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Abstract

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R. Ya. Levina, N. P. Shusherina, and M. Yu. Lur' e

δ-Lactones. Conversion of Dibromides of Unsaturated δ-Lactones into Bromine-Substituted δ-Ketonic Acids and Their Esters

(Presented by Academician A. N. Nesmeyanov, December 3, 1956)

In our previous communication (^{1}), the reaction between the dibromide of an unsaturated δ-lactone—5,6-dibromo-5,6-dimethyltetrahydro-α-pyrone (I)—and water was described for the first time; it was shown that the reaction consists in the addition of water with opening of the lactone ring and elimination of one molecule of hydrogen bromide, and leads to the formation of γ-bromo-γ-acetylvaleric acid (in quantitative yield):

$$\text{unsaturated } \delta\text{-lactone} \xrightarrow{Br_2} \text{5,6-dibromo-5,6-dimethyltetrahydro-}\alpha\text{-pyrone (I)}$$
$$\xrightarrow[-HBr]{+H_2O} CH_3COC(Br)(CH_3)CH_2CH_2COOH$$

The structure of the bromoketonic acid obtained in this way was proved by counter-synthesis—by bromination of γ-acetylvaleric acid with dioxane dibromide.

In the present work it was shown that the reaction between dibromides of unsaturated δ-lactones and water can serve as a general preparative method for obtaining γ- or ϵ-bromine-substituted δ-ketonic acids; the reaction proceeds in the cold, is completed within 0.5–1 hour, and leads to bromoketonic acids in high yields (70–100%, calculated on the starting unsaturated δ-lactone).

In this way, from the corresponding dibromolactones (II)—(V), the following compounds, not described in the literature, were obtained: 4-bromohexan-5-oic acid (VI), yield 70.0%; 6-bromo-4,4-dimethylhexan-5-oic acid (VII), 87.2%; 6-bromo-4,4,6-trimethylheptan-5-oic acid (VIII) (quantitative yield); and 2-bromo-2-[β-carboxyethyl]cyclopentanone (IX), 78%:

$$\text{unsaturated methyl } \delta\text{-lactone} \xrightarrow{Br_2} \text{dibromolactone (II)} \xrightarrow[-HBr]{+H_2O} CH_3COCH(Br)CH_2CH_2COOH \quad \text{(VI)}$$

$$\text{unsaturated dimethylidene-substituted } \delta\text{-lactone} \xrightarrow{Br_2} \text{dibromolactone (III)} \longrightarrow CH_2BrCOC(CH_3)_2CH_2CH_2C$$

$$\text{unsaturated trimethyl-isopropylidene-substituted } \delta\text{-lactone} \xrightarrow{Br_2} \text{dibromolactone (IV)} \longrightarrow CH_3C(Br)(CH_3)CC$$

$$\underset{}{\text{[structural formula]}} \xrightarrow{Br_2} \underset{\text{(V)}}{\text{[structural formula]}} \longrightarrow \underset{\text{(IX)}}{\text{[structural formula]}}$$

Continuing the study of the reactivity of dibromolactones, we have for the first time investigated their reaction with ethyl alcohol; it has been shown that in this case as well there occurs addition of the alcohol with opening of the lactone ring and elimination of one molecule of hydrogen bromide, with formation of the ethyl esters of γ- or ϵ-bromo-substituted δ-keto acids* (X–XIV). The reaction proceeds with strong self-heating and is completed within half an hour; the yields of the esters of bromoketo acids are 40–80%, calculated on the initial unsaturated δ-lactone.

