SYNTHESIS OF 2,3-DIHYDRO- AND 2,3,5,6-TETRAHYDRO DERIVATIVES OF IMIDAZO(2,1-B)-THIAZOLE*

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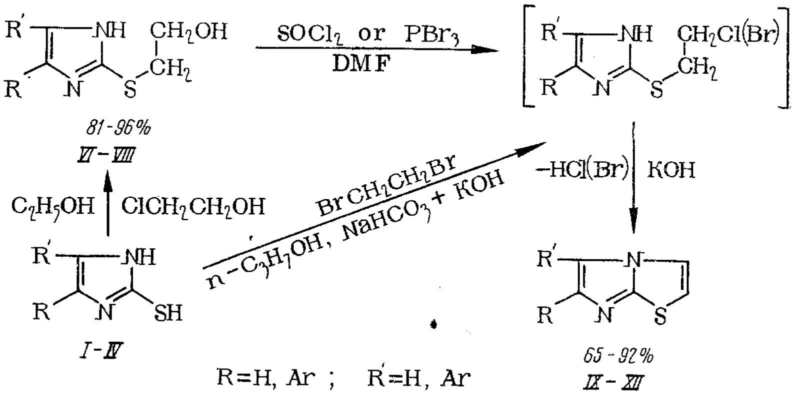
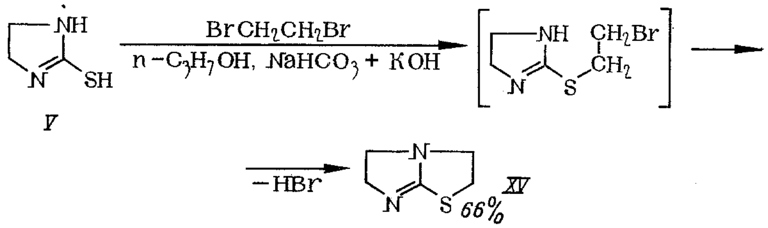
According to a recent communication, a new group of anthelmintics was discovered and identified as 5,6-dihydro- and 2,3,4,5-tetrahydro derivatives of imidazo(2,1-B)-thiazole; the hydrochloride of 6-phenylimidazolino(2,1-B)-thiazoline (tetranisole) was suggested as an anthelmintics preparation [1-8]. In continuation of the studies [9, 10], we have synthesized a number of 2,3-dihydro- and 2,3,5,6-tetrahydro derivatives of imidazo(2,1-B)-thiazole which are interesting for their use as anthelmintics.

A reaction of 4(5)-aryl- and 4,5-diaryl-2-mercaptoimidazoles (II-IV) with ethylenechlorohydrin yielded 2-(β-hydroxyethyl)mercaptoimidazoles (VI-VIII). Treatment of these compounds with thionyl chloride or phosphorus tribromide and subsequent heating of intermediate 2-(β-haloethyl)-mercaptoimidazoles with potassium hydroxide in methanol (synthesis of imidazolo(2,1-B)-thiazoline-XV [11]) yielded 5-aryl- and 5,6-diarylimidazo(2,1-B)-thiazolines (X-XII).





A simpler, single stage procedure for the preparation of imidazo(2,1-B)-thiazolines (IX-XII) and imidazolino(2,1-B)-thiazolino (XV) is the reaction of 2-mercaptoimidazoles (I-IV) and 2-mercaptoimidazoline (V) with 1,2-dibromoethane in the presence of bases (synthesis of 6-phenylimidazolino(2,1-B)-thiazoline [5]). Heating V with dibromoethane in an alcoholic solution in the absence of alkali leads [12-15] to the formation of di-(2-mercaptoimidazolyl)-ethane.

