Synthesis and Some Transformations of 2-Alkenyl-4-alkoxymethylbutanolides

T.V. Kochikyan, M.A. Samvelyan, E.V. Arutyunyan, V.S. Arutyunyan, and A.A. Avetisyan

Yerevan State University, Yerevan, 375025 Armenia

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Abstract—The alkylation of 4-alkoxymethyl-2-ethoxycarbonylbutanolides led to the formation of 2-alkenyl-4-alkoxymethyl-2-ethoxycarbonylbutanolides which at alkaline hydrolysis provided new 2-alkenyl-4-alkoxymethylbutanolides. By oxidation of the latter with a mixture of hydrogen peroxide and formic acid 4-alkoxymethyl-2-(2-R,2,3-dihydroxy)propylbutanolides were obtained. The diololactones were shown to suffer under the conditions of the pinacol-pinacolone rearrangement a conversion into previously unknown formyl- and epoxylactones.

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We formerly demonstrated that 4-alkoxymethyl-2-ethoxycarbonylbutanolides 1a and 1b were active CH-acids, and they were well suitable for application to the fine organic synthesis for preparation of various lactone-containing compounds [1–4]. In extension of research in the field of saturated γ-lactones and aiming at the preparation of new functionally-substituted butanolides we carried out an alkylation of reagents 1a and 1b with alkenyl halides in the presence of an equimolar amount of sodium ethylate in the anhydrous ethanol solution. As a result 2-alkenyl-4-alkoxymethyl-2-ethoxycarbonylbutanolides IIa–IIId were obtained in a high yield (75–90%). The alkaline hydrolysis and decarboxylation of the latter led to the formation of 2-alkenyl-4-alkoxy-methylbutanolides IIIa–IIIId.

The chemistry of α-glycols is sufficiently well understood, but the studies dedicated to heterocyclic α-glycols, in particular, to lactone-containing diols are scarce [5–9].

To synthesize diololactones we attempted an oxidation of reagents IIIa–IIIId with 30% hydrogen peroxide in the presence of 85% formic acid. Thus we obtained 4-alkoxymethyl-2-(2-R,2,3-dihydroxy)propylbutanolides IVa–IVd.

Some reaction of the latter were performed which, on the one hand, confirm the structure of compounds IVa–IVd, and on the other hand, produce new classes of lactone-containing compounds previously unmentioned in the literature.

We investigated the behavior of compounds IVa–IVd under the conditions of the pinacol-pinacolone rearrangement. It was established that in the presence of the
p-toluenesulfonic acid the primary-tertiary diolactones IVc and IVd readily underwent the pinacol-pinacolone rearrangement to give the corresponding aldehydolactones. The reaction occurred regioselectively leading to the formation in a high yield of 2-alkoxymethyl-2-(2-methyl-2-formyl)ethylbutanolides Va and Vb. The reaction of the primary-secondary diolactones IVa and IVb resulted in the formation of epoxylactones, 4-alkoxymethyl-2-(2,3-epoxy)propylbutanolides Vla and Vlb.

The different paths taken by the reaction may be ascribed to the difference in the stability of the carbocation site generated by the action of the p-toluenesulfonic acid. Presumably in the case of the less stable and consequently more reactive secondary carbocation the probability of a hydride shift sharply decreases and as sharply increases the possibility of an attack by the unshared electron pair of the oxygen in the neighboring hydroxy group; as a result form epoxylactones Vla and Vlb. The use of a stronger acid, like sulfuric acid, caused the tarring of the final products.

In order to develop a general procedure for epoxylactones preparation and to prove the structure of compounds Vla and Vlb the diolactones IVa–IVd were converted into the corresponding bromohydrines by treating with N-bromosuccinimide. The reaction should be carried out in aqueous-acetone medium for 4 h. Under these conditions 2-alkoxymethyl-2-(3-bromo-2-hydroxy)propylbutanolides VIIa–VIIId were obtained in high yields. The dehydrobromination of these bromohydrines with sodium alcololate resulted in the target epoxides Vla, Vlb and VIIIa, VIIIb.

