STUDIES ON THE IMIDAZOLE SERIES

XLV. Synthesis of Imidazo[2,1-b]thiazole and Some of Its Alkyl, Aryl, and 5,6-Dihydro Derivatives*

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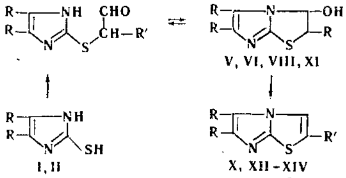
Imidazo[2,1-b]thiazole and its alkyl, aryl, and 5,6-dihydro derivatives have been synthesized by the reaction of 2-mercapto derivatives of imidazole and imidazoline with α-halogenoaldehydes or their acetals. Imidazo[2,1-b]thiazole has also been obtained by the decarboxylation of imidazo[2,1-b]thiazole-5-carboxylic acid.

In order to obtain imidazo[2,1-b]thiazole (X) [2, 3], and also its alkyl, aryl, and 5,6-dihydro derivatives, which are of interest for biological investigations, we have studied the reaction of 2-mercaptoimidazole (I), 2-mercapto-4,5-diphenylimidazole (II), and 2-mercaptoimidazoline (III) with the hydrate of the dimer of chloroacetaldehyde and with the diethyl acetals of bromoacetaldehyde and α-bromopropionaldehyde. When I and II were heated with the hydrate to the dimer of chloroacetaldehyde in ethanol, water, or dimethylformamide and with the bromoacetals mentioned in water, the corresponding 3-hydroxyimidazo[2,1-b]thiazolines (V, VI, VIII, XI) were obtained. The structure of the latter was established by means of their IR spectra, in which as in the IR spectrum of 3-hydroxy-6-phenylimidazo[2,1-b]thiazoline [4] there is no absorption band of a CO group in the 1630-1780 cm^{-1} region while there are absorption bands of an OH group in the 3070-3225 cm^{-1} region. In solution, these compounds can be converted into the open aldehyde forms, as is shown by the formation of derivatives with respect to the carbonyl group – for example, the p-nitrophenylhydrazone of (4,5-diphenylimidazol-2-ylthio)acetaldehyde (VII).

When V, VI, VIII, and XI were treated with phosphorus oxychloride, in the manner known for the synthesis of 6-aryl- and 5-methoxycarbonylimidazo[2,1-b]thiazoles [4, 5] they split off a molecule of water with the formation of X and XII-XIV. We also obtained X by another method – the decarboxylation of imidazo[2,1-b]thiazole-5-carboxylic acid (IX) [2], which was prepared by the saponification of its methyl ester (IV) [5]. Compounds XIII and XIV have been described in the literature [6], but were synthesized previously by a different method – by the reaction of 2-aminothiazole and of 2-amino-4-methylthiazole with desyl bromide.



I, V, X-XII R = H; II, VI, VIII, XIII, XIV R = Ph
V, VI, X, XIII R′ = H; VIII, XI, XII, XIV R′ = CH_3

In contrast to I and II, when 2-mercaptoimidazoline (III) was boiled with chloroacetaldehyde and also with the diethylacetals of bromoacetaldehyde and α-bromopropionaldehyde in water, 5,6-dihydro imidazo[2,1-b]thiazole (XVII) and its 2-methyl homolog (XVIII) were obtained in a single stage. Compound XVII has been synthesized previously [7] using the less accessible diethyl acetal of chloroacetaldehyde.

The reaction of III with the hydrate of the dimer of chloroacetaldehyde in dimethylformamide in the cold gave the intermediate 3-hydroxy-5,6-dihydroimidazo[2,1-b]thiazoline (XV), which, in solution, is capable of changing into (imidazolin-2-yl-thio)acetaldehyde, characterized as the p-nitrophenylhydrazone (XVI). Compound XV is less stable than 3-hydroxy-2,3-dihydroimidazo[2,1-b]thiazole (V), and when it is heated in hydrochloric acid or its hydrochloride is heated in ethanol or water it is readily dehydrated to form XVII.

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*For part XLIV, see [1].

