INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXII.* REACTION OF 2-MERCAPTONAPHTH[1,2-d]IMIDAZOLE WITH α-HALOALDEHYDES AND THEIR ACETALS

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The reaction of 2-mercaptonaphth[1,2-d]imidazole with chloroacetaldehyde, bromoacetaldehyde, and α-bromopropionaldehyde diethylacetals leads to the formation of (naphth[1,2-d]-2-mercaptoimidazolyl)acetaldehyde and α-(naphth[1,2-d]-2-mercaptoimidazolyl)propionaldehyde which in the solid state exist as tautomeric forms – 3-hydroxy derivatives of naphth[1,2-d]-imidazo[3,2-d]thiazoline. The corresponding naphth[1,2-d]imidazo[3,2-b]thiazoles were obtained by dehydration of the latter. The structure of the four-ring compounds was proved by reductive desulfurization to 3-alkylnaphth[1,2-d]imidazoles and alternative synthesis from 2-chloro-3-acylmethylnaphth[1,2-d]imidazoles.

We recently proposed a method for the preparation of the previously unknown naphth[1,2-d]imidazo-[3,2-b]thiazole (VIII) heteroaromatic system and its derivatives [2]. This paper is devoted to a more detailed discussion of the reaction of 2-mercaptonaphth[1,2-d]imidazole (I) with α-haloaldehydes and their acetals, to a study of the conditions for the cyclization of the intermediates to derivatives of VIII, and also to a proof of the structure of the four-ring compounds.

(2-Mercaptonaphthimidazolyl)acetaldehyde diethylacetal (III) was obtained by the reaction of 2-mercaptonaphth[1,2-d]imidazole (I) with bromoacetaldehyde diethylacetal in ethanol in the presence of sodium ethoxide. As in the case of the acetals of 2-imidazolyl- and 2-mercaptobenzimidazolylacetaldehydes [3, 4], heating of III with $POCl_3$ leads to splitting out of only one molecule of alcohol to form 3-ethoxynaphth[1,2-d]imidazo[3,2-b]thiazoline (IV). The picrate of IV was also isolated by heating the picrate of III above its melting point.

The same crystalline substance, which, according to the results of elemental analysis, is (2-naphthimidazolylmercapto)acetaldehyde (Va), was obtained by the hydrolysis of III and IV in hydrochloric acid and also by the reaction of I with the hydrate of chloroacetaldehyde dimer in dimethylformamide or with bromoacetaldehyde diethylacetal in water.

A study of the IR spectra of Va as well as the product of the reaction of I in aqueous ethanol with α-bromopropionaldehyde diethylacetal (VIIa) showed the absence of absorption bands of a C=O group in them. These aldehydes, like the corresponding aldehydes in the imidazole [3, 5, 6] and benzimidazole [4, 7, 8] series, apparently exist as cyclic tautomeric forms – 3-hydroxy derivatives of naphth[1,2-d]imidazo[3,2-b]thiazoline (Vb and VIIb). Compounds Vb and VIIb can react as the open aldehyde forms Va and VIIa, as attested to by the formation, for example, of the 2,4-dinitrophenylhydrazone (VI) of (2-naphthimidazolylmercapto)acetaldehyde.

*See [1] for communication LXI.