Reagents IVa–IVd were easily oxidized with lead tetraacetate giving the corresponding carbonyl compounds. At R’ = H formyllactones obtained, 4-alkoxymethyl-2-formylmethylbutanolides IXa and IXb, were prepared for the first time, whereas at R’ = Me the oxidation led to the formation of 4-alkoxymethyl-2-acetylbutanolides Xa and Xb identical to the ketolactones described in [10].

IX, X: R = Pr (a), Am (b).

Carboxylactones are known to be good synthons for preparation of lactone-containing thioureas and various classes of heterocycles [11–13]. Planning to obtain carbo-
oxylactones of new structure and at the same time to prove the structure of compounds Va, Vb and IXa, IXb the latter were subjected to oxidation under conditions of the Baeyer–Villiger reaction. The reaction was performed with the use of a mixture of 30% aqueous hydrogen peroxide and 85% formic acid. The 4-alkoxymethyl-2-carboxyalkylbutanolides XIA–XID were obtained in high yields. The compounds were quantitatively titrated with 1 equiv of 0.1 N NaOH in the cold and with 2 equiv at heating.

EXPERIMENTAL

IR spectra of compounds II–XI were recorded from thin films on a spectrophotometer Nicolet FTIR Nexus. TLC was carried out on Silufol UV-254 plates, eluent ethanol–benzene–hexane, 3:3:10, for compounds IVa–IVd, 2:1:1, development in iodine vapor.

Initial 4-alkoxymethyl-2-ethoxy carbonyl butanolides were prepared as described in [14].

2-Alkenyl-4-alkoxymethyl-2-ethoxycarboxylbutanolides IIa–IIId. To a solution obtained by dissolving 2.3 g (0.1 mol) of metal sodium in 20 ml of anhydrous ethanol was added dropwise 0.1 mol of an appropriate 4-alkoxymethyl-2-ethoxycarbonylbutanolide. The mixture was stirred for 15 min and then 0.11 mol of alkenyl halide was added dropwise. The reaction mixture was stirred for 2 h without heating and 4 h at 75–80°C. On distilling off the ethanol the residue was cooled, and water was added acidified with HCl to pH 2–3. The products were extracted into ether, the extracts were washed with water and dried with anhydrous magnesium sulfate. On removing the solvent the residue was subjected to distillation.

2-Allyl-4-propoxymethyl-2-ethoxycarbonylbutanolide (IIa). Yield 78%, bp 121–122°C (1 mm Hg), Rf 0.49, nD 1.4585, d4 1.0639. Found, %: C 62.40; H 8.00. C14H22O5. Calculated, %: C 62.22; H 8.15.

2-Allyl-4-amlyoxymethyl-2-ethoxycarbonylbutanolide (IIb). Yield 90%, bp 133–134°C (1 mm Hg), Rf 0.54, nD 1.4590, d4 1.0357. Found, %: C 64.55; H 8.60. C16H26O5. Calculated, %: C 64.43; H 8.72.

2-Methyl-2-propenyl-4-propoxymethyl-2-ethoxycarboxybutanolate (IIC). Yield 81%, bp 133°C (2 mm Hg), Rf 0.46, nD 1.4600, d4 1.0644. Found, %: C 63.20; H 8.60. C15H24O5. Calculated, %: C 63.38; H 8.45.

2-Methyl-2-propenyl-4-amyloxy methyl-2-ethoxy carbonylbutanolate (IIId). Yield 75%, bp 150°C (2 mm Hg), Rf 0.50, nD 1.4595, d4 1.0314. Found, %: C 65.25; H 9.00. C17H32O5. Calculated, %: C 65.38; H 8.97.

In the IR spectra of compounds IIa–IIId the following absorption bands were observed (cm⁻¹): 1760 (C=O lactone), 1725 (C=O ester), 1640 (C=C), 1190, 1210 (COC), 3080 (≈CH2).