Owing to tautomerism in the series of 4(5)-imidazole substituents, the cyclization of intermediate 4(5)-aryl-2(β-haloethyl)-mercaptoimidazoles yielded mixtures of 2 isomers, 5-arylimidazo(2,1-B)-thiazolines (X, XI) and 6-arylimidazo(2,1-B)-thiazolines (XIII, XIV). The process proceeds with the preferential formation of X and XI. The structure of X and XI was confirmed by the synthesis of isomeric XIII and XIV

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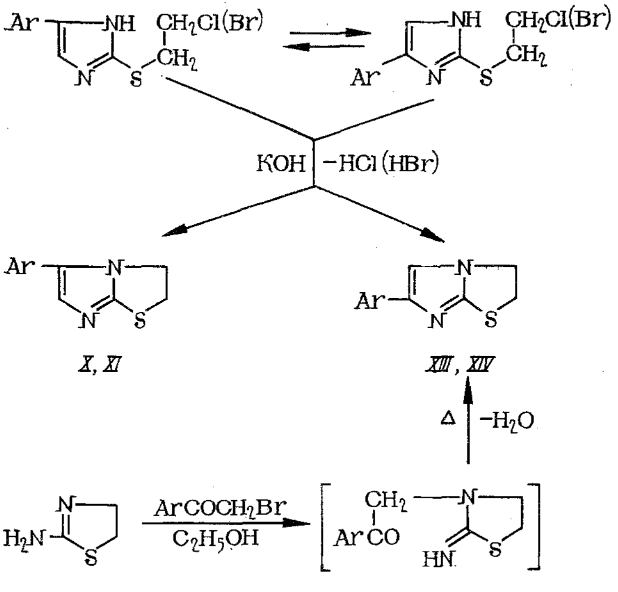
in the reaction of 2-aminothiazoline with phenacyl bromide and its p-nitro derivative by the procedure described by M. N. Shchukina and co-workers [16]. Compounds XIII and XIV differed from X and XI by the melting point and by R_f:



Ar = C_6H_5, $C_6H_4NO_2$-n

EXPERIMENTAL

Starting compounds 2-mercaptoimidazole (I), 4(5)-phenyl-2-mercaptoimidazole (II), 4(5)-p-nitrophenyl-2-mercaptoimidazole (III), 4,5-diphenyl-2-mercaptoimidazole (IV), and 2-mercaptoimidazoline (V) were prepared by the procedures reported earlier [17-20].

4(5)-Phenyl-2-(β-hydroxyethyl)-mercaptoimidazole (VI). A. To a solution of sodium ethylate prepared from 0.46 g of sodium and 40 ml of anhydrous ethanol were added 3.52 g of II and 1.76 g of ethylenechlorohydrin. The mixture was heated for 1 h at 60-65° and for another hour at the boiling point of the solution until the reaction was completed (neutral medium); the product was cooled, poured into water, precipitate filtered off, and washed with water. Yield, 3.6 g (81.8%), mp 104-106°. Colorless crystals, mp 109.5-111° (from dichloroethane). Found, %: C 59.68; H 5.12; N 12.61; S 14.51. $C_{11}H_{12}N_2OS$. Calculated, %: C 59.97; H 5.49; N 12.72; S 14.55.

B. A mixture of 3.52 g of II and 2 g of ethylenechlorohydrin in 40 ml of ethanol was refluxed for 10 h, the solution cooled, poured into water, neutralized with sodium carbonate, the precipitate filtered off, and washed with water. Yield 3.55 g (80.7%), mp 109.5-111° (from dichloroethane).

4(5)-p-Nitrophenyl-2-(β-hydroxyethyl)-mercaptoimidazole (VII). This compound was prepared similarly to VI (method A). Yield, 86.5%. Orange prisms, mp 204-205° (from butyl alcohol). Found, %: C 49.60; H 4.28; N 15.93; S 12.12. $C_{11}H_{11}N_3O_3S$. Calculated, %: C 49.80; H 4.18; N 15.84; S 12.09.

4,5-Diphenyl-2-(β-hydroxyethyl)-mercaptoimidazole (VIII). This compound was prepared similarly to VI (method A). Yield, 96.3 %. Colorless prisms, mp 167-168° (from dichloroethane). Found, %: C 68.87; H 5.49; N 9.48; S 10.98. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.89; H 5.44; N 9.45; S 10.82.

