E. E. NIFANT' EV, N. V. MOLODOTSOV, L. I. KUDRYASHOV, and N. K. KOCHETKOV

Readily available and reactive -keto acetals,

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Abstract

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E. E. NIFANT' EV, N. V. MOLODOTSOV, L. I. KUDRYASHOV, and N. K. KOCHETKOV

ETHYLENE ACETALS OF α-BROMOAROYLACETALDEHYDES AND THEIR TRANSFORMATIONS

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Readily available and reactive β-keto acetals, $RCO—CH_2CH(OR')_2$, are at present finding ever broader use in synthetic chemistry. Obviously, still broader prospects in this respect are offered by β-keto acetals containing functional groups in the molecule, which have remained almost unknown ([1]). In order to obtain compounds of this type, we have studied the reaction of replacement of the bromine atom in α-bromo-β-keto acetals,

$RCO—CHBr—CH(OR')_2$,

the method of synthesis of which was recently developed by us ([2]). Investigation of halogen-exchange reactions in halogen-substituted β-keto acetals is also of interest from a fundamental point of view, since it makes it possible, at least qualitatively, to compare the mobility of the halogen atom in them with the mobility of halogen in α-haloketones and thereby to assess the influence of the acetal grouping on halogen mobility.

For studying this reaction the most convenient objects proved to be α-bromo-substituted ethylene acetals of the aromatic series, of the type

$$ArCOCHBrCH(OCH_2)_2$$

Compounds of this type were obtained by us by bromination of ethylene acetals of aroylacetaldehydes, the synthesis of which was recently described by us ([3]).

$$ArCOCH_2—CH(OCH_2)_2 \xrightarrow[BaCO_3]{Br_2} ArCOCHBr—CH(OCH_2)_2$$

$$Ar = C_6H_5; \quad n\text{-}Cl—C_6H_4; \quad n\text{-}Br—C_6H_4; \quad n\text{-}NO_2—C_6H_4.$$

Bromination was carried out by the action of bromine in ether in the presence of barium carbonate, similarly to the bromination of β-keto acetals of the aliphatic series ([2]); it can also be effected by the action of bromosuccinimide, but this

variant of the reaction offers no advantages, since with bromination by bromine the reaction proceeds very smoothly and the yields are sufficiently high (about 60%).

The ethylene acetals of α-bromoaroylacetaldehydes obtained are stable crystalline substances, very convenient to work with. On interaction with salts of certain mineral acids, they rather readily exchange their bromine atom, forming the corresponding α-substituted ethylene acetals of aroylacetaldehydes:

$$ArCOCHBrCH(OCH_2)_2 \xrightarrow{MeX} ArCOCHXCH(OCH_2)_2$$

$$X = J, \quad SCN, \quad NO_2 \qquad Ar = C_6H_5; \quad n\text{-Br—}C_6H_4.$$

Thus, with sodium iodide in acetone and with potassium thiocyanate in aqueous acetone, α-iodo- and α-thiocyano-substituted ethylene acetals are obtained smoothly. Replacement of bromine by a nitro group proceeds somewhat more difficultly; however, on heating the bromide with sodium nitrite in dimethylformamide, the substitution reaction could also be carried out, with formation of an α-nitro-β-keto acetal. The compounds obtained are valuable starting materials for the synthesis of certain relatively inaccessible substances. Thus, for example, upon treatment of the ethylene acetal of α-thiocyanobenzoylacetaldehyde with dilute acid at room tem-

on warming it is converted into 4-benzoyl-2-oxythiazole ([4]). Its structure was confirmed by the absence of a reaction for an aldehyde group.

$$C_6H_5CO{-}CH(SCN){-}CH \begin{matrix} O{-}CH_2 \\ O{-}CH_2 \end{matrix} \xrightarrow{H^\circ} C_6H_5CO{-}\boxed{\begin{matrix} S & N \\ & \backslash C / \end{matrix}}{-}OH$$

The interaction of brominated keto acetals with mercaptans proceeds smoothly and without complications. Thus, in the reaction of ethylene acetal of α-bromobenzoylacetaldehyde with sodium benzyl mercaptide in methanol, ethylene acetal of α-benzylthiobenzoylacetaldehyde is formed:

$$C_6H_5COCHBrCH(OCH_2)_2 \xrightarrow{C_6H_5CH_2SH} C_6H_5COCH(S{-}CH_2C_6H_5)CH(OCH_2)_2$$

The structure of the compound obtained was confirmed by its UV spectrum (Fig. 1, *I*), containing absorption bands in the range 240-330 mμ, which is characteristic of compounds containing a benzoyl group.