2-Alkenyl-4-alkoxymethylbutanolides IIIa–IIIId. To a solution in 16 ml of water of 7 g (0.175 mol) of sodium hydroxide and 0.5 ml of Katamine AB was added dropwise 0.05 mol of reagent IIa–IIId, the mixture was stirred for 1 h at 20–25°C and 2 h at 55–60°C. On cooling the mixture was acidified with conc. HCl to pH 2–3, extracted with ether, the extracts were washed with water and dried with anhydrous magnesium sulfate. On removing the solvent the residue was subjected to distillation.

2-allyl-4-propoxymethylbutanolate (IIIa). Yield 87%, bp 92–93°C (2 mm Hg), Rf 0.47, nD 1.4533, d4 1.0022. Found, %: C 66.80; H 8.95. C11H16O3. Calculated, %: C 66.67; H 9.09.

2-Allyl-4-amlyoxymethylbutanolate (IIIB). Yield 92%, bp 110–112°C (2 mm Hg), Rf 0.49 nD 1.4580, d4 0.9782. Found, %: C 68.95; H 9.85. C13H22O3. Calculated, %: C 69.03; H 9.74.

2-Methyl-2-propenyl-4-propoxymethylbutanolate (IIIC). Yield 85%, bp 100°C (2 mm Hg), Rf 0.44, nD 1.4590, d4 0.9976. Found, %: C 68.05; H 9.30. C15H20O3. Calculated, %: C 67.92; H 9.43.

2-Methyl-2-propenyl-4-amyloxymethylbutanolate (IIID). Yield 90%, bp 111–112°C (1 mm Hg), Rf 0.48, nD 1.4585, d4 0.9744. Found, %: C 70.15; H 9.90. C15H22O3. Calculated, %: C 70.00; H 10.00.

In the IR spectra of compounds IIIa–IIId the following absorption bands were observed (cm⁻¹): 1765 (C=O lactone), 1640 (C=C), 1190, 1210 (COC), 3080 (≈CH2).

4-Alkoxymethyl-2-(2,3-dihydroxy)propylbutanolides IVa–IVd. A mixture of 0.53 mol of reagent IIIa–IIId, 2.9 ml (0.063 mol) of 85% formic acid, and 8.7 ml of 30% hydrogen peroxide was stirred for 3 h at 20–25°C and 17 h at 55–60°C. Water and formic acid were removed at a reduced pressure (15–20 mm Hg), and the residue was distilled in a vacuum.

2-(2,3-Dihydroxy)propyl-4-propoxymethylbutanolate (IVA). Yield 77%, bp 195–196°C (2 mm Hg), Rf 0.48, nD 1.4760, d4 1.1489. Found, %: C 56.55; H 8.75. C17H32O5. Calculated, %: C 56.69; H 8.62.
4-Amyloxymethyl-2-(2,3-dihydroxy)propylbutanolid (IVb). Yield 83%, bp 211–212°C (2 mm Hg), $R_f$ 0.50, $n_D^{20}$ 1.4750, $d_4^{20}$ 1.1091. Found, %: C 60.15; H 9.10. C$_{13}$H$_{20}$O$_5$. Calculated, %: C 60.00; H 9.23.

2-(2-Methyl-2,3-dihydroxy)propyl-4-propoxy-methylbutanolid (IVc). Yield 72%, bp 200–201°C (2 mm Hg), $R_f$ 0.51, $n_D^{20}$ 1.4765, $d_4^{20}$ 1.1182. Found, %: C 58.65; H 8.80. C$_{13}$H$_{22}$O$_5$. Calculated, %: C 58.54; H 8.94.

4-Amyloxymethyl-2-(2-methyl-2,3-dihydroxy)propylbutanolid (IVd). Yield 74%, bp 199–200°C (1 mm Hg), $R_f$ 0.53, $n_D^{20}$ 1.4710, $d_4^{20}$ 1.0825. Found, %: C 60.30; H 9.50. C$_{14}$H$_{26}$O$_5$. Calculated, %: C 60.43; H 9.35.