Imidazo(2,1-B)-thiazoline (IX). To a mixture of 20 ml of 1,2-dibromoethane, 20 g of $NaHCO_3$ and 100 ml of isopropanol was added dropwise a solution of 5 g of I in a mixture consisting of 20 ml 20% aqueous KOH solution and 50 ml of isopropanol. The reaction mixture was refluxed for 4 h, with stirring; the solvents and bromoethane excess distilled off in vacuo; to the residue 50 ml of 20% KOH solution was added, extracted with chloroform, the extract washed with water, dried over $MgSO_4$, and the solvent distilled off. Yield, 5.68 g (90.2%) of technical IX, oily liquid, soluble in water and organic solvents. Sulfate, mp 126-129° (from anhydrous ethanol). Found, %: C 27.04; H 3.64; N 12.92; S 28.44. $C_5H_6N_2 \cdot H_2SO_4$. Calculated, %: C 26.78; H 3.60; N 12.49; S 28.60. Picrate, mp 182-184° (decomp., from 30% ethanol). Found, %: C 37.10; H 2.80; N 20.05; S 9.33. $C_5H_6N_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 37.19; H 2.55; N 19.71; S 9.03. Iodomethylate (prepared by heating IX with CH_3I in acetone), colorless prisms of mp 171-173° (decomp., precipitated with ether from anhydrous ethanol). Found, %: C 26.97; H 3.55; I 47.64; N 10.01; S 11.80. $C_6H_9N_2SI$. Calculated, %: C 26.88; H 3.33; I 47.33; N 10.45; S 11.96.

5-Phenylimidazo(2,1-B)-thiazoline (X). A. To a solution of 3 g of VI in 20 ml of anhydrous dimethylformamide was added, with cooling, 2 ml of PBr_3; after 1-2 min, a precipitate began to form. The reaction mixture was allowed to stand for 2 h at 18-20°, the solvent decanted, the precipitate washed with ether, dissolved in 30 ml of methanol, 20 ml of 10% aqueous KOH solution added, the mixture refluxed for 3 h, poured into water, and extracted with chloroform. Distilling off the solvent yielded 0.91 g (76.4%) of technical X, as an oil, crystallized by triturating with ether. Colorless or slightly cream-colored crystals, mp 109-112°(from acetone–petroleum ether mixture, 1 : 20). A sample mixed with XIII gave a sharp depression in the melting point. Found, %: C 65.05; H 5.08; N 13.94; S 15.74. $C_{11}H_{10}N_2S$. Calculated, %: C 65.31; H 4.98; N 13.85; S 15.86. Picrate, mp 180-182° (decomp., from 70% ethanol). A sample mixed with picrate XIII melted at 173-178°. Found, %: C 47.39; H 3.23; N 16.21; S 7.78. $C_{11}H_{10}N_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 47.33; H 3.04; N 16.24; S 7.43. Iodomethylate (obtained by heating X with CH_3I in acetone), colorless prisms of mp 220-221° (decomp., 5° per min, from alcohol). Found, %: C 42.20; H 3.90; I 36.29; N 7.93; S 9.20. $C_{12}H_{13}IN_2S$. Calculated, %: C 41.87; H 3.81; I 36.87; N 8.14; S 9.31.

B. To a mixture of 10 ml of 1,2-dibromoethane, 100 ml of isopropanol and 15 g of $NaHCO_3$ was added dropwise over a period of 1 h a solution of 4 g of II in a mixture of 50 ml of isopropanol and 20 ml of 15% aqueous KOH solution. The reaction mixture was heated and treated as in the preparation of IX. Yield, 4 g (87.5%), mp 109-112° (from an acetone–petroleum ether mixture). A sample mixed with the product prepared by method A gave no depression in melting point. Picrate, mp 180-182° (decomp., from 70% ethanol).

2-p-Nitrophenylamidazo(2,1-B)-thiazoline (XI). To a solution of 2.1 g of VII in 20 ml of anhydrous dimethylformamide was added 1.4 g of $SOCl_2$, the mixture refluxed for 1 h, cooled, poured into water, neutralized with sodium carbonate, precipitate filtered off, and washed with water. Yield of technical XI, 1.8 g (91.7%), mp 172-175°. Yellow plates, mp 182-184° (from 20% methanol solution), R_f 0.75 (from 15% CH_3COOH solution). A sample mixed with XIV melted at 159-164°. Found, %: C 53.72; H 3.39; N 17.16; S 12.84. $C_{11}H_9N_3O_2S$. Calculated, %: C 53.43; H 3.67; N 16.99; S 12.97. As shown by chromatography, technical XI contained a small amount of XIV, R_f 0.66 (from 15% CH_3COOH solution).