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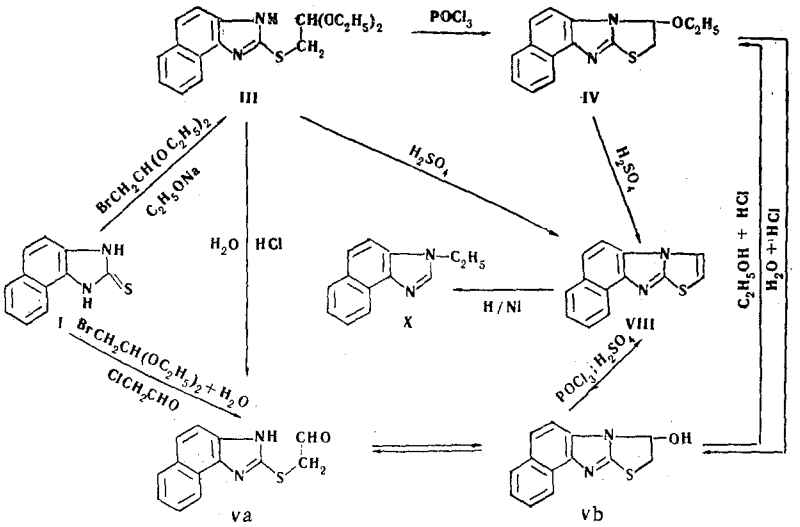
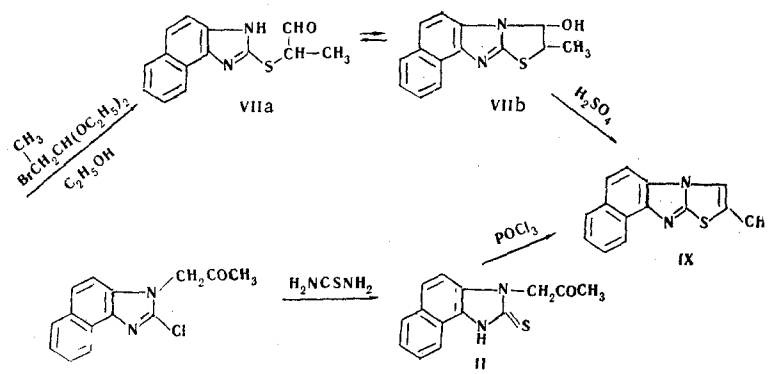
Compounds Vb and VIIb do not change when they are heated in concentrated hydrochloric acid, are converted to 3-ethoxy derivatives of naphth[1,2-d]imidazo[3,2-b]thiazoline by the action of alcoholic HCl (IV was obtained in this way), and readily split out a molecule of water to form VIII and IX on treatment with dehydrating agents ($POCl_3$ and concentrated H_2SO_4). Compound VIII was also obtained by treatment of III and V with concentrated H_2SO_4.



It is known that naphth[1,2-d]imidazole is a tautomeric system that contains two nonequivalent nitrogen atoms. Consequently, as a result of intramolecular cyclization of (2-naphthimidazolylmercapto)-substituted aldehydes and their acetals, like the alkylation of naphth[1,2-d]imidazoles [9-11] and its 2-substituted derivatives [12], the reaction could proceed at the 3 position as well as at the 1 position of the naphthimidazole ring ultimately leading to the formation of derivatives of VIII, derivatives of the previously undescribed naphth[1,2-d]imidazo[2,1-b]thiazole, or a mixture of isomers.

We obtained one substance in all cases. The purity of VIII was confirmed by chromatography, and its structure was confirmed by reductive desulfurization under the influence of a Raney nickel catalyst [13, 14]; the known 3-ethylnaphth[1,2-d]imidazole (X) was isolated [9].



The structure of IX was proved by alternative synthesis from 2-chloro-3-acetonylnaphth[1,2-d]imidazole [15] by its conversion to the corresponding thione (II) and subsequent cyclization of II under the influence of $POCl_3$.

EXPERIMENTAL

3-Acetonylnaphth[1,2-d]imidazole-2-thione (II). A solution of 0.9 g (0.0035 mole) of 2-chloro-3-acetonylnaphth[1,2-d]imidazole [15] and 0.5 g (0.007 mole) of thiourea in 20 ml of ethanol was refluxed for 2 h, cooled, and poured into water. The mixture was neutralized with ammonium hydroxide, and the precipitate was removed by filtration and washed with water to give 0.8 g (90%) of a product with mp 266-268°

(dec., from ethanol). IR spectrum, cm^{-1}: 1730 (CO), 3110 (NH). Found: C 66.0; H 4.4; N 10.6; S 12.7%. $C_{14}H_{12}N_2OS$. Calculated: C 65.6; H 4.7; N 10.9; S 12.5%.

(2-Naphth[1,2-d]imidazolylmercapto)acetaldehyde Diethylacetal (III). A total of 6 g (0.03 mole) of I [16] and 6.5 g (0.032 mole) of freshly distilled bromoacetaldehyde diethylacetal were added to a solution of sodium ethoxide prepared from 0.69 g (0.03 g-atom) of sodium and 50 ml of anhydrous ethanol. The mixture was refluxed for 11 h, cooled, and poured into water. The mixture was extracted with $CHCl_3$, and the extract was washed with water, dried over $MgSO_4$, and filtered. The solvent was removed completely by vacuum distillation to give 8 g (84%) of a light-yellow, syrupy liquid that was soluble in most organic solvents and insoluble in water. The preparation was suitable for most of the syntheses without additional purification. The picrate [purified by precipitation by the addition of water to a solution in ethanol–acetone (1:1) in the cold] melted at 122-123° (on insertion into an apparatus heated to 115-118°); at 125-128° the melt solidified and melted again at 195-196° (conversion to the picrate of IV), while at 200-202° the melt again solidified and then melted at 217-218° (conversion to the picrate of VIII). Found: C 50.7; H 4.1; N 12.6; S 6.0%. $C_{17}H_{20}N_2OS \cdot C_6H_3N_3O_7$. Calculated: C 50.6; H 4.2; N 12.8; S 5.9%.

