# SYNTHESIS OF ALKYL-SUBSTITUTED 2-HALO-4-AMINOMETHYL-2-BUTEN-4-OLIDES

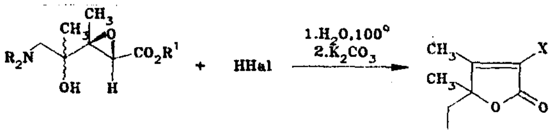
V. I. Tyvorskii, I. G. Tishchenko,
A. S. Kukharev, E. V. Yushkevich,
and S. F. Vlasov

UDC 547.724'466.3.07:543.422

The reaction of esters of alkyl-substituted (E)-5-amino-4-hydroxy-2,3,epoxyvaleric acids with some hydrohalic acids gave the corresponding 2-halo-4-aminomethyl-2-buten-4-olides, the hydrochlorides of which have diuretic activity.

Functional derivatives of unsaturated γ-lactones [1, 2], particularly γ-heteromethyl-substituted butenolides [3], are widely used in organic synthesis and are substances with high biological activity. A promising approach to the synthesis of this class of compounds on the basis of epoxy carboxylic acid derivatives (chiefly 4,5-epoxy-2-alkenoic acid esters) has been developed in recent years [3-6].

In the present research we have shown that (E)-5-dialkylamino-4-hydroxy-3,4-dimethyl-2,3-epoxyvaleric acid esters I-IV, which were obtained by the method that we described in [7], form the previously unknown N,N-disubstituted 2-halo-3,4-dimethyl-4-aminomethyl-2-buten-4-olides VI-XIII (Table 1) in 40-70% yields when they are heated with excess hydrochloric or hydrobromic acid.



Ia-c,II-V

VI-XIV

Ia–c, VI, X R=$CH_3$; II, VII, XI R—R=$(CH_2)_4$; III, VIII, XII R—R=$(CH_2)_6$; IV, IX, XIII R—R=$(CH_2)_2O(CH_2)_2$; V, XIV R—R=$(CH_2)_5$; Ia R$^1$=$C_2H_5$; Ib, II—V R$^1$==$CH(CH_3)_2$; Ic R$^1$=$C(CH_3)_3$; Hal=Cl, Br, I; VI—IX X=Cl,X—XIII X=Br, XIV X=H

The conversion of esters I-IV to lactones VI-XIII probably proceeds via the addition of the hydrogen halide to the oxirane ring and subsequent lactonization and dehydration of the intermediate halohydrin. It should be noted that butenolide VI is formed from isopropyl ester Ib in substantially higher yield than from ethyl and tert-butyl esters Ia and Ic under identical conditions (see Table 1). This is possibly associated with the relatively high rates of hydrolysis of esters Ia,c [8], which competes with opening of the epoxy ring.

The reaction of esters I-V with hydriodic acid under similar conditions is accompanied by considerable resinification of the reaction mixture and reductive processes. Thus, instead of the expected iodo-substituted analog of VI-XIII, 3,4-dimethyl-4-piperidinomethyl-2-buten-4-olide (XIV) (Table 1) was obtained in low yield as a result of the reaction of isopropyl 5-piperidino-4-hydroxy-3,4-dimethyl-2,3-epoxyvalerate (V) with HI.

The IR spectra of VI-XIV are characteristic for unsaturated γ-lactones and contain intense absorption bands of a carbonyl group at 1770-1780 $cm^{-1}$ and a C—O bond at 1000-1030 $cm^{-1}$, as well as a weak absorption band of a C=C bond at 1650 $cm^{-1}$. A peculiarity of the PMR spectra of butenolides VI-XIV (Table 2) is the significant difference in the chemical shifts of the protons of the methyl groups due to the deshielding effect of the C=C bond on the 3-$CH_3$ group. The signal of the 4-$CH_2$ group is observed in the form of a quartet with $J_{gem}$ = 14 Hz or a broad singlet. In contrast to halo-substituted lactones VI-XIII, the PMR spectrum of lactone XIV contains a quartet at weak field of the 2-H proton, which couples with the 3-$CH_3$ group.

---

V. I. Lenin Belorussian State University, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1471-1474, November, 1985. Original article submitted July 20, 1984.

