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CONVERSION OF 2-AMINOMETHYLBENZOTHIAZOLES INTO IMIDAZO[5,1-b]BENZOTHIAZOLES

V. V. Avidon, M. N. Shchukina

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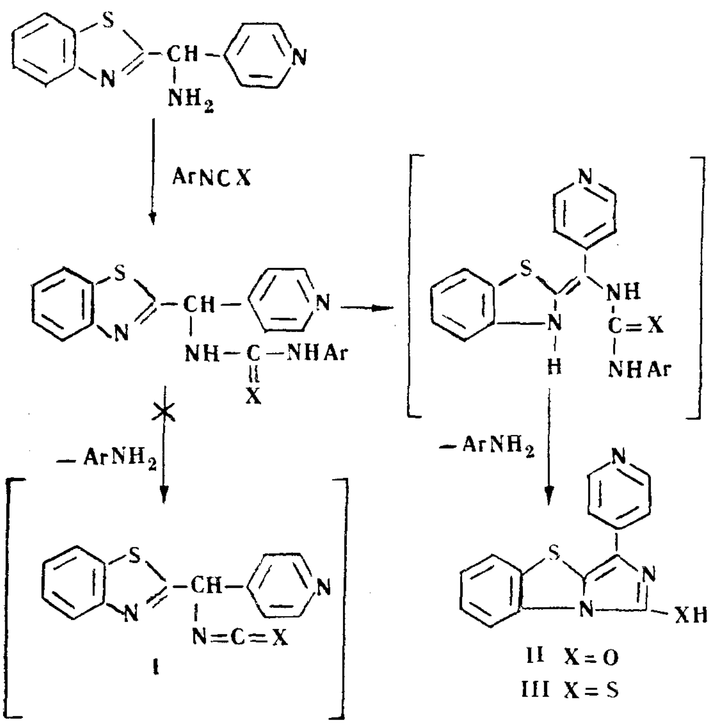
A number of substituted 2-aminomethylbenzothiazoles are synthesized. The corresponding ureas or thioureas are also obtained by reaction with arylisocyanates or arylisothiocyanates. Heating the substituted ureas or thioureas at temperatures above their melting points cyclizes them to 9-substituted 2-hydroxy- or 2-mercaptoimidazo[5,1-b]benzothiazoles, which are derivatives of a new heterocyclic system.

The preparation of 2-benzothiazolyl-4-pyridylaminomethane has already been described by the authors [1]. To characterize this amine it was reacted with phenyl isocyanate and p-ethoxyphenylisothiocyanate to give the corresponding urea and thiourea. When these substances are heated at temperatures above their melting points, an aromatic amine is split off, and new substances are formed which, from their elementary compositions, might be assumed to have the structure of an isocyanate or isothiocyanate I, or of the corresponding cyclization products, viz., 2-hydroxy-9-(pyridyl-4)-imidazo[5,1-b]benzothiazole II and 2-mercapto-9-(pyridyl-4)-imidazo[5,1-b]benzothiazole III, respectively.



I

II X=O

III X=S

The properties of the resultant compounds exclude the first hypothesis and confirm the second one. These substances do not react with aromatic amines, and the UV absorption spectra maxima are distinctly shifted toward longer wavelengths, indicating an increase in the system of conjugated double bonds. The tricyclic compounds II and III form salts with alkalies, compound III giving a positive Feigl qualitative reaction for the mercapto group [2].

The substances synthesized in this way are derivatives of a new type of heterocyclic system, imidazo[5,1-b]benzothiazole. It was of interest to prepare a series of other representatives of this group. Phenyl-, m-chlorophenyl-, and methyl-2-benzothiazole ketone were synthesized; the oximes prepared from them were reduced to amines. When the latter are treated with phenyl isocyanate in ether, they are converted into substituted 1-[(benzothiazolyl-2)-methyl]ureas, and, by treatment with p-ethoxyphenylisothiocyanate in boiling benzene, into substituted 1-[(benzothiazolyl-2)-methyl]-thioureas. When these compounds are heated in the corresponding selected solvents, they cyclize, with separation of aromatic amine, into 2-hydroxyimidazo[5,1-b]benzothiazoles. The present newly-discovered reaction resembles the reaction of formation of benzoimidazolones from o-phenylenediamine and ammonium cyanate or urea. In this case, however, the cyclization can be realized only through regrouping of bonds and migration of a methyl hydrogen to the nitrogen atom of the benzothiazole ring. It is interesting to note that, as previously described [1], under the action of acetic anhydride this hydrogen atom migrates to the nitrogen of the pyridine ring, while on heating in high-boiling neutral solvents hydrogen migration and ring closure occur in the thiazole ring.

