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Cyclizations of Thioureas with a Hydroxy Group at the β-Position of the *N*-Substituent. II. Oxidation with Thionyl Chloride to Benzothiazoles

Yoshio IWAKURA and Keisuke KURITA

Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo

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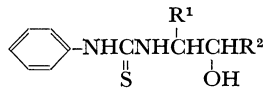
The reaction of *N*-alkyl and *N'*-phenyl substituted thioureas with a hydroxyl group at the β-position of the *N*-substituent with thionyl chloride gave benzothiazole derivatives by an oxidative cyclization reaction; no other products, such as thiazolines or oxazolines, were formed. The structure was confirmed by the various spectral and chemical data.

The dehydration of *N*-acyl derivatives of β-hydroxyalkylamines with thionyl chloride has been one of the most useful methods for preparing oxazoline derivatives since Bergman and Brand[1,2] found in thionyl chloride a mild and effective cyclizing agent; in this manner, 2-phenyl-5-phenoxymethyl-2-oxazoline was obtained from 1-benzamido-3-phenoxy-2-propanol in a quantitative yield, as has been described in a previous paper.[3] Roggero and Metzger[4] investigated the cyclization reaction of 1-thiobenzamido-2-propanol by several reagents, such as thionyl chloride, *p*-toluenesulfonyl chloride, and phosphorus pentoxide, and reported that the cyclization by thionyl chloride led to a mixture of 2-phenyl-5-methyl-2-thiazoline and the corresponding oxazoline, and that the product composition varied with the reaction temperature.

In a preceding paper,[5] it was shown that the cyclization of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea by various acids gave thiazoline, oxazoline, or a mixture of them, depending on the character of the acid used. The present investigation was undertaken in order to determine the cyclization products by thionyl chloride.

Results and Discussion

Reaction with Thionyl Chloride and Identification of the Products. The treatment of *N*-alkyl and *N'*-phenyl substituted thioureas with a hydroxyl group at the β-position of the *N*-substituent



Ia: $R^1=R^2=H$
Ib: $R^1=H$, $R^2=CH_3$
Ic: $R^1=H$, $R^2=CH_2O-$ 
Id: $R^1=CH_3$, $R^2=CH_3$ (*threo*)

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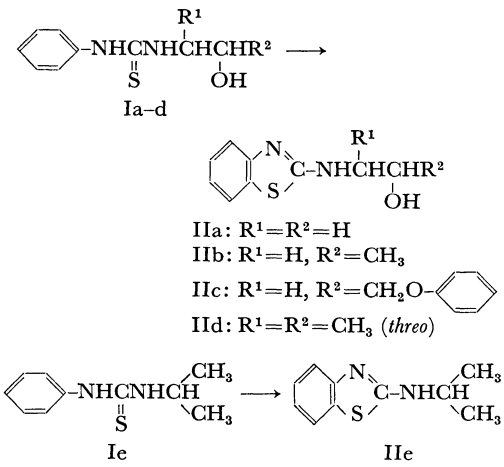
(hydroxythioureas) of such types as Ia—d with a large excess of thionyl chloride at room temperature resulted in the formation of the hydrochlorides of the basic materials, which were then converted to the free bases (IIa—d) with aqueous ammonia. The elemental analyses and the infrared spectra of these compounds showed, however, that they were identical with neither the thiazolines nor the oxazolines, nor were they identical with mixtures of the two, contrary to expectation. 1-Isopropyl-3-phenyl-2-thiourea (Ie), non-hydroxythiourea, gave a similar basic compound (IIe) by the same procedure, suggesting that this reaction proceeded independently of the existence of a hydroxyl group in the thioureas.

It is well known that thioureas are oxidized with bromine or thionyl chloride in chloroform to give the salts of bis(substituted formamidine)disulfides. However, the possibility that the above-obtained reaction products of thioureas Ia—e with thionyl chloride might be the bis(substituted formamidine)-disulfides can be ruled out, though the results of the elemental analysis were close to the calculated values. The salt of bis(substituted formamidine)-disulfide is known to be unstable to water or ethanol, and one of the two sulfur atoms is extruded on treatment with absolute ethanol or a mixture of absolute ethanol and benzene to give the monosulfide salt, followed by isomerization and cyclization to the so-called Hector's or Hugershoff's base.[6-14] Moreover, it has been reported that the disulfide base is too unstable to exist as a free base, and that it decomposes instantly, with the elimination of sulfur.

