INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXXII.* SYNTHESIS OF NAPHTH[1,2-d]IMIDAZO[3,2-b]-3-THIAZOLIDONE AND ITS DERIVATIVES

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Naphth[1,2-d]imidazo[3,2-b]-3-thiazolidone and its methyl homolog were synthesized by the reaction of 2-mercaptonaphth[1,2-d]imidazole with chloroacetic and α-chloropropionic acids with subsequent cyclization of the naphth[1,2-d]imidazole-2-mercaptoacetic acids. The reactions of the first of them at the methylene group with aldehydes, nitroso compounds, and benzenediazonium salts were studied; the corresponding arylidene and azomethine derivatives of naphthimidazo-3-thiazolidone and the arylhydrazones of naphth[1,2-d]imidazo[3,2-b]thiazoline-2,3-dione were obtained. The arylidene derivatives of naphthimidazo-3-thiazolidone were also obtained by the reaction of naphthimidazole-2-mercaptoacetic acid or its methyl ester with aldehydes or (in one step) by the reaction of 2-mercaptonaphth[1,2-d]imidazole with chloroacetic acid and carbonyl compounds.

Derivatives of imidazo[3,2-b]-3-thiazolidone and polycyclic systems including the indicated heterocycle are of interest in the search for biologically active substances and dyes [2-6].

We have studied the reaction of 2-mercaptonaphth[1,2-d]imidazole (I) with chloroacetic and α-chloropropionic acids to give naphth[1,2-d]imidazole-2-mercaptoacetic acids (II, III). Naphth[1,2-d]imidazo[3,2-b]-3-thiazolidone (VI) and its 2-methyl homolog (VII) were synthesized by heating these compounds with acetic anhydride. Two isomers – VI and naphth[1,2-d]imidazo[1,2-b]-3-thiazolidone – could be formed as a result of the dehydration of acid II. The purity of VI was established by paper chromatography, and its structure was established by IR spectroscopy (presence of the absorption band of a CO group at 1740 cm^{-1}) and by reduction with lithium aluminum hydride to the known naphth[1,2-d]imidazo[3,2-b]thiazoline (XX) [1]. The formation of thiazolidone VI as a result of intramolecular acylation is consequently in agreement with the data in one of our previous papers [7], in which it was demonstrated that the acylation of S-substituted 2-mercaptonaphth[1,2-d]imidazoles proceeds at the imino group in the 3 position of the naphthimidazole ring.

As in the case of esters of imidazole-2- and benzimidazole-2-mercaptoacetic acids [3, 6], the action of acetic anhydride on methyl naphthimidazole-2-mercaptoacetic acid (IV), obtained by the reaction of thiol I with $ClCH_2COOCH_3$ or $ClCH_2COOH$ in methanol, leads only to its acetylation to form methyl 3-acetylnaphth-[1,2-d]imidazole-2-mercaptoacetate (V).

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*See [1] for communication LXXI.

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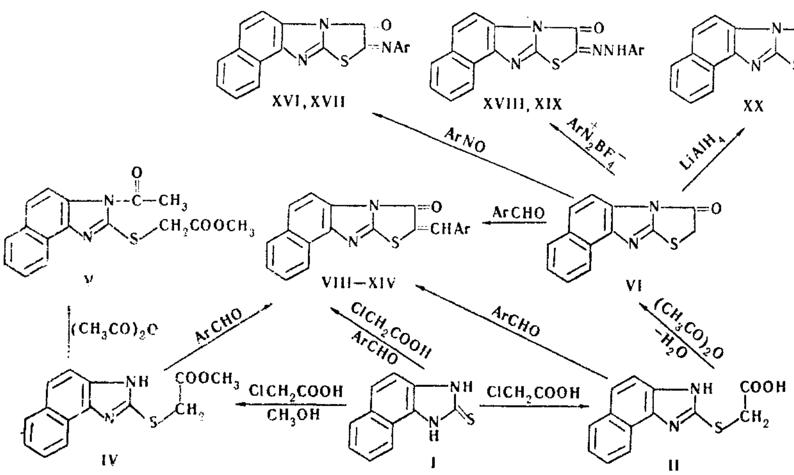


Cyclic amide VI contains an active methylene group and readily undergoes reaction with aldehydes, nitroso compounds, and benzenediazonium borofluorides to form the corresponding arylidene (XII) and azomethine (XVI, XVII) derivatives and arylhydrazones of naphth[1,2-d]imidazo[3,2-b]thiazoline-2,3-dione (XVIII, XIX) (see Table 1).

Like the synthesis of 2-arylidene-substituted benzimidazo[1,2-b]-3-thiazolidone [8-13], the arylidene derivatives of VI (VIII-XV) were also obtained by other simpler methods – by the reaction of acid II or its ester (IV) with aromatic aldehydes or of mercaptan I with chloroacetic acid and carbonyl compounds (aldehydes and isatin).