In contrast, the interaction of the same bromo acetal with sodium phenolate proceeds by another route. When the reaction was carried out in acetone, a complex mixture was obtained from which it was not possible to isolate an individual substance. On the contrary, in methanol sodium phenolate reacts very

smoothly with formation of a crystalline substance whose analysis corresponds to ethylene acetal of β-phenoxy-β-methoxy-α-hydroxydihydrocinnamaldehyde. The indicated compound gives a UV spectrum (Fig. 1, *II*) sharply different from the spectrum of ethylene acetal of benzoylacetaldehyde (Fig. 1, *III*) and of the α-benzylthio-substituted acetal, and contains no characteristic bands at 240–330 mμ. This indicates the absence of a benzoyl group in the compound and confirms its structure. Evidently, the interaction of ethylene acetal of α-bromobenzoylacetaldehyde with sodium phenolate proceeds through an intermediate α-oxide, similarly to what was shown by Temnikova ([5]) for analogous reactions with α-haloketones:

$$C_6H_5COCHBrCH \begin{matrix} O-CH_2 \\ O-CH_2 \end{matrix} \xrightarrow[CH_3OH]{C_6H_5ONa} \left[\begin{matrix} C_6H_5C-CH-CH \\ | \\ OC_6H_5 \quad O \quad \begin{matrix} O-CH_2 \\ O-CH_2 \end{matrix} \end{matrix} \right] \rightarrow$$

$$\rightarrow\ C_6H_5O \underset{OCH_3}{|} -CH \underset{OH}{|} -CH \begin{matrix} O-CH_2 \\ O-CH_2 \end{matrix}$$

The interaction of bromoketo acetals with amines is also complicated by the fact that, besides exchange of the bromine atom, the acetal grouping also enters into the reaction. Thus, on interaction of ethylene acetal of α-bromobenzoylacetaldehyde with piperidine, phenyl-α,β-di-N-piperidylvinyl ketone is formed in high yield:

$$C_6H_5COCHBrCH(OCH_2)_2 \xrightarrow{C_5H_{10}NH} C_6H_5CO-C{=}CH-N-C_5H_{10}$$

$$|\ N-C_5H_{10}$$

The structure of the compound obtained was confirmed by a strong bathochromic shift in the UV spectrum (Fig. 1, *IV*), characteristic of β-aminovinyl ketones ([6]). This complication of the reaction is not unexpected, since the analogous reaction of unsubstituted β-keto acetals with amines is well known ([7]).

In conclusion, it should be noted that the bromine-atom exchange reactions in β-keto acetals studied by us proceed under approximately the same conditions and with the same results as the corresponding reactions with α-bromoketones. Thus, the presence of a neighboring acetal grouping does not exert any noticeable influence on the mobility of the halogen atom.

Experimental Part

Ethylene acetals of α-bromoaroylacetaldehydes

To a mixture of 0.055 mole of the ethylene acetal of aroylacetaldehyde in 150 ml of anhydrous ether and 11.6 g of barium carbonate, with stirring and illumination by a strong lamp, 4.3 ml of bromine are added dropwise over 15 min. After the mixture is decolorized, the precipitate is filtered off, washed thoroughly with ether, and the filtrate

Fig. 1. UV absorption spectrum:

$$I - C_6H_5COCH(SCH_2C_6H_5)CH\begin{matrix}/O-CH_2\\ \backslash O-CH_2\end{matrix}$$

$$II - C_6H_5C\begin{matrix}OCH_3\\ |\\ OC_2H_5\end{matrix} - CH\begin{matrix}OH\\ |\end{matrix} - CH\begin{matrix}/O-CH_2\\ \backslash O-CH_2\end{matrix}$$

$$III - C_6H_5COCH_2CH\begin{matrix}/O-CH_2\\ \backslash O-CH_2\end{matrix}$$

$$IV - C_6H_5CO-C(NC_5H_{10})-CH-N-C_5H_{10}$$

is dried over magnesium sulfate, the ether is distilled off, and the residue, which crystallizes after several days in a refrigerator, is crystallized from methanol. The constants and yields of the substances obtained are given in Table 1.

Table 1

Synthesis of ethylene acetals of α-bromoaroylacetaldehydes

$$ArCOCHBr-CH\begin{matrix}/O-CH_2\\ \backslash O-CH_2\end{matrix}$$

Ar	m.p., °C	Yield, %	C, % found	C, % calcd.	H, % found	H, % calcd.	N, % found	N, % calcd.
C_6H_5	69-70	64	48.77	48.77	48.71	4.20	4.22	4.06	–	–
n-BrC_6H_4	96-97	62	37.54	37.62	37.78	2.91	2.84	2.86	–	–
n-ClC_6H_4	99.5-101	58	43.15		43.25	3.14		3.27	–	–
n-$NO_2C_6H_4$	85-86	54	–		–	–		–	4.39	4.20	4.42

Ethylene acetal of α-iodobenzoylacetaldehyde

5 g of the ethylene acetal of α-bromobenzoylacetaldehyde and 5.1 g of sodium iodide in 10 ml of acetone are heated for 5 hours at 55-60°; sodium bromide is filtered off, the filtrate is poured into water, extracted with ether (2 × 50 ml), the extracts are washed with thiosulfate, dried over magnesium sulfate, and the ether is distilled off. Obtained: 2.4 g (37.5%) of slightly yellowish crystals, m.p. 84-85°.