5,6-Diphenylimidazo(2,1-B)-thiazoline (XII). A. A mixture of 2.7 g of VIII and 15 ml of $SOCl_2$ was refluxed for 30 min, the $SOCl_2$ excess distilled in vacuo, 10 ml of chloroform added which was distilled off in vacuo. The residue was dissolved in 30 ml of ethanol, 15 ml 40% KOH solution added, the mixture refluxed for 4 h, cooled, poured into water, the residue filtered off, and washed with water. Yield, 1.65 g (65.2%). Colorless crystals, mp 185-187° (from acetone). Found, %: C 72.95; H 4.72; N 9.70; S 11.39. $C_{17}H_{14}N_2S$. Calculated, %: C 73.35; H 5.07; N 10.06; S 11.52. Hydrobromide, mp 186-188° (from ethanol). Found, %: Br 22.39. $C_{17}H_{14}N_2S \cdot HBr$. Calculated, %: Br 22.24.

B. To a mixture of 5 g of finely ground IV, 15 g of $NaHCO_3$, 15 ml of 1,2-dibromoethane, and 100 ml of isopropanol was added over a period of 1 h at 60-65°, with stirring, a mixture of 50 ml of isopropanol and 30 ml of 15% KOH solution. The reaction mixture was refluxed and heated as described in preparing IX. Yield, 4.1 g (75.9%), mp 185-187° (from acetone). A sample mixed with the product prepared by method A gave no depression in the melting point.

6-Phenylimidazo(2,1-B)-thiazoline (XIII). This compound was prepared by refluxing 2-aminothiazoline with phenacyl bromide in ethanol [16], mp 150-151° (from ethanol). Picrate, mp 210-212° (decomp., from 50% ethanol). Found, %: C 47.67; H 3.26; N 15.86; S 7.77. $C_{11}H_{10}N_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 47.33; H 3.04; N 16.23; S 7.33.

6-p-Nitrophenylimidazo(2,1-B)-thiazoline (XIV). This compound was prepared by refluxing 2-aminothiazoline with p-nitrophenacyl bromide in ethanol [16], mp 215-216° (decomp., from water), R_f 0.66 (15% CH_3COOH solution).

Imidazolino(2,1-B)-thiazoline (XV). To a mixture of 20 ml of 1,2-dibromoethane, 20 g of $NaHCO_3$, 100 ml of isopropanol, and 25 ml of water was added at 60-65°, with stirring, over a period of 1 h, 5 g of V in 50 ml of isopropanol. The reaction mixture was refluxed and treated as described in preparing IX. Yield of technical XV, yellow, noncrystallizing oil, 4.15 g (66.4%). Hydrobromide, mp 170-172° (by precipitating with ether from methanol). According to literature data [11], mp 176.5-177.5°. Found, %: C 28.57; H 4.17; Br 38.20; N 13.22; S 15.13. $C_5H_8N_2S \cdot HBr$. Calculated, %: C 28.72; H 4.34; Br 38.21; N 13.40; S 15.33. Picrate, mp 172-174° (from 20% ethanol solution). According to literature data [11], mp 173.5-174.5°.

CONCLUSIONS

The reaction of 2-mercapto-, 4(5)-aryl-2-mercapto-, and 4,5-diaryl-2-mercaptoimidazoles with 1,2-dibromoethane or ethylenechlorohydrin and subsequent cyclization of (β-hydroxyethyl)mercaptoimidazoles yielded imidazo(2,1-B)-thiazoline and its 5-aryl- and 5,6-diaryl substituents. A simpler synthesis of imidazolino(2,1-B)-thiazoline was realized by reacting 2-mercaptoimidazoline with dibromoethane.

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