

## 2-Amino-2-oxazolines, IV:

## Kurzmitteilung:

## Reactions with Bromo Esters, Synthesis of Some 3-Carboxyalkyl-2-imino-oxazolidines

## 2-Amino-2-oxazoline, 4. Mitt.: Reaktionen mit Bromestern, Synthese einiger 3-Carboxyalkyl-2-imino-oxazolidine

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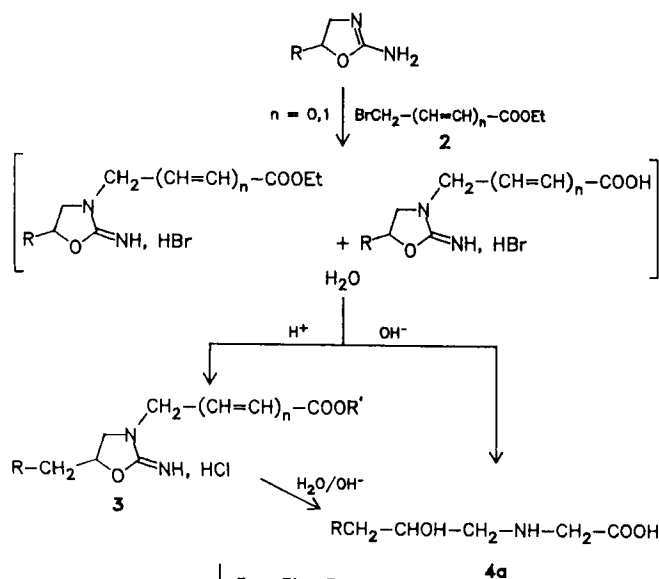
Heterocyclic systems having a five membered ring fused with another ring including a bridgehead N are widely described for their pharmacological activity<sup>1-5</sup>. A common method for the synthesis of these fused heterocyclic systems is the alkylation of heterocyclic amines having an amino group at the  $\alpha$ -position in respect to the ring N-atom with  $\alpha$ -halo carbonyl compounds<sup>6,7</sup>. In continuing our study on the reactivity of 2-amino-2-oxazolines<sup>8</sup>, we describe here the synthesis of 3-carboxyalkyl-2-imino-oxazolidines **3** by treatment of 5-substituted-2-amino-2-oxazolines **1** with the bromo esters **2**.

The two N-atoms of 2-amino-2-oxazolines are potent nucleophilic centers. Depending on the experimental condi-

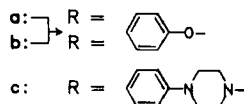
tions, substitutive reactions take place either on the endo or on the exo N of the amidine system. As we have noticed<sup>9</sup>, in the 2-amino-2-oxazoline form the endo N is more reactive than the exo one. At ambient temp. nucleophilic substitution preferably occurs on the endo N-atom. Substitutions on position 5 of the heterocycle are without effect on the reactivity indices calculated for the two nitrogens. The condensation of **1** with ethyl bromoacetate or ethyl 4-bromocrotonate in acetone at 0°C led to 3-carbethoxyalkyl-2-imino-oxazolidines as hydrobromine salts, with a small quantity of corresponding acid. HPLC analysis on a C18 reversed phase column (mobile phase: methanol-phosphate buffer M/30 pH 5.4) gave an integral ratio of 99/1. The alkylation reaction is generally believed to proceed by initial displacement of the bromine atom by the oxazoline ring nitrogen atom followed by rearrangement of the resonance stabilized oxazolinium salt<sup>10</sup>. An attempt to convert the 5-substituted-3-carboxymethyl-2-imino-oxazolidines to the corresponding imidazo[2,1-*b*]oxazoline by POCl<sub>3</sub> was performed according to lit.<sup>2,11</sup>; no cyclization occurred. A similar resistance to ring closure was observed with 3-phenacyl-2-imino-oxazolidines<sup>12</sup>.

The hydrolysis of reaction compounds can be performed in acidic or in basic conditions. With an excess of NaOH in boiling water, we observed the opening of the oxazolidine ring in **3a** leading to the N-substituted glycine **4a** after neutralization. This reaction might proceed via the corresponding 2-oxazolidinone<sup>13</sup>. In acidic conditions (excess of HCl in boiling water), only **3a** and **3b**, respectively, were isolated as hydrochloride salts. **3c** was obtained as sodium salt after treatment with Na<sub>2</sub>CO<sub>3</sub>.

The structures of all new synthesized products were investigated by spectral analyses. In <sup>1</sup>H-NMR spectra of **3** as hydrochlorides, an exchangeable singlet assigned to the N<sup>+</sup>H<sub>2</sub> was found near 9.8 ppm. The imine function (free bases obtained at ambient temp. after treatment with NH<sub>3</sub>) was assigned on the basis of IR-data (sharp peak at 3340 cm<sup>-1</sup>;  $\nu$  NH) and <sup>1</sup>H-NMR ( $\delta$  = 5.5 ppm for NH). As it was described<sup>9,12</sup>, in 2-iminooxazolidines C-5-H and C-4-H of the heterocycle from an ABX system. In compounds **3**, C-5-H appeared as a complex multiplet near 5.5 ppm. In <sup>13</sup>C-NMR spectra, C-2 of the oxazolidine ring was found at 158.5 ppm. This value is comparable to the one of a 2-imino-oxazolidine whose structure was established by X-ray crystallography<sup>9</sup>.



|    | 3a | 3b | 3c |
|----|----|----|----|
| n  | 0  | 1  | 0  |
| R' | H  | H  | Na |



The compounds **3a-c** were evaluated for their local anaesthetic activity on male guinea pigs using a standard procedure<sup>14)</sup> at the concentrations of 0.5 and 5%. No local anaesthetic activity was observed even at higher concentration.

