INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXXI.* 2,3-DIHYDRO DERIVATIVES OF NAPHTH[1,2-d]IMIDAZO[1,2-b]THIAZOLE AND NAPHTH[1,2-d]IMIDAZO[3,2-b]THIAZOLE

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The reactions of 2-mercaptonaphth[1,2-d]imidazole with 1,2-dichloro- and 1,2-dibromoethanes and the cyclization of 3-(β-hydroxyethyl)- and 2-(β-hydroxyethyl)mercaptonaphth[1,2-d]imidazoles were studied. 2,3-Dihydro derivatives of naphth[1,2-d]imidazo[1,2-b]thiazole and naphth[1,2-d]imidazo[3,2-b]thiazole were obtained.

In a continuation of the research in [2], as already briefly reported in [3], we studied various routes to the synthesis of the previously undescribed naphthimidazothiazoline systems, which are of interest for both chemical and biological investigations.

The reaction of 1-amino-2-(β-hydroxyethyl)aminonaphthalene (I) with potassium xanthate or of 2-chloro-3-(β-hydroxyethyl)naphth[1,2-d]imidazole (II) with thiourea gave 2-mercapto-3-(β-hydroxyethyl)-naphth[1,2-d]miidazole (IV). Like 2-mercaptonaphth[1,2-d]imidazole (III) and its 3-acylmethyl-substituted derivatives [4], this compound judging from its spectrum, exists as the thione in the solid state. Heating IV with $SOCl_2$ in dimethylformamide (DMF) gave 2,3-dihydronaphth[1,2-d]imidazo[3,2-b]thiazole (VI).

2-(β-Hydroxyethyl)mercaptonaphth[1,2-d]imidazole (V) was isolated from the reaction of III with ethylene chlorohydrin. Treatment of this compound with $SOCl_2$ or $POCl_3$ and subsequent cyclization of the intermediate 2-(β-chloroethyl)mercaptonaphth[1,2-d]imidazole under the action of alkali in ethanol or by heating in a high-boiling solvent (toluene, DMF) leads to the formation of a mixture of two isomers – VI and 2,3-dihydronaphth[1,2-d]imidazo[1,2-b]thiazole (VII), which was established by means of paper chromatography. The conversion of a mixture of VI and VII to the hydrobromides and subsequent crystallization gave the hydrobromide of VII, and the free base (VII) was obtained from it. Isomers VI and VII differ not only with respect to physical constants and R_f values but also with respect to their UV spectra.

The reaction of III with 1,2-dichloro- and 1,2-dibromoethanesproceeds in a more complex manner. When the reaction is carried out in ethanol in the presence of sodium ethoxide, 1,2-bis(2-naphthimidazolylmercapto)ethane (VIII) is formed along with VI and VII. Only pure VII and VIII could be isolated from this mixture.

It is interesting to note that the cyclization of 2-acylalkylmercaptonaphth[1,2-d]imidazoles proceeds selectively only at N_3 to give naphth[1,2-d]imidazo[3,2-b]thiazole derivatives [2]. The mechanism of the closing of the thiazole ring in the cyclization of 2-(β-haloethyl)mercaptonaphth[1,2-d]imidazoles to give a mixture of VI and VII is probably similar to the alkylation of naphth[1,2-d]imidazole (IX) and its 2-chloro-substituted derivative by alkyl halides, which, as is well-known, can proceed at both the 3 position and the 1 position of the naphthimidazole ring [5, 6].

* See [1] for communication LXX.

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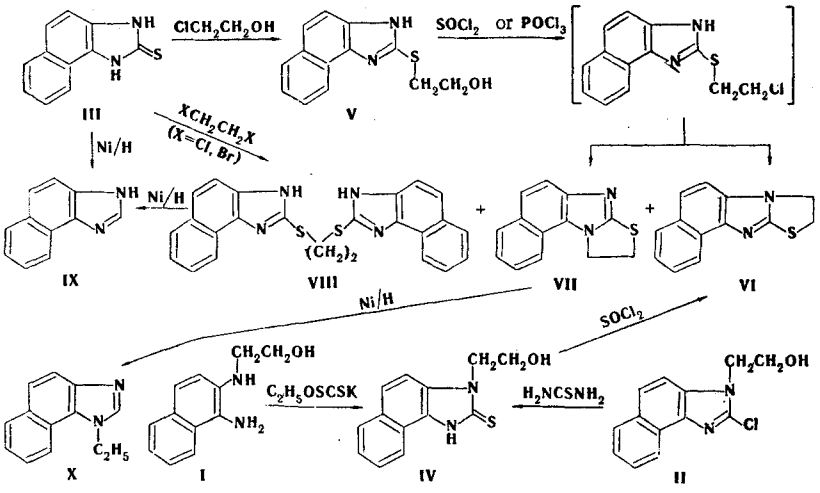
The structures of VII and VIII were established by means of the IR spectra (the presence of an absorption band of the NH group in VIII) and by reductive desulfurization under the influence of Raney nickel [2] to give 1-ethylnaphth[1,2-d]imidazole (X) and naphth[1,2-d]imidazole (IX), respectively. We also obtained the latter by heating III with Raney nickel under the conditions of the desulfurization of 2-mercaptobenzimidazole [7], which is the first instance of this reaction in the naphthimidazole series.