EXPERIMENTAL

2-Mercaptoimidazole (I) [8], 2-mercapto-4,5-diphenylimidazole (II) [9], 2-mercaptoimidazoline (III) [10], and methyl imidazo[2,1-b]thiazole-5-carboxylate (IV) [5] were prepared by known methods. In the preparation of IV, a modification was made by using the hydrate of the dimer of chloroacetaldehyde in place of di(bromomethyl) ether.*

3-Hydroxy-2,3-dihydroimidazo[2,1-b]thiazole (V). A solution of 5 g (0.05 mole) of I and 5 g (0.029 mole) of the hydrate of the dimer of chloroacetaldehyde in 50 ml of ethanol was boiled for 1 hr and cooled, the solvent was distilled off in vacuum, and the residue was washed with ether. This gave 6.62 g (87.1%) of the technical hydrochloride of V, the decomposition of which with sodium bicarbonate gave the base V. Oily liquid soluble in water and organic solvents. Picrate of V, mp 143.5-145°C (from water). IR spectrum: 3410, 3225 cm^{-1} (ν_{OH}). Found %: C 36.2; H 2.6; N 18.5; S 9.0. $C_5H_6N_2OS \cdot C_6H_3N_3O_7$. Calculated %: C 35.6; H 2.4; N 18.9; S 8.6.

3-Hydroxy-5,6-diphenyl-2,3-dihydroimidazo[2,1-b]thiazole (VI). A solution of 6.57 g (0.026 mole) of II and 2.9 g (0.016 mole) of the hydrate of the dimer of chloroacetaldehyde in 60 ml of dimethylformamide was heated at 60-65°C (bath temperature) for 3 hr and was cooled, and the precipitate of the hydrochloride of VI was filtered off and washed with water. Yield 7.66 g (77.4%), mp 195-196°C (decomp., from dimethylformamide). Found %: Cl 11.0. Calculated for $C_{17}H_{14}N_2OS \cdot HCl$, %: Cl 10.7. The decomposition of the hydrochloride with sodium bicarbonate gave the base VI, mp 187-188°C (decomp., from dichloroethane). IR spectrum: 3070 cm^{-1} (ν_{OH}). Found %: C 69.3; H 4.7; N 9.2; S 10.8. $C_{17}H_{14}N_2OS$. Calculated %: C 69.4; H 4.8; N 9.5; S 10.9.

p-Nitrophenylhydrazone of (4,5-diphenylimidazo-2-ylthioacetaldehyde (VII). This was obtained by heating VI with p-nitrophenylhydrazine in glacial CH_3COOH. Orange crystals, mp 174-175°C (decomp., from ethanol). Found %: C 64.5; H 4.5. $C_{23}H_{19}N_5O_2S$. Calculated %: C 64.3; H 4.6.

3-Hydroxy-2-methyl-5,6-diphenyl-2,3-dihydroimidazo[2,1-b]thiazole (VIII). A mixture of 5.08 g (0.02 mole of II and 4.66 g (0.022 mole) of the dimethyl acetal of α-bromopropionaldehyde in 50 ml of 50% ethanol was boiled for 8 hr, cooled, poured into water, and neutralized with sodium bicarbonate, and the precipitate was filtered off. Yield 5.92 g (96.1%), mp 172.5-174.5°C (from dichloroethane). IR spectrum: 3070 cm^{-1} (ν_{OH}). Found %: C 70.4; H 5.0; N 9.3; S 10.6. $C_{18}H_{16}N_2OS$. Calculated %: C 70.1; H 5.2; N 9.1; S 10.4.

Imidazo[2,1-b]thiazole-5-carboxylic acid (IX). A) A solution of 6 g (0.033 mole) of IV in 60 ml of 10% HCl was boiled for 1 hr and evaporated in vacuum, and the residue was dried. The yield of the hydrochloride of IX was 6.45 g (96.5%), mp 239-240°C (decomp., precipitated by ether from methanol). Found %: Cl 17.1. $C_2H_4N_2O_2S \cdot HCl$. Calculated %: Cl 17.3. To obtain compound IX, a solution of 1.5 g of its hydrochloride in 50 ml of water was passed through the anion-exchanger DAUOS 2 × 10 (20 g), being eluted with 5% aqueous HCOOH (about 400 ml), and the eluate was evaporated and the residue was dried. Yield 1.2 g (97.5%), mp 236-237°C (with decarboxylation, from water). Found %: C 42.7; H 2.4; N 16.4; S 19.2. $C_6H_4N_2O_2S$. Calculated %: C 42.8; H 2.4; N 16.7; S 19.1. Picrate of IX, mp 194-196°C (decomp., from water). Found %: N 17.6. $C_6H_4N_2O_2S \cdot C_6H_3N_3O_7$. Calculated %: N 17.6.