## Experimental Part

### General procedure for the synthesis of the 5-substituted-3-carboxyalkyl-2-imino-oxazolidines **3**

0.1 Mole of bromo ester in 50 ml of acetone was added at 0°C to 0.1 mole of 5-substituted-2-amino-2-oxazoline in suspension in 250 ml of acetone. The mixture was stirred 8 h at 0°C, then at ambient temp. until the consumption of the oxazoline controlled by TLC. The mixture was concentrated and the collected solid was washed twice with acetone.

### 5-Phenoxymethyl-3-carboxymethyl-2-imino-oxazolidine, HBr

Mp. 204°C (heptane). - IR (KBr): 1735 (C=O), 1685 (C=N) cm<sup>-1</sup>. - <sup>1</sup>H-NMR (DMSO-D<sub>6</sub>), δ (ppm) = 9-8.5 (N<sup>+</sup>H<sub>2</sub>), 7.5-6.8 (m, 5H, phenyl), 5.7-5.4 (m, 1H, C-5-H), 4.8 (s, 2H, NCH<sub>2</sub>), 4.4-3.6 (m, 6H, CH<sub>2</sub>), 1.2 (t, 3H, CH<sub>3</sub>). After 3 recrystallizations in heptane, HPLC analysis (C18 μ Bondapack column 30 cm x 3.9 mm I.D., 10 μ particle size - UV detection 270 nm) indicated the presence of 1.6 % of the corresponding acid (retention times 2.60 min for acid and 4.36 min for ester).

An equivalent of 0.01 mole of the precedent solid in 100 ml of water was heated 3 h with 0.03 mole of HCl. The homogenized mixture was concentrated under reduced pressure and a solid crystallized after trituration with acetone.

### 5-Phenoxymethyl-3-carboxymethyl-2-imino-oxazolidine, HCl (**3a**)

Yield 31 %; mp. 178°C (acetone). - IR (KBr): 1735 (C=O), 1695 (C=N) cm<sup>-1</sup>. - <sup>1</sup>H-NMR (DMSO-D<sub>6</sub>), δ (ppm) = 13.9-11.9 (COOH), 9.8 (s, 2H, N<sup>+</sup>H<sub>2</sub>), 7.6-6.9 (m, 5H, phenyl), 5.8-5.3 (m, 1H, C-5-H), 4.8-3.6 (m, 6H, CH<sub>2</sub>). - <sup>13</sup>C-NMR (DMSO-D<sub>6</sub>), δ (ppm) = COOH 172.2, C-2 158.5, phenyl 157, 129.5, 120.6, 114.5, C-4 51.9, C-5 67, OCH<sub>2</sub> 69.9, NCH<sub>2</sub> 45.2.

### 5-Phenoxymethyl-3-(1-carboxy-1-propenyl)-2-imino-oxazolidine, HCl (**3b**)

Yield 21 %; mp. 201°C (chloroform). - IR (KBr): 1690 (C=O), 1665 (C=N) cm<sup>-1</sup>. - <sup>1</sup>H-NMR (DMSO-D<sub>6</sub>), δ (ppm) = 12.8-10.8 (COOH), 9.6 (s, 2H, N<sup>+</sup>H<sub>2</sub>), 7.5-6.6 (m, 6H, phenyl and =CH), 6.15 (d, 1H, =CH, J = 16 Hz), 5.7-5.3 (m, 1H, C-5-H), 4.5-3.6 (m, 6H, CH<sub>2</sub>).

**3c** was obtained as a Na-salt in water by addition of Na<sub>2</sub>CO<sub>3</sub> until pH 8.

### 5-(1-Phenyl-4-piperazino)methyl-3-carboxymethyl-2-imino-oxazolidine (**3c**)

Yield 23 %; mp. > 250°C. - IR (KBr): 1660 (C=O), 1610 (C=O) cm<sup>-1</sup>. - <sup>1</sup>H-NMR (D<sub>2</sub>O), δ (ppm) = 7.4-6.8 (m, 5H, phenyl), 5-4.4 (m, 1H, C-5-H), 3.9-2.4 (m, 14H, CH<sub>2</sub>).

### 1-Carboxymethylamino-3-phenoxy-propane-2-ol (**4a**)

2.87 g (0.01 mole) of **3a** in 50 ml of water were heated 3 h with 0.04 mole of NaOH in 10 ml of water. After cooling the mixture was neutralized by HCl until pH 6. The solid collected was recrystallized from C<sub>2</sub>HCl<sub>3</sub> to yield 1.2 g of **4a** (53 %); mp. 140°C. - IR (KBr): 3490 (NH), 3160 (OH), 1710 (CO) cm<sup>-1</sup>. - <sup>1</sup>H-NMR (DMSO-D<sub>6</sub>), δ (ppm) = 10.6 (s, 1H, COOH), 7.5-6.8 (m, 5H, phenyl), 5.3 (OH), 4.3-3.8 (m, 6H, NH, 2 CH<sub>2</sub> and CH), 3.5-3.1 (d, 2H, NCH<sub>2</sub>, J = 4.8 Hz).

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