3-Ethoxynaphth[1,2-d]imidazo[3,2-b]thiazoline (IV). A) A solution of 3.16 g of III in 15 ml of $POCl_3$ was refluxed for 1 h and 20 min, and the solvent was removed by vacuum distillation. The residue was decomposed with water, neutralized with sodium carbonate, and extracted with $CHCl_3$. The extract was worked up as described for the preparation of III to give 2,3 g (93%) of IV as a syrupy liquid that was soluble in organic solvents and insoluble in water. The picrate melted at 198-200° (from anhydrous ethanol); at 200-202° the melt solidified and then remelted at 220-221° (conversion to the picrate of VIII). Found: C 50.7; H 3.4; N 13.9; S 6.5%. $C_{15}H_{14}N_2OS \cdot C_6H_3N_3O_7$. Calculated: C 50.5; H 3.4; N 14.0; S 6.4%.

B) About 0.1 g of picrate of III was heated in a capillary tube to 122-123°, and the fused and resolidified melt of picrate of IV was cooled and crystallized from ethanol to give a product with mp 198-200°.

C) A solution of 1 g of Vb in 30 ml of alcoholic HCl was refluxed for 1 h, neutralized with sodium acetate, and poured into water. The mixture was worked up as in the isolation of III to give 0.95 g (86%) of IV. The picrate melted at 198-200°. Mixtures of picrates of IV prepared by methods A-C did not show any melting point depression.

3-Hydroxynaphth[1,2-d]imidazo[3,2-b]thiazoline (Vb). A) A 3.7 g (0.04 mole) sample of the hydrate of chloroacetaldehyde dimer was added to a solution of 8 g (0.04 mole) of I in 30 ml of dimethylformamide, and the mixture was heated at 60-65° for 1 h. It was then cooled and poured into water. The mixture was neutralized with sodium carbonate, and the precipitate was removed by filtration to give 8.9 g (92%) of a product with mp 210-213° (dec., from propanol). IR spectrum: 3100 cm^{-1} (OH). Found: C 64.6; H 4.2; N 11.5; S 13.0%. $C_{13}H_{10}N_2OS$. Calculated: C 64.4; H 4.2; N 11.6; S 13.2%.

B) A mixture of 4 g (0.02 mole) of I and 4 g (0.02 mole) of bromoacetaldehyde diethylacetal in 30 ml of water was refluxed for 3 h and worked up as in experiment A to give 3.7 g (77%) of product.

C) A solution of 2.2 g of II in 20 ml of concentrated hydrochloric acid was refluxed for 1.5 h, cooled, and worked up as in experiment A to give 1.7 g (80%) of product.

D) A solution of 1 g of IV in 10 ml of concentrated hydrochloric acid was refluxed for 1 h and worked up as in experiment A to give 0.7 g (74%) of product. Mixtures of samples of Vb obtained by methods A-D did not show any melting point depression.

(2-Naphth[1,2-d]imidazolylmercapto)acetaldehyde 2,4-Dinitrophenylhydrazone (VI). A solution of 2.5 g (0.0125 mole) of Vb and 2.5 g (0.0125 mole) of 2,4-dinitrophenylhydrazine in 75 ml of glacial acetic acid was refluxed for 30 min and cooled. The precipitate was removed by filtration and washed with ether to give 3 g (62%) of red-brown needles with mp 214-216° (dec., from glacial acetic acid). Found: C 54.5; H 3.4; N 19.9; S 7.6%. $C_{19}H_{14}N_6O_4S$. Calculated: C 54.0; H 3.3; N 19.9; S 7.6%.

2-Methyl-3-hydroxynaphth[1,2-d]imidazo[3,2-b]thiazoline (VIIb). A mixture of 10 g (0.05 mole) of I and 11.6 g (0.055 mole) of α-bromopropionaldehyde diethylacetal in 200 ml of 50% ethanol was refluxed for 3 h, after which the solution was worked up as described for Vb (experiment A) to give 11.7 g (96%) of a product with mp 208-209° (dec., from ethanol). IR spectrum: 3070 cm^{-1} (OH). Found: C 65.4; H 4.8; N 10.6; S 12.6%. $C_{14}H_{12}N_2OS$. Calculated: C 65.6; H 4.7; N 10.9; S 12.5%.