The structures of derivatives VIII-XIX were confirmed by the IR spectra, which contain absorption bands of the CO groups. In addition, the absorption band of an NH group is observed at 3170 cm^{-1} in the IR spectra of arylhydrazones XVIII and XIX. It has been reported that the products of the azo coupling of imidazo[2,1-b]-3-thiazolidones [2] and benzimidazo[2,1-b]-3-thiazolidones [3] also have arylhydrazone structures.

EXPERIMENTAL

Naphth[1,2-d]imidazole-2-mercaptoacetic Acid (II). A solution of 4 g (0.02 mole) of I [14] and 2 g (0.02 mole) of chloroacetic acid in 50 ml of dimethylformamide (DMF) was heated at 60-65° for 1 h, 2 g of sodium acetate was added, and the mixture was cooled and poured into water. The precipitate was removed by filtration and washed with water to give 4.2 g (81%) of a product with mp 225-227° (dec., from aqueous DMF). IR spectrum, cm^{-1}: 1710 (CO), 3070, 3230 (OH, NH). Found: C 60.7; H 3.7; N 10.8; S 12.2%. $C_{13}H_{10}N_2O_2S$. Calculated: C 60.4; H 3.9; N 10.8; S 12.4%.

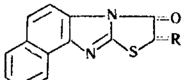
Naphth[1,2-d]imidazole-2-mercaptopropionic Acid (III). This compound was similarly obtained in 96% yield and had mp 220-221° (dec., from ethanol). Found: C 61.6; H 4.3; N 10.5; S 11.9%. $C_{14}H_{12}N_2O_2S$. Calculated: C 61.7; H 4.4; N 10.3; S 11.8%.

Methyl Naphth[1,2-d]imidazole-2-mercaptoacetate (IV). A) A mixture of 2 g (0.01 mole) of I and 1.53 g (0.01 mole) of methyl chloroacetate in 30 ml of methanol was refluxed for 2 h, cooled, and poured into water. The mixture was neutralized with sodium acetate, and the precipitate was removed by filtration and washed with water to give 1.9 g (70%) of a product with mp 114-115° (dec., from CCl_4). IR spectrum, cm^{-1}: 1730 (CO), 3080, 3280 (NH). Found: C 61.9; H 4.6; N 10.6; S 11.7%. $C_{14}H_{12}N_2O_2S$. Calculated: C 61.8; H 4.4; N 10.3; S 11.8%.

B) A mixture of 2 g (0.01 mole) of I and 1 g (0.01 mole) of chloroacetic acid in 30 ml of absolute methanol was refluxed for 10 h and worked up as in experiment A to give 2.2 g (81%) of a product with mp 114-115°. This product did not depress the melting point of IV obtained by method A.

Methyl 3-Acetylnaphth[1,2-d]imidazole-2-mercaptoacetate (V). A mixture of 2.7 g of IV and 20 ml of acetic anhydride was refluxed for 1 h, cooled, and poured into water. The precipitate was removed by filtration and washed with water to give 2.7 g (87%) of a product with mp 166-168° (dec., from dioxane). IR spectrum, cm^{-1}: 1705, 1740 (CO). Found: C 61.0; H 4.4; N 8.9; S 10.6%. $C_{16}H_{14}N_2O_3S$. Calculated: C 61.1; H 4.5; N 8.9; S 10.2%.

TABLE 1



XVI–XIX

Compound	R	Mp (dec.), °C	IR spectrum (CO or NH), cm^{-1}	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	N	S	C	H	N	S	
VI	H_2	212—213	1740	$C_{13}H_8N_2OS$*	65,0	3,4	11,7	13,2	64,7	3,8	11,6	13,3	95
VII	H, CH_3	125—127	1735	$C_{14}H_{10}N_2OS$	66,1	4,0	11,4	12,4	66,1	4,0	11,0	12,1	90
VIII	C_6H_5CH	239—240	1720	$C_{20}H_{12}N_2OS$	73,0	3,6	8,6	9,6	73,1	3,7	8,5	9,8	52
IX	p-$(CH_3)_2CHC_6H_4CH$	181—182	1715	$C_{23}H_{18}N_2OS$	74,9	5,3	7,7	8,6	74,6	4,9	7,6	8,6	51
X	o-$O_2NC_6H_4CH$	247—248	1730	$C_{20}H_{11}N_3O_3S$	64,7	3,0	10,8	8,2	64,3	3,0	11,2	8,5	36
XI	m-$O_2NC_6H_4CH$	275—276	1715	$C_{20}H_{11}N_3O_3S$	64,5	3,0	11,3	8,4	64,3	3,0	11,2	8,5	49
XII	p-$O_2NC_6H_4CH$	270—271	1725	$C_{20}H_{11}N_3O_3S$	64,7	3,4	11,0	8,7	64,3	3,0	11,2	8,5	27—99
XIII	$C_6H_5CH{=}CHCH$	258—259	1715	$C_{22}H_{14}N_2OS$	75,0	4,3	8,3	9,3	74,6	4,0	8,0	9,0	58
XIV	2-Furfurylidene	271—272	1715	$C_{17}H_{10}N_2O_2S$	68,0	3,4	8,8	10,3	67,9	3,2	8,8	10,1	50
XV	3-Isatinylidene	>360	1695; 1670; 3140	$C_{21}H_{11}N_3O_2S$	68,6	3,4	11,7	8,8	68,3	3,0	11,4	8,7	30
XVI	p-$(CH_3)_2NC_6H_4N$	205—206	1695	$C_{21}H_{16}N_4OS$	68,8	4,2	14,8	8,5	68,6	4,4	14,5	8,3	77
XVII	p-$(C_2H_5)_2NC_6H_4N$	202—203	—	$C_{23}H_{20}N_4OS$	68,5	4,7	14,0	8,2	68,9	5,0	14,0	8,2	50
XVIII	p-$CH_3OC_6H_4NHN$	222—223	1715; 3170	$C_{20}H_{14}N_4O_2S$	64,1	4,2	14,6	8,2	64,2	3,8	14,9	8,2	68
XIX	p-BrC_6H_4NHN	252—253	1720; 3170	$C_{19}H_{11}BrN_4OS$†	53,5	2,6	12,8	7,3	53,9	2,6	13,2	7,6	95