On the basis of the spectral and chemical data, as will be mentioned later, it is very likely that IIa—e has a benzothiazole structure. The oxidation of aryl thioureas with bromine[15] is a very convenient method for preparing benzothiazoles; other oxidizing reagents, such as sulfuryl chloride and sulfur monochloride, have also been reported



in several papers[16-18] and patents.[19-21]

The products obtained here were found to be resistive to such reducing agents as lithium aluminum hydride and zinc in acidic media. For instance, IIc was recovered quantitatively after being heated in refluxing tetrahydrofuran with a large excess of lithium aluminum hydride for 20 hr. Thermal analysis revealed that they were fairly stable to heat, that they decomposed thermally in a nitrogen atmosphere above 200°C, and that each compound showed only one DTA peak (endothermic) corresponding to its melting point. The molecular weight of IIc as determined by the Rast method (299), was very close to that of the starting thiourea, Ic (302). The mass spectra of IIa, IIb, IIc, IId, and IIe exhibited the molecular ion peak at *m/e*, 194, 208, 300, 222, and 192 respectively, as was to be expected from the benzothiazole structure. In the NMR spectra of IIc and IId, the ratio of the integration of aromatic protons to that of the aliphatic ones gave a better agreement with the benzothiazole than with the disulfide structure: 9/5 for IIc and 4/8 for IId. Figure 1 represents the NMR spectrum of IId. Beilstein's test was negative for all the compounds, IIa—e, showing that none of these was chlorinated under the conditions used.

Tables 1 and 2 summarize the properties of the benzothiazoles obtained. The melting point of IIe was practically the same as that of the reported 2-isopropylaminobenzothiazole, mp 95°C, prepared from 2-methylsulfonylbenzothiazole and isopropyl-

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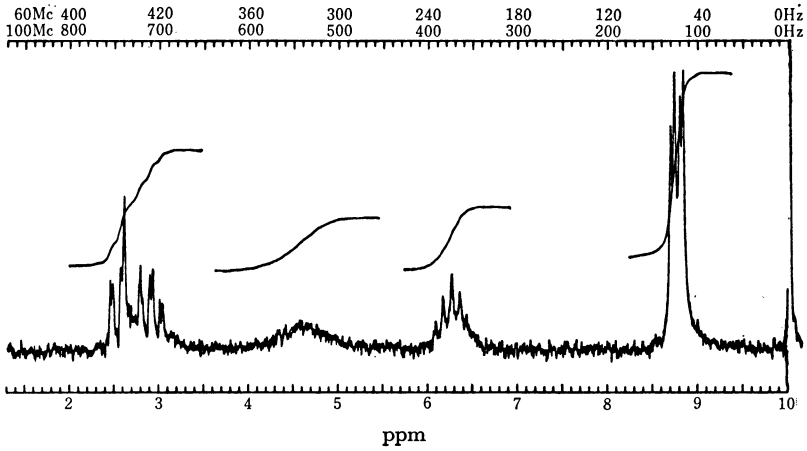
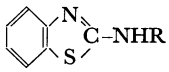


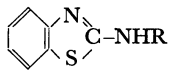
Fig. 1. NMR spectra of IId in $CDCl_3$ (60 Mc).

Table 1. Properties of the benzothiazoles (1)



No.	Yield %	Mp °C	Calcd, %				Found, %			
			C	H	N	S	C	H	N	S
IIa	88	104—105.5	55.66	5.19	14.43	16.48	55.18	5.06	14.25	16.63
IIb	80	107—108.5	57.68	5.81	13.46	15.37	57.23	5.57	14.20	15.63
IIc	91	137—139	63.99	5.37	9.33	10.66	64.11	5.35	9.22	11.08
IId	78	109—111	59.45	6.35	12.60		59.05	6.47	12.10	
IIe	90	93— 94.5	62.48	6.29	14.58	16.65	62.09	6.15	14.44	16.56