EXPERIMENTAL

2-Mercapto-3-(β-hydroxyethyl)naphth[1,2-d]imidazole (IV). A) A solution of 2 g (0.01 mole) of I [8] and 2.4 g (0.015 mole) of potassium ethylxanthate in 50 ml of ethanol was refluxed for 3 h, cooled, and poured into water. The resulting mixture was neutralized with acetic acid, and the precipitate was removed by filtration and washed with water to give 1.9 g (90%) of a product with mp 250-252°C [dec., from ethanol–DMF (1:1)]. IR spectrum: 3260 cm^{-1} (OH, NH). Found: C 63.7; H 5.0; N 11.2; S 13.3%. $C_{13}H_{12}N_2OS$. Calculated: C 63.9; H 4.9; N 11.5; S 13.1%.

B) A solution of 1.2 g (0.005 mole) of II [8] and 1.5 g (0.02 mole) of thiourea in 20 ml of ethanol was refluxed for 1 h, cooled, and poured into water. The resulting mixture was neutralized with ammonium hydroxide, and the precipitate was removed by filtration and washed with water to give 0.9 g (82%) of a product with mp 250-252°. A sample of this product did not depress the melting point of a sample of IV obtained by method A.

2-(β-Hydroxyethyl)mercaptonapth[1,2-d]imidazole (V). A solution of 10 g (0.05 mole) of III [9], 4.2 g (0.0505 mole) of ethylene chlorohydrin, and 0.05 mole of sodium ethoxide in 150 ml of ethanol was heated at 60-65° for 1 h and poured into water. The precipitate was removed by filtration and washed with water to give 12 g (98%) of a product with mp 159-160° (from aqueous ethanol). IR spectrum, cm^{-1}: 3190, 3220, 3260, (OH, NH). Found: C 63.7; H 5.1; N 11.2; S 13.2%. $C_{13}H_{12}N_2OS$. Calculated: C 63.9; H 5.0; N 11.5; S 13.1%.

Naphth[1,2-d]imidazo[3,2-b]thiazoline (VI). A solution of 1.1 g of IV in 5 ml of $SOCl_2$ was refluxed for 20 min and cooled, and 20 ml of DMF was added. The mixture was refluxed for 1 h, cooled, and neutralized with ammonium hydroxide. The mixture was poured into water, and the precipitate was removed by filtration to give 0.7 g (70%) of slightly cream-colored needles with mp 169-170° (dec., from aqueous ethanol) and R_f 0.45 (40% methanol), 0.93 [butanol–acetic acid–water (4:1:2)], and 0.89 [pyridine–butanol–water (6:4:3)]. UV spectrum, λ_{max}, nm (log ε): 240 (4.7), 320 (3.86), 334 (3.93). Found: C 69.0; H 4.7; N 12.1; S 14.0%. $C_{13}H_{10}N_2S$. Calculated: C 69.0; H 4.5; N 12.4; S 14.2%.

Naphth[1,2-d]imidazo[1,2-b]thiazoline (VII) and 1,2-Bis(2-naphthimidazolylmercapto)ethane (VIII). A) A solution of 2.4 g of V in 20 ml of $SOCl_2$ or $POCl_3$ was refluxed for 30 min, and the $SOCl_2$ or $POCl_3$ was removed by vacuum distillation. The residual 2-(β-chloroethyl)mercaptonaphth[1,2-d]imidazole hydrochloride was dissolved in 30 ml of ethanol, 30 ml of 30% aqueous NaOH or KOH was added, and the mixture was refluxed for 2 h, cooled, and poured into water. The aqueous mixture was extracted with chloroform, and the extract was dried with $CaCl_2$. The solvent was removed by vacuum distillation to give 1.6-2.2 g (81-98%) of a mixture of VI and VII (the chromatogram contained two spots with R_f 0.45 and 0.38,