In the IR spectra of compounds IV the following absorption bands were observed (cm$^{-1}$): 1760 (C=O lactone), 1145, 1190 (COC), 3415 (OH-associated).

2-(2-Methyl-2-formyl)ethyl-4-propoxy-methylbutanolid (Va). A mixture of 12.3 g (0.05 mol) of compound IVc, 0.5 g of p-toluenesulfonic acid, and 100 ml of benzene was boiled with a Dean–Stark trap till the end of water liberation (4h), then the mixture was cooled, washed with water, and dried with anhydrous magnesium sulfate. On removing the solvent the residue was subjected to distillation. Yield 8.3 g (73%), bp 141°C (1 mm Hg), $R_f$ 0.48, $n_D^{20}$ 1.4610, $d_4^{20}$ 1.0597. Found, %: C 63.25; H 8.65. C$_{13}$H$_{25}$O$_5$. Calculated, %: C 63.16; H 8.77. Thiosemicarbazone: mp 101–102°C.

Likewise was obtained 4-amyloxymethyl-2-(2-methyl-2-formyl)ethylbutanolid (Vb). Yield 78%, bp 160–161°C (1 mm Hg), $R_f$ 0.45, $n_D^{20}$ 1.4615, $d_4^{20}$ 1.0319. Found, %: C 65.75; H 9.15. C$_{14}$H$_{24}$O$_4$. Calculated, %: C 63.63; H 8.77. Thiosemicarbazone: mp 112–113°C.

In the IR spectra of compounds Va and Vb the following absorption bands were observed (cm$^{-1}$): 1770 (C=O lactone), 1725 (C=O aldehyde), 2735 (C=H aldehyde), 1130, 1180 (COC).

4-Propoxy-methyl-2-(2,3-epoxypropyl)butanolid (VIa) was similarly prepared from 9.3 g (0.04 mol) of 4-propoxy-methyl-2-(2,3-dihydroxy)propylbutanolid, 0.4 g of p-toluenesulfonic acid, and 80 ml of benzene. Yield 6.3 g (69%), bp 139–140°C (1 mm Hg), $R_f$ 0.49, $n_D^{20}$ 1.4600, $d_4^{20}$ 1.0589. Found, %: C 65.75; H 9.15. C$_{12}$H$_{20}$O$_4$. Calculated, %: C 63.16; H 8.77.

Likewise was obtained 4-amyloxymethyl-2-(2,3-epoxypropyl)butanolid (Vib). Yield 69%, bp 139–140°C (1 mm Hg), $R_f$ 0.49, $n_D^{20}$ 1.4600, $d_4^{20}$ 1.0589. Found, %: C 65.75; H 9.15. C$_{12}$H$_{20}$O$_4$. Calculated, %: C 63.16; H 8.77.

4-Alkoxy-methyl-2-(2-R-2-hydroxy-3-bromo)propylbutanolides VIIa–VIIId. A mixture of 0.05 mol of an appropriate 4-alkoxy-methyl-2-substituted butanolid, 13.4 g (0.075 mol) of N-bromosuccinimide, 10 ml of acetone, and 15 ml of water was stirred for 1 h at 20–25°C and 4 h at 55–60°C. Acetone was distilled off, the residue was cooled, extracted with ether, the extracts were washed with water and dried with anhydrous magnesium sulfate. On removing the solvent the residue was subjected to distillation.

2-(3-Bromo-2-hydroxy-2-methylpropyl)-4-propoxy-methylbutanolid (VIIa). Yield 68%, bp 163–165°C (1 mm Hg), $R_f$ 0.51, $n_D^{20}$ 1.4920, $d_4^{20}$ 1.3222. Found, %: C 46.70; H 6.70; Br 26.00. C$_{15}$H$_{21}$O$_4$Br. Calculated, %: C 46.60; H 6.80; Br 25.89.