0009-3122/85/2111-1210$09.50

TABLE 1. Physicochemical Characteristics of VI-XIV and Their Hydrochlorides

| Compound | mp, °C | Found, % | | | | Empirical formula | Calculated, % | | | | Yield, % | Hydrochlorides | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | Hal | N | | C | H | Hal | N | | mp, °C | Cl found, %* | empirical formula | Cl calculated, % |
| VI | 41—42 | 53,2 | 6,8 | 17,5 | 6,7 | $C_9H_{14}ClNO_2$ | 53,1 | 6,9 | 17,4 | 6,8 | 58† | 192 | 14,5 | $C_9H_{14}ClNO_2 \cdot HCl$ | 14,7 |
| VII | 74 | 57,7 | 7,1 | 15,3 | 6,0 | $C_{11}H_{16}ClNO_2$ | 57,5 | 7,0 | 15,4 | 6,1 | 57 | 201 | 13,5 | $C_{11}H_{16}ClNO_2 \cdot HCl$ | 13,3 |
| VIII | 37 | 60,2 | 8,0 | 13,8 | 5,3 | $C_{13}H_{20}ClNO_2$ | 60,5 | 7,8 | 13,8 | 5,4 | 42 | 187—188 | 12,0 | $C_{13}H_{20}ClNO_2 \cdot HCl$ | 12,1 |
| IX | 47 | 53,6 | 6,5 | 14,6 | 5,5 | $C_{11}H_{16}ClNO_3$ | 53,8 | 6,6 | 14,4 | 5,7 | 54 | 200 | 12,8 | $C_{11}H_{16}ClNO_3 \cdot HCl$ | 12,6 |
| X | 51—52 | 43,7 | 5,8 | 32,2 | 5,7 | $C_9H_{14}BrNO_2$ | 43,6 | 5,7 | 32,2 | 5,6 | 58 | 216 | 12,4 | $C_9H_{14}BrNO_2 \cdot HCl$ | 12,5 |
| XI | 78 | 48,4 | 5,8 | 29,3 | 4,8 | $C_{11}H_{16}BrNO_2$ | 48,2 | 5,9 | 29,2 | 5,1 | 59 | 207 | 11,7 | $C_{11}H_{16}BrNO_2 \cdot HCl$ | 11,4 |
| XII | 62 | 52,0 | 6,8 | 26,3 | 4,5 | $C_{13}H_{20}BrNO_2$ | 51,7 | 6,7 | 26,4 | 4,6 | 40 | 184—185 | 10,6 | $C_{13}H_{20}BrNO_2 \cdot HCl$ | 10,5 |
| XIII | 50 | 45,4 | 5,6 | 27,8 | 4,7 | $C_{11}H_{16}BrNO_3$ | 45,5 | 5,6 | 27,5 | 4,8 | 73‡ | 210 | 10,8 | $C_{11}H_{16}BrNO_3 \cdot HCl$ | 10,9 |
| XIV | 56—57 | 68,8 | 8,8 | | 6,5 | $C_{12}H_{19}NO_2$ | 68,8 | 9,1 | | 6,7 | 15 | | | | |

---

*Data on the mercurometric determination of ionically bonded chlorine are presented.

†The yields of lactone VI were 30% and 32%, respectively, when esters Ia and Ic were used.

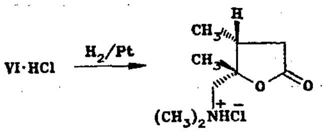
‡This yield is based on the hydrochloride, which was obtained by passing HCl into the ether extracts from the reaction mixture after it was treated with potassium carbonate.