Found, %: C 41.71; 41.59; H 3.91; 4.08
$C_{11}H_{11}JO_3$. Calculated, %: C 41.53; H 3.49

Ethylene acetal of *n*-bromobenzoyl-α-iodoacetaldehyde

Obtained analogously from 0.75 g of the ethylene acetal and *n*-bromobenzoyl-α-bromoacetaldehyde, 1 g of sodium iodide in 6 ml of acetone. Yield 0.35 g (41%), m.p. 111–111.5°.

$C_{11}H_{10}BrJO_3$.	Found, %:	C 33.43; 33.33; H 7.56; 7.65
	Calculated, %:	C 33.25; H 2.54.

On oxidation of the substance with potassium permanganate in alkaline medium, only *p*-bromobenzoic acid was obtained.

Ethylene acetal of α-rhodanobenzoylacetaldehyde. A solution of 5.4 g of the ethylene acetal of α-bromobenzoylacetaldehyde and 3.9 g of potassium rhodanide in a mixture of 30 ml of acetone and 2.5 ml of water is heated for 4 h at 55–60°, poured into water, extracted with ether (2–50 ml), the extracts are dried over magnesium sulfate, the ether is distilled off, and after recrystallization of the residue from alcohol, 3.25 g (65%) of yellowish crystals with m.p. 74–76° are obtained.

$C_{12}H_{11}NO_3S$.	Found, %:	C 57.97; 57.91; H 4.87; 4.67
	Calculated, %:	C 57.81; H 4.45.

4-Benzoyl-2-oxythiazole. 1 g of the ethylene acetal of benzoyl-α-rhodanoacetaldehyde is stirred for six days with 3 ml of 5% HCl; the precipitate is filtered off and crystallized from 5% HCl. 0.4 g (50%) of colorless plates with m.p. 149–150° is obtained.

$C_{10}H_7NO_2S$.	Found, %:	C 58.90; 58.74; H 3.68; 3.45
	Calculated, %:	C 58.53; H 3.66.

Ethylene acetal of β-methoxy-β-phenoxy-α-oxyhydrocinnamaldehyde. To a solution of 2.7 g of the ethylene acetal of α-bromobenzoylacetaldehyde in 25 ml of methanol is added a mixture (2.8 g of phenol, 1.4 g of caustic potash,

and 1.4 g of potash in 50 ml of methanol). After standing for 3 days at room temperature, the mixture is poured into water and extracted with ether. After the usual work-up, 1.2 g (38%) of colorless needles, m.p. 54–56° (from alcohol), is obtained.

$C_{18}H_{20}O_5$.	Found, %:	C 68.48; 68.38; H 6.5; 6.39
	Calculated, %:	C 68.50; H 6.33.

Ethylene acetal of α-thiobenzoxybenzoylacetaldehyde. To a solution of 2.71 g of the ethylene acetal of α-bromobenzoylacetaldehyde in 10 ml of methanol is added a solution of 1.46 g of sodium benzyl mercaptide in 20 ml of methanol, and the mixture is heated for 4 h with a reflux condenser. After the usual work-up, 1.4 g (45%) of colorless needles with m.p. 67.5–68.5° (from methanol) is obtained.

$C_{18}H_{18}O_3S$.	Found, %:	C 66.92; 66.79; H 5.38; 5.40
	Calculated, %:	C 66.81; H 5.24.

Phenyl-α, β-di-*N*-piperidylvinyl ketone. A solution of 3 g of the ethylene acetal of α-bromobenzoylacetaldehyde in 10 ml of benzene is mixed with 4.8 ml of piperidine and heated for 4 h with a reflux condenser. After cooling of the reaction mixture, the crystals that have separated are filtered off. The principal amount of benzene is distilled off from the mother liquor in vacuo. The crystals that have separated are filtered and recrystallized from ether. 2.9 g (91%) of yellow crystals with m.p. 105–106° is obtained.

$C_{19}H_{26}N_2O$.	Found, %:	C 76.53; 76.49; H 9.06; 8.93
	Calculated, %:	C 76.65; H 8.74.

Moscow State University
named after M. V. Lomonosov

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Note: Figure translations are in progress. See original paper for figures.