Table 2. Properties of the benzothiazoles (2)



No.	Mass *m/e*	IR cm^{-1}	Picrate								
			Mp °C	Calcd, %				Found, %			
				C,	H,	N,	S,	C,	H,	N,	S,
IIa	194	1600 1570 1560	199—200								
IIb	208	1600 1580 1560	176—177.5	43.94	3.46	16.02		43.65	3.38	16.24	
IIc	300	1600 1580 1560	194—196.5	49.90	3.62	13.23	6.06	49.87	3.66	12.96	6.01
IId	222	1595 1575 1540	183.5—185	45.24	3.80	15.52	7.10	45.49	3.87	15.96	7.18
IIe	192	1615 1575 1550	211—212	45.61	3.59	16.62		45.58	3.58	16.90	

TABLE 3. ABSORPTION MAXIMA OF THE BENZOTHIAZOLES

No.	λ_{max} mμ (log ε)	
IIa	226 (4.54)	268 (4.18)
IIb	225 (4.59)	268 (4.22)
IIc	223 (4.56)	269 (4.26)
IId	226 (4.57)	269 (4.22)
IIe	226 (4.57)	269 (4.21)

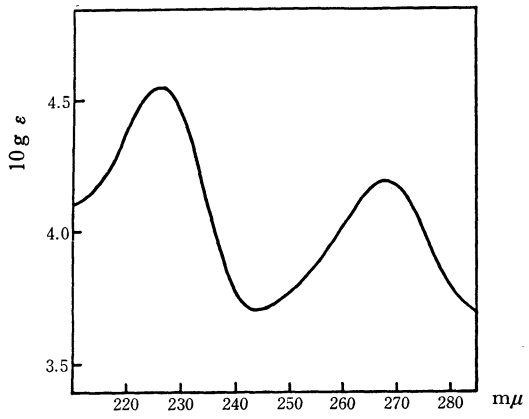
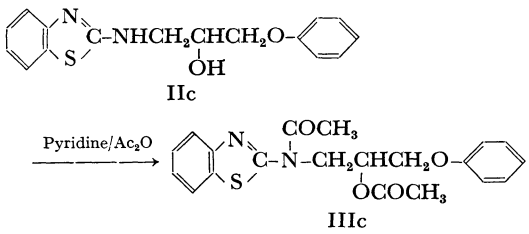


Fig. 2. UV spectra of IId in 95% ethanol.

amine.[22] The elemental analyses of IIa—e and those of the picrates show good agreement with the calculated values for benzothiazoles and their picrates, as these tables show.

The ultraviolet spectra of IIa—e in 95% ethanol were very similar to each other and showed the λ_{max} at 223—226 and 268—269 mμ. The results (Table 3) correspond very well with the reported data that 2-aminobenzothiazole has the λ_{max} at 222 (log ε=4.52) and 264 mμ (log ε=4.09),[23] or 263 mμ (log ε=4.11)[24] in ethanol in the UV. A typical example of the ultraviolet spectrum is shown in Fig. 2.

The Acetylation of IIc and the Hydrolysis of IIc Diacetylate. Acetylation of IIc was carried out by treating IIc with a mixture of pyridine and acetic anhydride to give a diacetylated compound (IIIc).



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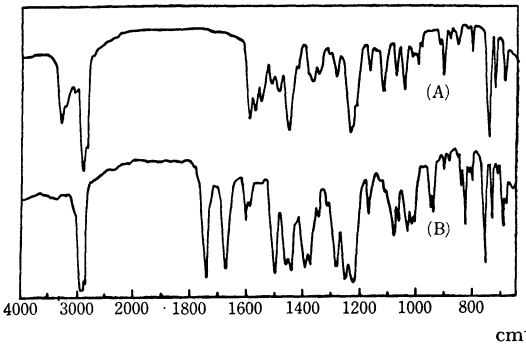

Fig. 3. Infrared spectra of IIc (A) and IIIc (B), (Nujol).