TABLE 2. Data from the PMR Spectra of Butenolides VI-XIV

| Compound | δ, ppm | | | |
|---|---|---|---|---|
| | 3-$CH_3$ (s) | 4-$CH_3$ (s) | 4-$CH_2$ (dd, $J$=14 Hz) | $R_2N$ and other protons |
| VI | 2,00 | 1,33 | 2,37; 2,68 | 2,20 (6H, s, $2CH_3$) |
| VII | 2,00 | 1,35 | 2,73 br s | 1,46—1,84 (4H, m, $2CH_2$); 2,23—2,63 (4H, m, $CH_2NCH_2$) |
| VIII | 2,00 | 1,38 | 2,80; 2,95 | 1,52 (8H, br s, $4CH_2$); 2,60—2,87 (4H, m, $CH_2NCH_2$) |
| IX | 1,96 | 1,33 | 2,26; 2,56 | 2,20—2,60 (4H, m, $CH_2NCH_2$); 3,33—3,60 (4H, m $CH_2OCH_2$) |
| X | 2,00 | 1,33 | 2,41; 2,71 | 2,22 (6H, s., $2CH_3$) |
| XI | 1,93 | 1,30 | 2,70 br s | 1,45—1,80 (4H, m, $2CH_2$); 2,28—2,62 (4H, m, $CH_2NCH_2$) |
| XII | 1,90 | 1,28 | 2,65; 2,90 | 1,40 (8H, br s, $4CH_2$); 2,40—2,73 (4H, m., $CH_2NCH_2$) |
| XIII | 1,95 | 1,38 | 2,41; 2,71 | 2,33—2,48 (4H, m, $CH_2NCH_2$); 3,40—3,63 (4H, m., $CH_2OCH_2$) |
| XIV | 1,93 br s | 1,26 | 2,28; 2,56 | 1,20—1,63 (6H, m, $3CH_2$); 2,22—2,40 (4H, m, $CH_2NCH_2$); 5,53 (1H, q, $J$=1,5Hz, 2-H) |

The mass spectra of VI-XIII are characteristic for monohalo-substituted derivatives. The molecular-ion peak ($M^+$) is of low intensity and is accompanied in all cases by an $[M + 2]^+$ peak; the intensity of the latter for chloro-substituted lactones VI-IX is approximately one third the intensity of the $M^+$ peak. The intensities of the peaks of these ions are approximately equal for bromo derivatives X-XIII. The most intense peaks in the mass spectra of butenolides VI-XIII correspond to $[R_2NCH_2]^+$ ions and have m/z values of 58, 84, 100, and 112 (for $R_2N$ = dimethylamino, pyrrolidino, morpholino, and homopiperidino, respectively).

In order to confirm the structure of lactones VI-XIII we realized the hydrogenation of the hydrochloride of VI in the presence of platinum dioxide. We found that in this case, in addition to the addition of hydrogen to the C=C bond on the side of the 4-$CH_3$ group, which is less bulky than the protonated dimethylaminomethyl group, the C—Cl bond undergoes hydrogenolysis, which leads to the formation in 83% yield of (Z)-3,4-dimethyl-4-dimethylaminomethylbutan-4-olide hydrochloride (XV), which we previously synthesized via another method [9]:



XV

We obtained the hydrochlorides of 2-halo-4-aminomethyl-2-buten-4-olides VI-XIII and studied their toxicities and diuretic and cardiotropic activity. A study of the acute toxicity in white mice in the case of intravenous administration showed that the indicated compounds differ appreciably with respect to the $LD_{50}$ index, which ranges from 66.8 mg/kg (VIII hydrochloride) to 306.9 mg/kg (XIII hydrochloride). In experiments with white rats it was established that all of the investigated VI-XIII hydrochlorides have pronounced diuretic activity that is comparable in magnitude to the effect of the known diuretic agent furosemide. Experiments conducted on the isolated heart of a frog did not reveal cardiotropic activity for X. This makes it possible to assume that the diuretic activity of the investigated compounds is associated with a direct effect on the functional state of the kidneys.

## EXPERIMENTAL

The IR spectra of solutions (0.1 mole/liter) of the substances in $CCl_4$ (layer thickness 0.01 cm) were recorded with a Specord 75-IR spectrometer. The PMR spectra of solutions in $CCl_4$ were measured with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with a Varian MAT-311 spectrometer with a system for direct introduction of the samples at an ion-source temperature of 100-150°C and an ionizing-electron energy of 70 eV. The course of the reaction and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on activity II $Al_2O_3$ with development by iodine vapors.

Esters I-V were obtained by the method in [7].

