-110°. It darkens on storage.

Found, %: C 28.61; 28.66; H 3.17; 3.14
$C_4H_5O_2Br$. Calculated, %: C 29.05; H 3.15.

Bromination of the ethylene glycol acetal of acetoacetaldehyde in ether. To a mixture of 26.2 g of acetal, 40 g of barium carbonate, and 70 ml of ether, with stirring and illumination by a lamp, 10.5 ml of bromine is added dropwise. During the first 5-7 min the reaction proceeds very slowly, thereafter vigorously. After completion of the addition of bromine, the reaction mixture is stirred for 1-2 min. The mineral residue is filtered off and thoroughly

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* With the participation of N. V. Molodtsov and V. N. Kulakov.

washed with ether. The ethereal filtrate is dried over sodium sulfate. After removal of the ether, the residue is distilled under vacuum, collecting the fraction 104-107°/6 mm. Yield 17 g (41%). After repeated distillation it has the following constants: b.p. 104-104.5°/6 mm, n_D^{20} 1.4938, d_4^{20} 1.5840, $MR_{D\text{found}}$ 38.50, MR_{calc} 38.77.

Found, %: C 34.19; 34.14; H 4.29; 4.31
$C_6H_9O_3Br$. Calculated, %: C 34.41; H 4.30.

A colorless oil with a sharp odor. Unstable on storage.

Reaction of the mesobromo ethylene glycol acetal of acetoacetaldehyde with alcoholic alkali. 4 g of bromoacetal, 1.1 g of caustic potash, and 13 ml of methanol are mixed in the cold and then heated on a water bath for 2 hours. The mineral precipitate is filtered off by suction, and the remaining oil is distilled under vacuum. The fraction 65-73°/10 mm (1.8 g) is distilled a second time, collecting the methyl ester of acetoacetic acid at 69-70.5°/10 mm. The substance has n_D^{20} 1.4183, d_4^{20} 1.0769. Literature data(12): b.p. 73-74°/12 mm, n_D^{20} 1.4186, d_4^{20} 1.0769.

Found, %: C 51.74; 51.60; H 6.98; 7.04
$C_5H_8O_3$. Calculated, %: C 51.81; H 6.92.

Ethylene glycol acetal of β-benzoylketene. 4 g of the mesobromo acetal of benzoylacetaldehyde, 20 ml of abs. benzene, and 1.3 g of powdered caustic potash are stirred at first without heating, then at 70-80° for 4 hours; the organic layer is poured off, and the benzene is removed from it under vacuum. The remaining oil is diluted with one and a half volumes of ether and cooled to −70°. The precipitated crystals are rapidly filtered off by suction and washed with chilled ether. Yield of the ethylene glycol acetal of benzoylacetaldehyde 0.75 g (27%). After recrystallization from chloroform, colorless needles, m.p. 61-61.5°.

Found, %: C 69.21; 69.08; H 5.80; 5.87
$C_{11}H_{10}O_3$. Calculated, %: C 69.42; H 5.41.

Bromination of the ethylene glycol acetal of benzoylacetaldehyde. To a solution of 15 g of acetal in 250 ml of abs. ether, with stirring and illumination by a lamp, 5 ml of bromine is added dropwise. After completion of the addition of bromine, the reaction mixture is stirred—

The mixture is heated for another 15 min, the ether is distilled off, and the residue is left for several days in a refrigerator, where it crystallizes. The crystals are pressed on a porous plate and recrystallized from methanol. Yield 8.4 g (50%), mp 66-67°.

Found, %: C 48.77; 48.77; H 4.20; 4.22
$C_{11}H_{11}O_3Br$. Calculated, %: C 48.71; H 4.06.

Oxidation of the dimethyl acetal of acetylacetaldehyde with lead tetraacetate. To a suspension of 41 g of lead tetraacetate in 30 ml of acetic acid, with stirring and heating to 60°, 12 g of the acetal are added dropwise. After 20 min the addition of the acetal is completed and the temperature of the reaction mixture is raised to 70-80°. After 1.5 h the temperature is lowered to 65°, and the reaction mixture is stirred for another 5 h, after which it is cooled. The mineral precipitate is filtered off and washed with ether; the combined organic filtrates are treated with water, and the aqueous layer is extracted with ether. The ether extracts are dried over sodium sulfate, the ether is distilled off, and the residue is distilled in vacuo, collecting the fraction 67-69°/15 mm (3 g), which is the starting acetal, and the fraction 142-145°/15 mm, which proved to be α-,β-acetoxy-β-methoxymethylethyl ketone. Yield 5.2 g (35%, calculated on the acetal that entered into reaction). After redistillation the substance has the following constants: bp 144-145°/15 mm, n_D^{20} 1.4334, d_4^{20} 1.1460.

Found, %: C 49.71; 49.54; H 7.03; 6.94
$C_9H_{14}O_6$. Calculated, %: C 49.52; H 6.47.

Interaction of the ethylene glycol acetal of benzoylacetaldehyde with benzaldehyde. A stream of dry hydrogen chloride is passed for 2-3 min through a mixture of 3 g of the acetal, 5 g of benzaldehyde, and 5 ml of methanol. The reaction mixture becomes strongly heated. After cooling, an abundant precipitate forms in the flask; it is filtered with suction and washed with a small amount of methanol. The yield of β-chloro-β-phenylpropiophenone is almost quantitative, mp 114.5-115.5°.

Found, %: C 73.72; 73.77; H 5.42; 5.49
$C_{15}H_{13}OCl$. Calculated, %: C 73.45; H 5.30.

The substance obtained forms, with hydroxylamine, 3,5-diphenylisoxazoline with mp 74-74.5°.

Literature data for 3,5-diphenylisoxazoline ([12]): mp 73°.

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