The infrared spectra of IIc and IIIc are shown in Fig. 3. The most characteristic absorption bands of IIIc are found at 1740 and 1670 cm^{-1}, assignable to the carbonyl groups of the *O*- and the *N*-acetyl group respectively. The NMR spectrum of IIIc in $CDCl_3$ showed two singlets at 8.00 τ and 7.46 τ (both 3 protons), indicating that acetylation had taken place at both OH and NH, and a peak due to the methine proton which appeared at 5.75 τ in IIc, was shifted downfield by the acetylation of hydroxyl group and appeared as a multiplet at 4.30 τ.

Diacetylated benzothiazole, IIIc, was subjected to alkaline hydrolysis to give the original benzothiazole, IIc, in a quantitative yield.

In view of the above facts, it can be concluded that the benzothiazoles were obtained quantitatively by the oxidation reaction of 1-aryl-3-alkyl-2-thioureas with thionyl chloride. Benzothiazoles are at a higher oxidation stage than disulfides, and Barnikow and Bödeker[13] have reported that the disulfides which were obtained by the oxidation of thioureas with bromine were further oxidized by bromine to give benzothiazoles. This reaction presumably proceeds also through the disulfides; then these disulfides are oxidized further by thionyl chloride to yield the benzothiazoles.

It is noteworthy that the hydroxythioureas, Ia—d, gave the benzothiazoles in preference to the thiazolines or the oxazolines, since a thioamide with a hydroxyl group at the β-position gave a mixture of a thiazoline and an oxazoline, as has already been mentioned in the introduction.

Experimental

Thioureas. The hydroxythioureas, Ia, Ib and Id, and the non-hydroxythiourea, Ie, were synthesized from the corresponding aminoalcohols or amine and phenyl isothiocyanate by the method previously used in the preparation of hydroxythiourea, Ic.[5] The results are listed in Table 4.

2-(3-Phenoxy-2-hydroxypropylamino)benzothiazole. To 20 ml of thionyl chloride we added 5 g (0.0165 mol) of 1-(3-phenoxy-2-hydroxypropyl)-3-

Table 4. Preparation of thioureas

No.	Yield %	Mp °C	
Ia	90	136—137	(lit, 138[25])
Ib	81	105—106	(lit, 108—109[26])
Ic	85	142—143.5[5]	
Id	84	97—99*	
Ie	85	99—100	(lit, 100—101[27])

* Found: C, 58.96; H, 7.09; N, 12.63%. Calcd for $C_{11}H_{16}N_2SO$: C, 58.91; H, 7.19; N, 12.49%.

phenyl-2-thiourea at 0°C. After the vigorous evolution of gas had ceased, the reaction mixture was allowed to warm to room temperature and was then stirred for an additional hour. The solution was then poured into 300 m*l* of ether and allowed to stand in a refrigerator overnight. The precipitated salt was collected by filtration, washed with ether to remove the excess thionyl chloride, and dried. The benzothiazole hydrochloride was treated with aqueous ammonia to give the free base, which weighed 4.5 g (9.1%). Recrystallization from a mixture of benzene and *n*-hexane gave white crystals; mp 137—139°C.

The other benzothiazoles were prepared by virtually the same procedure.

Acetylation of Benzothiazole, IIc. A mixture of pyridine and acetic anhydride (15 m*l* each)was added to 1.7 g (0.0057 mol) of benzothiazole, IIc. The solution was allowed to stand at room temperature for 1 day and was then concentrated under reduced pressure. The residual solid was recrystallized from cyclohexane to give 1.8 g (83%) of diacetylated benzothiazole, IIIc; mp 149—150°C.

Found: C, 62.64; H, 5.36; N, 7.16; S, 8.29%. Calcd for $C_{20}H_{20}N_2SO_4$: C, 62.49; H, 5.24; N, 7.29; S, 8.33%.

Alkaline Hydrolysis of Diacetylated Benzothiazole, IIIc. To a solution of 0.7 g (0.0018 mol) of diacetylated benzothiazole, IIIc, in 50 m*l* of acetone, we added 20 m*l* of 0.2N sodium hydroxide. The mixture was stirred at 50°C for 5 hr, and then the solvent was evaporated under reduced pressure. The residual white solid was washed well with water and dried. The benzothiazole, IIc, was thus obtained; it weighed 0.53 g (97%).

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