By this reaction—the interaction of dibromolactones (I–V) with ethyl alcohol—there were obtained ethyl esters, not described in the literature, (X–XIV) of the above-mentioned bromoketo acids (ethyl ester XIV, on distillation, eliminates hydrogen bromide and is converted into the ester of the unsaturated keto acid XV):

$$\text{(I)} \quad \xrightarrow[-HBr]{+C_2H_5OH} CH_3COC(Br)(CH_3)CH_2CH_2COOC_2H_5 \qquad \text{(X)}$$

$$\text{(II)} \quad \longrightarrow CH_3COCH(Br)CH_2CH_2COOC_2H_5 \qquad \text{(XI)}$$

$$\text{(III)} \quad \longrightarrow CH_2BrCOC(CH_3)_2CH_2CH_2COOC_2H_5 \qquad \text{(XII)}$$

$$\text{(IV)} \quad \longrightarrow CH_3C(Br)(CH_3)COC(CH_3)_2CH_2CH_2COOC_2H_5 \qquad \text{(XIII)}$$

$$\text{(V)} \quad \longrightarrow \text{[[cyclic bromo keto ester structural formula]]} \qquad \text{(XIV)} \longrightarrow$$

$$\longrightarrow \text{[unsaturated cyclic keto ester structural formula]} \qquad \text{XV} \quad \left(\begin{array}{r} \text{with possible impu} \\ \text{[isomeric unsaturated cyclic keto est} \end{array} \right.$$

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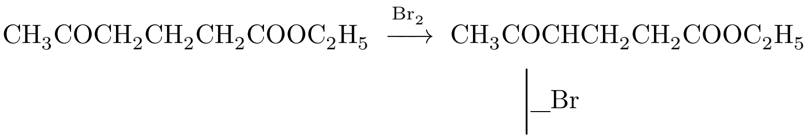
* The behavior of dibromo-δ-lactones in reaction with alcohol recalls, to a certain degree, the behavior of dibromides of complex vinyl ethers; thus, for example, dibromides of enol acetates of ketones, on reaction with alcohols, form α-bromo-substituted ketones (^{2}):

$$\mathrm{C_4H_9CH{=}C(CH_3)OCOCH_3} \xrightarrow{+\mathrm{Br_2}} \mathrm{C_4H_9CHBr{-}CBr(CH_3)OCOCH_3} \xrightarrow[-\mathrm{HBr}]{+\mathrm{CH_3OH}} \mathrm{C_4H_9CHBrCOCH_3} + \mathrm{CH_3COOC}$$

The structure of the esters obtained was proved by a counter-synthesis of one of them: by the action of dioxane dibromide on ethyl γ-acetylbutyrate, ester XI was obtained:



$$\mathrm{CH_3COCH_2CH_2CH_2COOC_2H_5} \xrightarrow{\mathrm{Br_2}} \mathrm{CH_3CO\underset{|\,\_Br}{C}HCH_2CH_2COOC_2H_5}$$

(XI)

Thus, the reaction of dibromides of unsaturated δ-lactones with water and alcohols may serve as a new preparative method for obtaining γ- or ϵ-bromo-substituted δ-keto acids and their esters.

Experimental Part

Dibromolactones. Unsaturated δ-lactones (5,6-dimethyl-3,4-dihydro-α-pyrone[1]; 6-methyl-3,4-dihydro-α-pyrone[3]; 5,5-dimethyl-6-isopropylidene-3,4-dihydro-α-pyrone[4]; 5,5-dimethyl-6-methylene-3,4-dihydro-α-pyrone[4] and 5,6-cyclopentano-3,4-dihydro-α-pyrone[5]) were brominated in ethereal solution with an equimolar amount of bromine at −10 to −15°. After evaporation of the ether in vacuo in a stream of dry air, dibromides were obtained; these were introduced into reaction with water or ethyl alcohol immediately after evaporation of the ether, since on standing they readily split off hydrogen bromide[6].

γ- or ϵ-Bromo-δ-keto acids. Dibromolactones (II)*–(V) were treated with water with vigorous stirring and cooling with ice. The reaction was complete within 0.5–1 hour. The crystalline bromoketo acids formed were filtered off and dissolved in ether; after drying the ethereal solutions and evaporating the ether in vacuo, the bromoketo acids were recrystallized from petroleum ether or benzine. The melting points, yields, and analyses of the bromoketo acids obtained are given in Table 1.