4-Amyloxymethyl-2-(3-bromo-2-hydroxy-2-methylpropyl)butanolid (VIIb). Yield 65%, bp 175–176°C (1 mm Hg), $R_f$ 0.50, $n_D^{20}$ 1.4935, $d_4^{20}$ 1.2734. Found, %: C 50.00; H 7.30; Br 23.65. C$_{14}$H$_{25}$O$_4$Br. Calculated, %: C 49.85; H 7.42; Br 23.74.

2-(3-Bromo-2-hydroxypropyl)-4-propoxy-methylbutanolid (VIIc). Yield 70%, bp 154–155°C (1 mm Hg), $R_f$ 0.52, $n_D^{20}$ 1.4910, $d_4^{20}$ 1.3468. Found, %: C 44.85; H 6.30; Br 27.00. C$_{11}$H$_{19}$O$_4$Br. Calculated, %: C 44.75; H 6.44; Br 27.12.

4-Amyloxymethyl-2-(3-bromo-2-hydroxypropyl)butanolid (VIIId). Yield 67%, bp 168–169°C (1 mm Hg), $R_f$ 0.49, $n_D^{20}$ 1.4925, $d_4^{20}$ 1.2905. Found, %: C 48.40; H 7.05; Br 24.15. C$_{13}$H$_{25}$O$_4$Br. Calculated, %: C 48.30; H 7.12; Br 24.77.

In the IR spectra of compounds VIIa–VIIId the following absorption bands were observed (cm$^{-1}$): 1765 (C=O lactone), 1145, 1190 (COC), 3400 (OH), 920 (C=Br).

4-Alkoxy-methyl-2-(2-R,2,3-epoxy)propylbutanolides VIIa, VIIb, VIIIa, and VIIIb. To sodium ethylate prepared from 0.5 g (0.02 mol) of metal sodium and 8.5 ml of anhydrous EtOH was added 10 ml of anhydrous benzene and then dropwise 0.02 mol of bromohydrin VIIa–VIIId in 50 ml of anhydrous benzene. The mixture was stirred for 10 h at 20–25°C and 1 h at 50–55°C. On cooling water acidified with HCl was added to the reaction mixture, the products were extracted into benzene, the extracts were washed with water and dried with anhydrous magnesium sulfate. On removing the solvent the residue was subjected to distillation.
In the IR spectra of compounds VI and VIII the following absorption bands were observed (cm⁻¹): 1780 (C=O lactone), 1130, 1180 (COC).

2-(2-Epoxypropyl)-4-propoxymethylbutanolid (VIA). Yield 69%, bp 135–136°C (1 mm Hg), \( R_0 0.54, n_1 1.4760, d_4^{20} 1.1263 \). Found, %: C 67.20; H 8.55. \( C_{11}H_{18}O_4 \) Calculated, %: C 67.29; H 8.41.

4-Amyloxymethyl-2-(2-epoxypropyl)butanolid (VIB). Yield 73%, bp 147°C (1 mm Hg), \( R_0 0.53, n_1 1.4765, d_4^{20} 1.0859 \). Found, %: C 64.55; H 8.95. \( C_{13}H_{22}O_4 \) Calculated, %: C 64.46; H 9.09.

2-(2-Methyl-2,3-epoxypropyl)-4-propoxymethylbutanolid (VIIA). Yield 87%, bp 148–149°C (1 mm Hg), \( R_0 0.56, n_1 1.4765, d_4^{20} 1.1102 \). Found, %: C 63.30; H 8.90. \( C_{12}H_{22}O_4 \) Calculated, %: C 63.16; H 8.77.

4-Amyloxymethyl-2-(2-methyl-2,3-epoxypropyl)butanolid (VIIIB). Yield 71%, bp 166–167°C (1 mm Hg), \( R_0 0.55, n_1 1.4770, d_4^{20} 1.0784 \). Found, %: C 65.80; H 9.65. \( C_{14}H_{24}O_4 \) Calculated, %: C 65.63; H 9.38.