2-Halo-3,4-dimethyl-4-dialkylaminomethyl-2-buten-4-olides VI-XIII. A solution of 30 mmole of ester I-IV in 15 ml (175 mmole) of 36% HCl or 20 ml (175 mmole) of 48% HBr was refluxed for 5 h, after which it was saturated with hydrogen chloride or, respectively, 10 ml of 48% HBr was added, and the mixture was refluxed for 5 h. It was then treated with a saturated solution of potassium carbonate until the liberation of carbon dioxide ceased, and the mixture was extracted with ether. The extract was dried with sodium sulfate, the ether was evaporated *in vacuo*, and the residue was crystallized from hexane—isopropyl alcohol (10:1). Mass spectra, m/z (relative intensity, %): VI: $[M + 2]^+$ 205 (1), $M^+$ 203 (3), 188 (1), 161 (1), 159 (3), 147 (2), 145 (6), 124 (4), 108 (2), 100 (7), 96 (6), 67 (20), 65 (12), 59 (32), 58 (100), 57 (27), 44 (24), 43 (45), 42 (43); IX: $[M + 2]^+$ 247 (1), $M^+$ 245 (3), 149 (6), 147 (4), 146 (4), 145 (8), 102 (8), 101 (45), 100 (100), 99 (7), 98 (43), 78 (8), 72 (37), 70 (41), 60 (9), 59 (50), 58 (25), 57 (53), 44 (27), 43 (45), 42 (46), 41 (37); X: $[M + 2]^+$ 249 (3), $M^+$ 247 (3), 205 (4), 203 (5), 189 (3), 187 (3), 149 (6), 124 (15), 108 (6), 100 (10), 96 (8), 67 (25), 65 (10), 59 (36), 58 (100), 57 (32), 44 (22), 43 (40), 42 (42). The hydrochlorides of VI-XIII were obtained by passing HCl into solutions of lactones VI-XIII in dry ether; the precipitates were separated and crystallized from acetone—methanol (2:1).

3,4-Dimethyl-4-piperidinomethyl-2-buten-4-olide (XIV). This compound was similarly obtained by the reaction of 57% HI on ester III. The residue remaining after removal of the solvent from the ether extracts was chromatographed with a column packed with activity II $Al_2O_3$ by elution with ether—hexane (5:1) with collection of the fraction with $R_f$ 0.82. Lactone XIV was crystallized from hexane.

(Z)-3,4-Dimethyl-4-dimethylaminomethylbutan-4-olide (XV). A solution of 3.0 g (12.5 mmole) of the hydrochloride of amine VI in 25 ml of absolute methanol was stirred in a hydrogen atmosphere in the presence of 0.1 g of platinum dioxide until 610 ml (25.0 mmole; 745 mm, 18°C) of $H_2$ had been absorbed, after which the catalyst was removed by filtration, the methanol was removed by distillation, and the residue was crystallized from acetone—methanol (10:1) to give 2.1 g (83%) of the hydrochloride of XV with mp 182°C. Free base XV was isolated by the action of potassium carbonate on an aqueous solution of the hydrochloride and subsequent extraction with ether. The ether was removed, and the residue was distilled in vacuo with collection of the fraction with bp 66°C (3 mm) and $n_D^{20}$ 1.4553. PMR spectrum: 0.92-1.26 (1H, m, 3-H), 0.98 (3H, d, J = 7 Hz, $3\text{-}CH_3$), 1.11 (3H, s, $4\text{-}CH_3$), 2.02-2.64 (4H, m, $2CH_2$), and 2.22 ppm [6H, s, $N(CH_3)_2$]. Compound XV was identical to the compound obtained by the method in [9] with respect to its PMR spectrum and the melting point observed for a mixture of hydrochlorides of the samples.

## LITERATURE CITED

1. A. A. Avetisyan and M. T. Dangyan, Usp. Khim., 46, 1250 (1977).
2. Y. S. Rao, Chem. Rev., 76, 625 (1976).
3. J. Cardellach, C. Estopa, J. Font, M. Moreno-Manas, R. M. Ortuno, F. Sanchez-Ferrando, S. Valle, and L. Vilamajo, Tetrahedron, 38, 2377 (1982).
4. N. Bensel, J. Höhn, H. Marschall, and P. Weyerstahl, Chem. Ber., 112, 2256 (1979).
5. H. Orszanska, K. Witkewicz, and Z. Chabudzinski, Pol. J. Chem., 54, 45 (1980).
6. G. Van de Löcht, H. Marschall, and P. Weyerstahl, Ann. Chem., No. 6, 1150 (1982).
7. L. S. Stanishevskii, I. G. Tishchenko, V. I. Tyvorskii, L. A. Khil'manovich, A. S. Zakharevskii, and A. V. Miklevich, Khim. Geterotsikl. Soedin., No. 11, 1443 (1973).
8. C. K. Ingold, Theoretical Foundations of Organic Chemistry [Russian translation], Mir, Moscow (1973), p. 957.
9. L. S. Stanishevskii, I. G. Tishchenko, V. I. Tyvorskii, and L. A. Khil'manovich, Khim. Geterotsikl. Soedin., No. 5, 594 (1975).