Table 1

Compound	M.p., °C	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
4-Bromohexanone-5-oic acid (VI) (γ-bromo-γ-acetylbutyric acid)	39–41 (without petroleum ether)	70	34.66 34.62	4.56 4.49	34.48	4.35
6-Bromo-4,4-dimethylhexanone-5-oic acid (VII)	75.5–76 (from benzine)	87.2	40.71 40.70	5.45 5.50	40.53	5.65
6-Bromo-4,4,6-trimethylheptanone-5-oic acid (VIII)	48 (from benzine)	quant.	45.32 45.40	6.35 6.50	45.27	6.46
2-Bromo-2-(β-carboxyethyl)cyclopentanone (IX)	55–56 (from ether–petroleum ether mixture)	78	40.74 40.88	4.95 4.96	40.89	4.71

Ethyl esters of γ- or ϵ-bromo-δ-keto acids. To dibromides (I)–(V), with stirring and in the cold, a six- to sevenfold excess of absolute ethyl alcohol was added; the dibromides dissolved completely in the alcohol with strong self-heating. After 30–40 min, the reaction mixture was poured into cold water and the aqueous-alcoholic solution was extracted with ether. The constants, yields, and analyses of the esters obtained (X)–(XIII), after their distillation in vacuo, are given in Table 2.

* The treatment of dibromolactones (II) and (V) with water should be carried out with very vigorous stirring and cooling to –30°; otherwise it is not possible to isolate bromoketo acids (VI) and (IX) in crystalline form because of their further transformations.

Vacuum distillation of the bromo-substituted ester XIV, obtained from dibromolactone V, is accompanied by elimination of hydrogen bromide and leads to the ethyl ester of the unsaturated δ-keto acid XV.

Table 2

Compound	B.p., °C	n_D^{20}	d_4^{20}	MR_D, found	MR_D, calcd.	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Ethyl ester of 4-bromo-4-methylhexan-5-oic acid (X)	134—135 (12 mm)	1,4700	1,3090	53,51	53,37	65	43,24 43,34	6,27 6,15	43,04	6,02
Ethyl ester of 4-bromohexan-5-oic acid (XI)	124—126 (10 mm)	1,4640	1,3352	49,00	49,46	72	40,62 40,90	5,71 5,78	40,53	5,52
Ethyl ester of 6-bromo-4,4-dimethylhexan-5-oic acid (XII)	162—163 (10—12 mm)	1,4749	1,2860	58,03	57,81	80	45,61 45,73	6,35 6,51	45,30	6,46

Compound	B.p., °C	n_D^{20}	d_4^{20}	MR_D, found	MR_D, calcd.	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Ethyl ester of 6-bromo-4,4,6-trimethylheptan-5-oic acid (XIII)	145–147 (8–10 mm)	1,4742	1,2342	66,80	67,04	84	49,43 49,21	7,16 7,13	49,13	7,55
2-(β-Carboxyethyl)cyclopenten-2-one (XV)*	149–150 (10–12 mm)	1,4780	1,0760	47,92	47,37	40	65,49 65,82	7,94 7,95	65,89	7,74

* EM_D 0,55.

Independent synthesis of ethyl ester of 4-bromohexanone-5-oic acid (XI). To 7 g (0.044 mole) of the ethyl ester of γ-acetylbutyric acid (^{3}), with cooling by water, 12 g (0.048 mole) of dioxane dibromide was added in small portions, and the mixture was left for 0.5 h. After removal of dioxane and distillation of the residue in vacuo, 5 g (yield 50%) of ester XI was isolated, b.p. 123–124° at 10 mm, n_D^{20} 1,4650, d_4^{20} 1,3360.

Moscow State University
named after M. V. Lomonosov

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