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*R_f 0.93 (ethanol), 0.45 (methanol), 0.95 (dioxane).

†Found: Br 18.7%. Calculated: Br 18.9%.

Naphth[1,2-d]imidazo[3,2-b]-3-thiazolidones (VI, VII, Table 1). A 0.01-mole sample of II or III was refluxed in 10 ml of acetic anhydride for 10 min, and the mixture was cooled. The precipitate was removed by filtration and washed with ether. Evaporation of the mother liquors gave an additional amount of substances. Samples of VI and VII were purified for analysis by crystallization from ethanol.

2-Arylidenenaphth[1,2-d]imidazo[3,2-b]-3-thiazolidones (VIII-XV, Table 1). A) A solution of 1.2 g (0.005 mole of VI and 0.75 g (0.005 mole) of p-nitrobenzaldehyde in 60 ml of ethanol was refluxed for 2 h and cooled. The precipitate was removed by filtration and washed with ethanol to give 0.6 g (33%) of XII.

B) A solution of 1.3 g (0.005 mole) of II, 1.3 g of sodium acetate, and 0.75 g (0.005 mole) of p-nitrobenzaldehyde in 30 ml of acetic acid was refluxed for 2 h and cooled. The precipitate was removed by filtration and washed with water to give 0.5 g (27%) of XII.

C) A solution of 0.68 g (0.0025 mole) of IV, 0.68 g of sodium acetate, and 0.32 g (0.0025 mole) of p-nitrobenzaldehyde in 15 ml of acetic acid was refluxed for 30 min and worked up as in experiment B to give 0.9 g (99%) of XII.

D) A mixture of 0.01 mole of I, 0.01 mole of chloroacetic acid, 0.01 mole of aldehyde or isatin, and 0.01 mole of sodium acetate in 30 ml of acetic acid was refluxed for 6 h and cooled. The precipitated VIII-XV was removed by filtration and washed with water. A sample of this product did not depress the melting point of a sample obtained by method A. The yellow (VIII, IX, XI, XIV), orange (XIII), or red (XII, XV) crystalline substances were only slightly soluble in most organic solvents. The compounds were purified for analysis by crystallization from acetic acid (VIII) and DMF (IX-XV).

2-Aryliminonaphth[1,2-d]imidazo[3,2-b]-3-thiazolidones (XVI, XVII, Table 1). A solution of 0.005 mole of VI and 0.005 mole of nitroso compound in 50 ml of absolute ethanol was refluxed for 1 h and cooled. The precipitate was removed by filtration and washed with ethanol to give dark-red crystalline substances that were only slightly soluble in ethanol and other organic solvents. Compounds XVI and XVII were purified for analysis by crystallization from dichloroethane.

Naphth[1,2-d]imidazo[3,2-b]thiazoline-2,3-dione 2-Arylhydrazones (XVIII, XIX, Table 1). Sodium acetate (2 g), 10 ml of acetic anhydride, and 0.01 mole of a suspension of arenediazonium borofluoride in 50 ml of anhydrous ethanol and 5 ml of acetic anhydride were added to a solution of 0.01 mole of VI in 50 ml of acetic acid. The reaction mass was allowed to stand in the dark at 18-20° for 24 h, and the precipitate was removed by filtration and washed with water. The yellow (XVIII) or brown (XIX) crystalline substances were only slightly soluble in most organic solvents. The compounds were purified for analysis by crystallization from ethanol (XVIII) or acetic acid (XIX).

Naphth[1,2-d]imidazo[3,2-b]thiazoline (XX). A 5-g (0.13 mole) sample of $LiAlH_4$ was added to a solution of 2.4 g (0.01 mole) of VI in 60 ml of absolute tetrahydrofuran, and the mixture was refluxed for 10 h. The excess lithium aluminum hydride was decomposed initially with moist ether and then with water, and the solution was filtered. The ether was removed by vacuum distillation to give 0.45 g (20%) of a product with mp 169-170° (dec., from aqueous ethanol). The product did not depress the melting point of an authentic sample [1].

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