EXPERIMENTAL

Phenyl-2-benzothiazolyl ketone. 30.04 g ethyl benzoate in 80 ml ether is added dropwise to 0.2 mole benzothiazolyl lithium [3] in 600 ml dry ether, the temperature not being allowed to rise above –45°, the mixture stirred 2 hr at –45° to –25°, and then poured into 300 ml 1:2 hydrochloric acid. The ether layer is separated, washed with water, and dried over magnesium sulfate, and the ether taken off in a vacuum. The residue is recrystallized from 50 ml alcohol, to give 27.8 g (58.6%) of the ketone, m.p. 102.0°-102.7° (cf. [3]).

m-Chlorophenyl-2-benzothiazolyl ketone. 18.5 g ethyl m-chlorobenzoate in 40 ml ether is added dropwise to 0.1 mole benzothiazolyl lithium in 300 ml dry ether, the temperature being held at –60° to –50°. The mixture is stirred for 1 1/2 hr at –50° to –35°, and then poured into 150 ml 1:2 hydrochloric acid. The ethereal layer is separated off, washed with water, dried, and evaporated in a vacuum. The residue is recrystallized from methanol to give 17.84 g (65.0%) ketone as colorless crystals, m.p. 98.2-98.5°; soluble in alcohol, acetone, and benzene, but insoluble in water and petroleum ether. Found: C 61.42; H 2.92; Cl 13.39; N 5.29; S 11.92%. Calculated for $C_{14}H_8ClNOS$: C 61.42; H 2.95; Cl 12.95; N 5.12; S 11.72%.

Methyl-2-benzothiazolyl ketone. A solution of 14.9 g ethyl acetate in 80 ml ether is added dropwise to 0.2 mole benzothiazolyl lithium held at –55° to –50°, the mixture stirred for 1 1/2 hr – 50° to –20°, and worked up as described above to give 11 g (31.0%) ketone, m.p. 110.3-111.3° (from acetone-petroleum ether) [4, 5].

Phenyl-2-benzothiazolyl ketoxime. 5 g ketone, 1.5 g hydroxylamine hydrochloride, 25 ml absolute alcohol, and 25 ml anhydrous pyridine are boiled for 4 hr, the solvents are then distilled off in a vacuum, the residue is triturated with 35 ml water, and the oxime is filtered off. The yield is almost quantitative. Colorless crystals, m.p. 150-151° (from aqueous alcohol). Found: C 66.03; H 3.99; N 10.98; S 12.60%. Calculated for $C_{14}H_{10}N_2OS$: C 66.12; H 3.97; N 11.01; S 12.61%.

m-Chlorophenyl-2-benzothiazolyl ketoxime. This is prepared in a similar way. Yield 90.5%, m.p. 161-161.5° (from methanol). Found: C 58.14; H 3.36; N 9.76; S 11.28%. Calculated for $C_{14}H_9ClN_2OS$: C 58.23; H 3.14; N 9.70; S 11.11%.

Methyl-2-benzothiazolyl ketoxime. This is prepared in a similar way. Yield almost quantitative, m.p. 204.5-206° (from alcohol). Found: 55.74; H 4.32; N 15.03; S 16.61%. Calculated for $C_9H_8N_2OS$: C 56.23; H 4.20; N 14.57; S 16.68%.

2-(α-Aminobenzyl)benzothiazole. A suspension of 3 g phenyl-2-benzothiazolyl ketoxime in 300 ml aqueous ammonia and 30 ml alcohol is treated with 2.3 g zinc dust, the mixture stirred 30 min at 40-60°, a further 1.3 g zinc dust is added, and stirring continued until decolorization occurs. The hot mass is filtered, and the residue washed a few times with 60 ml hot alcohol; when cold the filtrate gives 1.98 g (70%) amine. Colorless crystals, m.p. 70.5-71.0° (from petroleum ether), insoluble in water, but soluble in most organic solvents. Found: C 70.6; H 5.02; N 11.95; S 13.51%. Calculated for $C_{14}H_{12}N_2S$: C 69.96; H 5.04; N 11.65; S 13.35%.

The acetyl derivative forms colorless crystals, m.p. 156.5-157.5° (from ethyl acetate). Found: C 68.05; H 5.05. Calculated for $C_{16}H_{14}N_2OS$: C 68.07; H 4.99%.

2-(α-Amino-m-chlorobenzyl)benzothiazole. Prepared in the way described above. Yield 80.2%, forms colorless crystals, m.p. 81.5-82.5° (from 1:2 acetone-petroleum ether). Found: C 60.88; H 4.06; N 9.98; S 12.10%. Calculated for $C_{14}H_{11}ClN_2S$: C 61.19; H 4.04; N 10.20; S 11.67%.

The acetyl derivative forms colorless crystals, m.p. 160.8-161.6° (from alcohol). Found: C 60.64; H 4.27; N 8.70; S 10.10%. Calculated for $C_{16}H_{13}ClN_2OS$: C 60.66; H 4.14; N 8.84; S 10.12%.

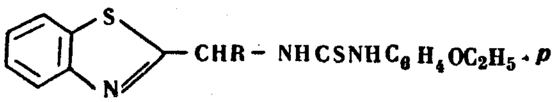
2-(α-Aminoethyl)benzothiazole. Methyl-2-benzothiazolyl ketoxime is reduced in the way described above, but the filtrate is extracted with ether. 2.08 g of a yellowish oil, yield 73.0%, are obtained. The product was used for further reaction without identification.