Naphth[1,2-d]imidazo[3,2-b]thiazole (VIII). A) A solution of 3.6 g of Vb in 50 ml of $POCl_3$ was refluxed for 2 h, the $POCl_3$ was removed by vacuum distillation, and the residue was decomposed with water and neutralized with sodium carbonate. The precipitate was removed by filtration to give 2.9 g (87%) of a product with mp 195-196° (dec., from ethanol), Paper chromatography (Filtrak No. 11) gave one spot with R_f 0.89 [in n-C_4H_9OH-CH_3COOH-H_2O system (4:1:2)], 0.88 [in a C_5H_5N-n-C_4H_9OH-H_2O system (6:4:3)], and 0.80 (in 80% methanol or 50% acetic acid). Found: C 69.5; H 3.7; N 12.4; S 14.0%. $C_{13}H_8N_2S$. Calculated: C 69.6; H 3.6; N 12.5; S 14.3%. The hydrochloride melted at 235-237° (dec., from ethanol). Found: Cl 13.0%. $C_{13}H_8N_2S \cdot HCl \cdot H_2O$. Calculated: Cl 12.7%. The picrate melted at 233-234° (dec., from glacial acetic acid). Found: N 15.2%. $C_{13}H_8N_2S \cdot C_6H_3N_3O_7$. Calculated: N 15.4%.

B) A solution of 3.6 g of Vb and 20 ml of concentrated H_2SO_4 was held at 18-20° for 24 h, poured into water, and neutralized with ammonium hydroxide. The precipitate was removed by filtration to give 2.2 g (66%) of product.

C) A solution of 1.66 g of III in 10 ml of concentrated H_2SO_4 was allowed to stand at 18-20° for 24 h, after which it was worked up as in experiment B to give 0.5 g (64%) of product.

D) A solution of 1.3 g of IV in 10 ml of concentrated H_2SO_4 was treated and worked up as in experiment B to give 1 g (91%) of product. Mixtures of samples of VIII obtained by methods A-D did not show any melting point depression.

2-Methylnaphth[1,2-d]imidazo[3,2-b]thiazole (IX). A) A solution of 2.6 g of VII in 10 ml of concentrated H_2SO_4 was allowed to stand at 18-20° for 4 h, after which it was worked up as described in the preparation of VIII (method B) to give 2.4 g (96%) of a product with mp 184-185° (dec., from ethanol) (mp 184-185° [17]).

B) A solution of 0.26 g of II in 10 ml of $POCl_3$ was refluxed for 1 h, the $POCl_3$ was removed in vacuo, and the residue was decomposed with water and neutralized with ammonium hydroxide. The precipitate was removed by filtration and washed with water to give 0.23 g (95%) of a product with mp 184-185° (from ethanol). This product did not depress the melting point of IX obtained by method A.

3-Ethylnaphth[1,2-d]imidazole (X). A) A mixture of 2.2 g of VIII and 35 g of a Raney nickel paste in 50 ml of ethanol was refluxed for 15 h. The catalyst was removed by filtration, and the solvent was removed by vacuum distillation. The residue was dissolved in $CHCl_3$, and the solution was washed with water and dried over $CaCl_2$. The solvent was removed by distillation to give 1.8 g (92%) of a product with mp 119-121°. Colorless prisms with mp 124-125° were obtained from aqueous dioxane. According to [9], base X is an oil. Found: C 79.7; H 6.0; N 14.3%. $C_{13}H_{12}N_2$. Calculated: C 79.6; H 6.2; N 14.3%. The hydrochloride melted at 237-238° (dec., from ethanol) (mp 226° [9]). Found: Cl 15.3%. $C_{13}H_{12}N_2 \cdot HCl$. Calculated: Cl 15.2%. The picrate melted at 250-251° (dec., from ethanol). Found: N 16.2%. $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 16.5%.

B) A 1.7 g (0.01 mole) sample of naphth[1,2-d]imidazole [18] and 3.1 g (0.02 mole) of ethyl iodide were added to a solution of 1.1 g (0.02 mole) of KOH in 20 ml of ethanol. The mixture was refluxed for 1 h, cooled, and poured into water. The mixture was extracted with ether, and the extract was washed with 20% KOH solution and water and worked up as in A to give 1.5 g (77%) of a product with mp 124-125° (from aqueous dioxane). The picrate melted at 250-251° (dec., from ethanol).

C) A solution of 10 g of 1-amino-2-ethylaminonaphthalene[19] in 30 ml of 85% formic acid was refluxed 2 h, cooled, and neutralized with ammonium hydroxide. The mixture was extracted with ether to give 8 g (81%) of a product with mp 124-125° (from aqueous dioxane). The picrate melted at 250-251°. Mixtures of samples X and its picrate with samples obtained by methods A-C did not show any melting point depression.

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