respectively, with 40% methanol as the solvent.) Repeated crystallization of the mixture from 40 ml of 10% hydrobromic acid gave 0.4 g (36%) of the hydrobromide of VII with mp 264-266°. Found: Br 25.9%. $C_{13}H_{10}N_2S \cdot HBr$. Calculated: Br 25.7%. Decomposition of the hydrobromide with ammonium hydroxide gave base VII with mp 139-140° (from aqueous ethanol) and R_f 0.38 (40% methanol), 0.9 [butanol–acetic acid–water (4:1:2)], and 0.87 [pyridine–butanol–water (6:4:3)]. UV spectrum, λ_{max}, nm (log ε): 228 (4.51), 252 (4.75), 322 (3.63), and 336 (3.71). Found: C 69.0; H 4.6; N 12.4; S 14.4%. $C_{13}H_{10}N_2S$. Calculated: C 69.0; H 4.5; N 12.4; S 14.2%. The picrate had mp 237-238° (dec., from acetic acid). Found: N 15.7%. $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 15.4%.

B) A solution of 1.2 g of V in 10 ml of $SOCl_2$ was refluxed for 30 min, the $SOCl_2$ was removed by vacuum distillation, and 20 ml of toluene was added to the residue. The mixture was refluxed for 2 h and cooled. The solvent was decanted, and the viscous residue was dissolved in water. The aqueous solution was neutralized with ammonium hydroxide and worked up as described in method A to give 0.9 g (82%) of a mixture of VI and VII (the chromatogram contained two spots with R_f 0.45 and 0.38). Crystallization of the mixture as described above gave 0.4 g (36%) of the hydrobromide of VII, the decomposition of which gave VII with mp 139-140°.

C) A mixture of 1.2 g of V, 5 ml of $SOCl_2$, and 10 ml of anhydrous DMF was refluxed for 1 h, cooled, and poured into water. The aqueous solution was neutralized with ammonium hydroxide and worked up as described in method A to give 1 g (90%) of a mixture of VI and VII (the chromatogram contained two spots with R_f 0.45 and 0.38.) Separation of the mixture as described above gave 0.3 g (27%) of the hydrobromide of VII, from which base VII with mp 139-140° was obtained.

D) A solution of 0.03 mole of III, 0.03 mole of 1,2-dichloroethane or 1,2-dibromoethane, and 0.06 mole of sodium ethoxide in 60 ml of anhydrous ethanol was refluxed for 3 h, cooled, and poured into water. The aqueous mixture was worked up as in method A to give 6.3 g of a mixture of VI, VII, and 1,2-di(naphthimidazolyl)ethane VIII (the chromatogram contained two spots with R_f 0.45 and 0.38; VIII was at the start with a 40% methanol system.) The mixture of VI-VIII was heated with 100 ml of 10% hydrobromic acid, and the hot solution was filtered to separate it from the undissolved hydrobromide of VIII. Decomposition of the latter with ammonium hydroxide gave 2.8 g (40%) of base VIII as colorless prisms with mp 222-223° (dec., from ethanol). IR spectrum: 3060 cm^{-1} (NH). Found: C 67.2; H 4.5; N 13.0; S 14.7%. $C_{24}H_{18}N_4S_2$. Calculated: C 67.6 H 4.3; N 13.1; S 15.0%. The mother liquor from the separation of the hydrobromide of VIII was neutralized with ammonium hydroxide, and the precipitate was removed by filtration and crystallized from aqueous ethanol to give 2.3 g (34%) of VII with mp 139-140°. Samples of the compounds obtained by methods A-D did not depress the melting point of VII but did depress the melting point of VI to 105-110°.

Naphth[1,2-d]imidazole (IX). A mixture of 1.6 g of VIII and 30 g of Raney nickel paste in 100 ml of ethanol was refluxed for 7 h, cooled, and filtered. The solvent was removed by vacuum distillation to give 0.6 g of IX with mp 174° (from aqueous methanol). A sample of this product did not depress the melting point (174°) of a genuine sample of IX obtained via the method in [10] or by dethionation of III by the action of Raney nickel under the conditions described above (the yield of IX was 30%).

1-Ethylnaphth[1,2-d]imidazole (X). A mixture of 1.1 g of VII and 30 g of Raney nickel paste in 30 ml of ethanol was refluxed and worked up as described for the dethionation of VIII to give 0.5 g (50%) of crude X. The picrate had mp 205-208° (dec., from ethanol). A mixture of this picrate and the picrate of 3-ethylnaphth[1,2-d]imidazole (mp 250-251° [2]) melted at 186-195°. Found: C 53.7; H 3.4; N 16.6%. $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 53.6; H 3.6; N 16.5%. According to [5], base X has mp 129-130°.

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