B) A mixture of 4 g (0.022 mole) of IV and 214 ml of 0.1 N NaOH (0.022 mole) was boiled for 4 hr and filtered, the filtrate was passed through a column of a KU-2 cation-exchanger (13.5 g), and the acid was eluted with 5% aqueous HCOOH (400 ml). Yield 2.95 g (83.6%), mp 239-240°C (from water).

Imidazo[2,1-b]thiazole (X). A) Some 1.5 g (0.009 mole) of IX was heated in a current of nitrogen at the melting point until the evolution of CO_2 ceased. The liquid was cooled and dissolved in ether, the solution was heated with carbon and filtered, and the solvent was distilled off in vacuum. This gave 1.09 g (93.7%) of technical X in the form of a brown liquid which, after redistillation in vacuum, immediately crystallized. Bp 110-112°C (2 mm), mp 60-61°C. Colorless crystals, soluble in water and organic solvents. Found %: C 48.3; H 3.0; N 22.5; S 26.1. $C_5H_4N_2S$. Calculated %: C 48.4; H 3.2; N 22.6; S 25.8. Hydrochloride of X [7], mp 117.5-119°C (from acetone). Found %: C 33.5; H 3.9; Cl 19.8; N 16.2; S 17.9. $C_5H_4N_2S \cdot HCl \cdot H_2O$. Calculated %: C 33.6; H 3.9; Cl 19.8; N 15.7; S 17.9. Picrate of X mp 193-194°C (from ethanol). Found %: N 20.2. $C_5H_4N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 19.8. Methiodide of X, colorless crystals darkening at 150°C and decomposing above 200°C (by precipitation with ether from ethanol). Found %: C 26.7; H 2.7; I 47.9; N 10.9; S 11.6. C_6H-IN_2S. Calculated %: C 27.1; H 2.6; I 47.7; N 10.5; S 12.0.

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*We take this opportunity to express our thanks to B. Yu. Yasnitskii for providing this substance.

B) A solution of 5 g (0.05 mole) of I and 5 g (0.029 mole) of the hydrate of the dimer of chloroacetaldehyde in 50 ml of ethanol was boiled for 1-1.5 hr, the solvent was distilled off in vacuum, the residue of the hydrochloride of V was boiled with 35 ml of $POCl_3$ for 1 hr, the $POCl_3$ was distilled off in vacuum, the residue was dissolved in water, the solution was made alkaline and extracted with chloroform, and the solvent was distilled off. This gave 4.93 g (79.5%) of technical X in the form of a viscous liquid crystallizing after vacuum distillation, mp 60-61°C.

C) A mixture of 10 g (0.1 mole) of I and 20 g (0.1 mole) of the bromoacetal in 100 ml of water was boiled for 4 hr, the solution was evaporated in vacuum, and the residue of the hydrobromide of V was boiled with $POCl_3$ (100 ml) for 1 hr and was treated further as in the preceding experiment. Yield 8.75 g (70.6%), mp 60-61°C (after vacuum distillation).

2-Methylimidazo[2,1-b]thiazole (XII). A mixture of 6 g (0.06 mole) of I, 13.5 g (0.064 mole) of the diethyl acetal of α-bromopropionaldehyde, two drops of 46% HBr, and 50 ml of 50% ethanol was boiled for 5 hr. The solvent was distilled off in vacuum, and the residue of the hydrobromide of 3-hydroxy-2-methyl-2,3-dihydroimidazo[2,1-b]thiazole (XI) was boiled with $POCl_3$ (40 ml) and treated subsequently as described for X (method "B"). Yield 6.25 g (75.5%). Viscous liquid soluble in water and organic solvents. Sulfate of XII, mp 135-136.5°C (from ethanol). Found %: C 30.9; H 3.6; N 11.8; S 26.7. $C_6H_6N_2S \cdot H_2SO_4$. Calculated %: C 30.5; H 3.4; N 11.9; S 27.1. Picrate of XII, mp 203-204.5°C (decomp., from water). Found %: N 19.2. $C_6H_6N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 19.1.

5,6-Diphenylimidazo[2,1-b]thiazole (XIII). A solution of 4.8 g (0.015 mole) of the hydrochloride of VI in 48 ml of $POCl_3$ was heated at 100°C for 1.5 hr, the $POCl_3$ was distilled off in vacuum, water was added to the residue, the solution was neutralized with ammonia, and the precipitate was filtered off. The yield of XIII was 3.92 g (97.7%), mp 135-136°C (from methanol). According to the literature [6], mp 136°C.