4-Propoxymethyl-2-formylmethylbutanolid (IXA). To a solution of 9.3 g (0.04 mol) of compound IVA in 100 ml of anhydrous benzene was added by portions 17.7 g (0.04 mol) of lead tetraacetate, the mixture was stirred for 4 h, filtered, and on removal of the solvent the residue was distilled. Yield 5.4 g (67%), bp 129–130°C (1 mm Hg), \( R_0 0.51, n_1 1.4595, d_4^{20} 1.1012 \). Found, %: C 60.10; H 7.90. \( C_{10}H_{16}O_4 \) Calculated, %: C 60.00; H 8.00. Thiosemicarbazone: mp 85–86°C.

Likewise was obtained 4-amyloxymethyl-2-formylmethylbutanolid (IXB). Yield 69%, bp 139–140°C (1 mm Hg), \( R_0 0.49, n_1 1.4600, d_4^{20} 1.0589 \). Found, %: C 65.75; H 9.15. \( C_{12}H_{24}O_4 \) Calculated, %: C 63.16; H 8.77. Thiosemicarbazone: mp 81–82°C.

In the IR spectra of compounds IXA and IXB the following absorption bands were observed (cm⁻¹): 1780 (C=O lactone), 1730 (C=O aldehyde), 2750 (C=H aldehyde), 1130, 1180 (COC).

2-Acetyl-4-propoxymethylbutanolid (X). was prepared analogously from 11.6 g (0.05 mol) of compound IVc, and 22.2 g (0.05 mol) of lead tetraacetate. Yield 8 g (75%), bp 135°C (2 mm Hg), \( R_0 0.48, n_1 1.4585 \) [10].

Likewise was obtained 4-amyloxymethyl-2-acetomethylbutanolid (XB). Yield 82%, bp 129–130°C (1 mm Hg), \( R_0 0.53, n_1 1.4565 \) [10].

3-(5-Alkoxymethyl-2-oxotetrahydro-3-furyl)propanoic acids XIA–XII. To a mixture of 0.05 mol of aldehdydolactone Va, Vb, or IXA, IXB and 25 ml of 85% formic acid was added dropwise at stirring 7.5 ml of 30% hydrogen peroxide solution. The mixture was stirred for 4 h at 20–25°C and 8 h at 50–55°C. Water and formic acid were removed at a reduced pressure (15–20 mm Hg), and the residue was distilled in a vacuum.

2-Methyl-3-(2-oxo-3-propoxymethyltetrahydro-3-furyl)propanoic acid (XIA). Yield 76%, bp 181–182°C (1 mm Hg), \( n_1 1.4615, d_4^{20} 1.1103 \). Found, %: C 59.20; H 8.35. \( C_{12}H_{20}O_5 \) Calculated, %: C 59.02; H 8.20.

3-(5-Amyloxymethyl-2-oxotetrahydro-3-furyl)-2-methylpropanoic acid (XIB). Yield 72%, bp 195°C (1 mm Hg), \( n_1 1.4630, d_4^{20} 1.0793 \). Found, %: C 61.85; H 9.00. \( C_{14}H_{23}O_5 \) Calculated, %: C 61.76; H 9.82.

2-(Ox-5-propoxymethyltetrahydro-3-furyl)propanoic acid (XIC). Yield 80%, bp 166°C (1 mm Hg), \( n_1 1.4660, d_4^{20} 1.1683 \). Found, %: C 55.70; H 7.30. \( C_{10}H_{16}O_5 \) Calculated, %: C 55.55; H 7.41.

2-(5-Amyloxymethyl-2-oxotetrahydro-3-furyl)propanoic acid (XID). Yield 81%, bp 178°C (1 mm Hg), \( n_1 1.4655, d_4^{20} 1.1129 \). Found, %: C 59.00; H 8.10. \( C_{12}H_{20}O_5 \) Calculated, %: C 59.02; H 8.20.

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