Urea derivatives of amines (Table 1). A solution of 0.01 mole amine and 0.01 mole p-ethoxyphenylisothiocyanate in 10 ml benzene is boiled for 2 hr; the thiourea derivative precipitates on cooling.

Urea derivative of 4-pyridyl-2'-benzothiazolylaminomethane (II). A mixture of 1 g amine (I) and 0.46 ml phenylisocyanate in 20 ml dry ether is boiled for 1 hr and cooled to give 1.37 g (92%) colorless needles, m.p. 190-195° (from alcohol). Found: C 66.42; H 4.50; N 15.42; S 9.01%. Calculated for $C_{20}H_{16}N_4OS$: C 66.65; H 4.47; N 15.53; S 8.90%.

Thiourea derivative of 2-(α-aminobenzyl)benzothiazole is prepared in a similar way; yield 93.5%, colorless crystals, m.p. 216-217° (from n-butanol). Found: C 70.33; H 5.03; N 11.79; S 8.71%. Calculated for $C_{21}H_{17}N_3OS$: C 70.17; H 4.77; N 11.69; S 8.92%.

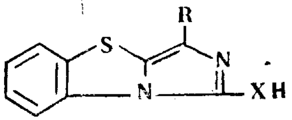
TABLE 1



R	Yield, %	M.p., °C (from ethyl acetate)	Empirical formula	Found, %				Calculated, %				λ_{max}, mμ
				C	H	N	S	C	H	N	S	
4-pyridyl	67.7	155—157*	$C_{22}H_{20}N_4OS_2$	62.82	4.88	13.00	15.20	62.84	4.81	13.32	15.25	220
C_6H_5	80.5	153—154	$C_{23}H_{21}N_3OS_2$	65.77	5.07	10.26	15.38	65.84	5.05	10.02	15.28	220
3-ClC_6H_4	75.0	157—159	$C_{23}H_{20}ClN_3OS_2$	60.63	4.49	9.28	14.11	60.84	4.44	9.26	14.13	—
CH_3	83.0	175—176	$C_{18}H_{19}N_3OS_2$	60.51	5.42	12.20	17.91	60.47	5.36	11.75	17.94	—

*From alcohol

TABLE 2



R	X	Reaction solvent	Yield, %	M.p., °C (from n-butanol	Empirical formula	Found, %				Calculated, %				λ_{max}, mμ
						C	H	N	S	C	H	N	S	
4-pyridyl	S	Cyclohexanol	92.9	265—267**	$C_{14}H_9N_3S_2$	59.30	3.45	15.25	22.11	59.33	3.21	14.81	22.62	340
4-pyridyl	O	Tetralin	48.4	292—294**	$C_{14}H_9N_3OS$	62.96	3.43	15.73	11.96	62.89	3.40	15.72	12.00	360
C_6H_5	S	Phenetole	80.9	263—264	$C_{15}H_{10}N_2S_2$	63.73	3.59	10.36	22.94	63.80	3.57	9.92	22.71	340
C_6H_5	O	Dietaylene-glycol	21.0	252—254	$C_{15}H_{10}N_2OS$	67.49	3.93	10.42	12.21	67.65	3.79	10.52	12.04	360
3-ClC_6H_4	S	Phenetole	84.0	252—255	$C_{15}H_9ClN_2S_2$	57.04	2.90	8.59	20.57	56.86	2.86	8.84	20.24	
CH_3	S	Tetralin	86.3	238.5—240.5	$C_{10}H_8N_2S_2$	54.48	3.68	12.58	29.13	54.51	3.66	12.72	29.11	

*All the substance melts with decomposition.

**From alcohol-dimethylformanide (2:3).

2,9-Disubstituted imidazo[5,1-b]benzothiazoles (Table 2). 1-2 g of the thiourea or urea derivative of the amine is boiled for 2-5 min in 4-5 ml high-boiling solvent, cooled, and diluted with ether. The tricyclic compound is filtered off and washed with ether. The mother liquors from the isolation of 2-mercapto-9-(pyridyl-4)imidazo[5,1-b]-benzothiazole are diluted with 70 ml ether and twice extracted with 30 ml 10% hydrochloric acid. The acid extracts are made alkaline with 40% sodium hydroxide solution and extracted with ether (3 x 20 ml). The ether solution is dried, and 3 ml of a solution of hydrogen chloride in ether are added to it; the crystals of p-phenetidine hydrochloride precipitated are filtered off and recrystallized from alcohol-ethyl acetate, m.p. 232-234°.

Sodium salt of 2-mercapto-9-(4-pyridyl)-imidazo[5,1-b]benzothiazole. 0.5 g 2-mercapto-9-(4-pyridyl)-imidazo[5,1-b]benzothiazole is heated in 25 ml 1 N sodium hydroxide solution. On cooling colorless crystals are precipitated; these are readily soluble in hot water and hot alcohol. They decompose, but do not melt. An aqueous solution of the salt is acidified with 10% acetic acid, and the starting mercapto compound precipitated.

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Ordzhonikidze All-Union Chemical-Pharmaceutical
Scientific Research Institute, Moscow