2-Methyl-5,6-diphenylimidazo[2,1-b]thiazole (XIV). A solution of 3.2 g (0.0104 mole) of VIII in 16 ml of $POCl_3$ was heated and treated as in the procedure for XIII. Yield 2.89 g (96.0%), mp 181.5-183.5°C (from methanol). According to the literature [6], mp 189°C. Found %: C 74.5; H 5.0; N 9.4; S 10.7. $C_{18}H_{14}N_2S$. Calculated %: C 74.4; H 4.9; N 9.6; S 11.0.

3-Hydroxy-5,6-dihydroimidazo[2,1-b]thiazoline (XV). To a solution of 10.2 g (0.1 mole) of III in 50 ml of dimethylformamide was added 9.6 g (0.055 mole) of the hydrate of the dimer of chloroacetaldehyde, the mixture was left at 18-20°C for 18 hr, and the precipitate was filtered off and washed with ether. The yield of the hydrochloride of XV was 15.25 g (84.4%), mp 122.5-124.5°C (from ethanol). IR spectrum: 3150 cm^{-1} (ν_{OH}). Found %: Cl 20.0. $C_5H_8NOS \cdot HCl$. Calculated %: 19.6. The addition of alkali to an aqueous solution of hydrochloride liberated the base XV, mp 123-124°C (from methanol). IR spectrum: 3170, 2730, 2670 cm^{-1} (ν_{OH}). Found %: C 42.0; H 5.3; N 19.7; S 22.0. $C_5H_8N_2OS$. Calculated %: C 41.6; H 5.6; N 19.4; S 22.2. Picrate, mp 122-123°C (from water). Found %: N 19.1. $C_5H_8N_2OS \cdot C_6H_3N_3O_7$. Calculated %: N 18.8.

p-Nitrophenylhydrazone of (imidazolin-2-ylthio)acetaldehyde (XVI). This was obtained by boiling XV with p-nitrophenylhydrazine in methanol. Red crystals with mp 299-300°C [decomp., from dimethylformamide-acetic acid (1 : 3)]. Found %: N 25.4. $C_{11}H_{13}N_5O_2S$. Calculated %: N 25.1.

5,6-Dihydroimidazo[2,1-b]thiazole (XVII). A) A mixture of 4.08 g (0.04 mole) of III and 16 ml (0.04 mole) of 20% aqueous chloroacetaldehyde (or the corresponding amount of the hydrate of the dimer of chloroacetaldehyde) was boiled for 1 hr 45 min, the solution was evaporated in vacuum, and the residual moisture was eliminated by the addition of absolute ethanol and its removal by distillation. The yield of the hydrochloride of XVII was 6.15 g (95.2%), mp 180.5-182.5°C (decomp., by reprecipitation from absolute ethanol with acetone). According to the literature [7], mp 183-186°C. Picrate of XVII, mp 189.5-191°C (from ethanol). Found %: N 19.6. $C_5H_6N_2OS \cdot C_6H_3N_3O_7$. Calculated %: N 19.7.

B) A solution of 0.15 g (0.0012 mole) of the hydrochloride of XV in 5 ml of water was boiled for 1.5 hr and evaporated in vacuum, and the residue was dried. The yield of the hydrochloride of XVII was 0.12 g (88.9%), mp 180.5-182.5°C (decomp., by reprecipitation from absolute ethanol with acetone).

2-Methyl-5,6-dihydroimidazo[2,1-b]thiazole (XVIII). A mixture of 4.08 g (0.04 mole) of III, 9 g (0.045 mole) of the diethyl acetal of α-bromopropionaldehyde, two drops of 46% HBr, and 25 ml of water was boiled for 3 hr, the solvent was distilled off in vacuum, and the residue was washed with acetone and ether. The yield of the hydrobromide of XVIII was 8.5 g (96.1%), mp 179-181°C (from absolute ethanol). Found %: Br 35.8. $C_6H_8N_2S \cdot HBr$. Calculated %: Br 36.1. By neutralization with sodium bicarbonate and extraction of the solution of chloroform, the hydrobromide yielded the base

XVIII, mp 104-106°C [from acetone-petroleum ether (1:4)]. Found %: C 45.4; H 6.2; N 17.6; S 20.4. $C_6H_8N_2S \cdot H_2O$. Calculated %: C 45.5; H 6.4; N 17.7; S 20.3. **Picrate of XVIII**, mp 182-183°C (decomp., from ethanol). Found %: N 18.9. $C_6H_8N_2S \cdot C_6H_3N_3O_7$. Calculated %: N 19.0.

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