574. *Nucleophilic Substitution Reactions of 2-Chlorobenzimidazoles. Part II.*[1] *Formation of Benzimidazoline-2-thiones and Related Compounds*

By D. Harrison and J. T. Ralph

Benzimidazoline-2-thiones have been prepared by reaction of 2-chlorobenzimidazoles with thiourea. An alternative route using sodium hydrosulphide was only satisfactory for 1-substituted 2-chlorobenzimidazoles. Nucleophilic displacement of chlorine from 2-chlorobenzimidazoles by means of benzimidazoline-2-thiones afforded a series of dibenzimidazol-2-yl sulphides. Similar reactions using thiophenol as the nucleophile unexpectedly gave benzimidazol-2-yl phenyl sulphides only from 2-chlorobenzimidazoles without nitro substituents. A 1-methyl derivative was obtained by methylation of 2-chloro-5,6-dinitrobenzimidazole.

Displacement of chlorine from 2-chlorobenzimidazoles which are unsubstituted in the 1-position has been observed mainly with nucleophilic reagents which are only weak bases. More strongly basic reagents convert the chloro-compound into the anion which is more resistant to nucleophilic attack. Thus, neither OH^- nor OR^- (R = alkyl) is effective under normal conditions,[1] although chlorine is displaced from certain 2-chlorobenzimidazoles by weaker bases, *e.g.*, ammonia, amines, and hydrazine.[2-4] The present Paper is concerned with substitution reactions in which sulphur compounds are used as nucleophiles.

Thiourea appears to have the required combination of considerable nucleophilic power but only weak basic strength ($pK_a \sim -1{\cdot}0$) and, as expected, it reacted readily with all the 2-chlorobenzimidazoles studied. The reaction gave the corresponding benzimidazoline-2-thiones directly in excellent yields. The initial stage is probably the formation of an *S*-benzimidazol-2-ylthiouronium chloride (I). The benzimidazoline-2-thione then results from an elimination reaction involving the free isothiourea (II) in equilibrium with the thiouronium salt. The reactions of thiourea with halogen compounds of many heterocyclic systems have been studied. These include pyridines,[5] quinolines,[6] pyrimidines,[7]

[1] Part I, D. Harrison and J. T. Ralph, *J.*, 1965, 236.

[2] O. Kym and L. Ratner, *Ber.*, 1912, **45**, 3238; N. P. Bednyagina and I. Y. Postovskii, *Zhur. obshchei Khim.*, 1960, **30**, 1431; L. S. Efros, B. A. Porai-Koshits, and S. G. Farbenstein, *ibid.*, 1953, **23**, 1691; A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, 1961, **44**, 1273.

[3] G. T. James and E. E. Turner, *J.*, 1950, 1515.

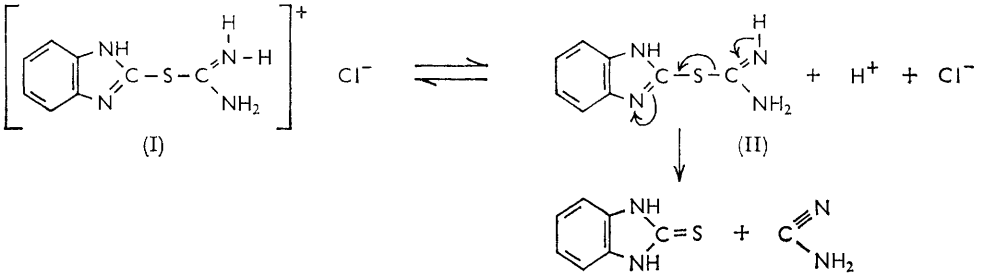
[4] D. Harrison, J. T. Ralph, and A. C. B. Smith, *J.*, 1963, 2930.

[5] A. R. Surrey and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1940, **62**, 1697; M. A. Phillips and H. Shapiro, *J.*, 1942, 584.

[6] E. Rosenhauer, H. Hoffmann, and W. Heuser, *Ber.*, 1929, **62***B*, 2730; A. G. Renfrew, *J. Amer. Chem. Soc.*, 1946, **68**, 1433.

[7] M. P. V. Boarland and J. F. W. McOmie, *J.*, 1951, 1218; M. Polonovski and H. Schmitt, *Bull. Soc. chim. France*, 1950, 616.

quinoxalines,[8] and benzothiazoles.[9,10] In a few cases, thiouronium salts were isolated, but usually only thiols (thiones) or sulphides were obtained. It was hoped that in dry ethanol thiouronium salts might be obtained from 2-chlorobenzimidazoles and thiourea, but only in one case (2-chlorobenzimidazole) a solid separated after 15 min. at the b. p. which appeared to be a mixture of the required thiouronium salt and unchanged chloro-compound, but attempts to purify it caused decomposition. Hence we have been unable



(I) (II)

to establish definitely that thiouronium salts are intermediates in the conversion of 2-chloro-benzimidazoles into benzimidazoline-2-thiones by means of thiourea.

2-Chlorobenzoxazoles[11] and 2-chlorobenzothiazoles[12] have been converted into the corresponding thiones by the action of sodium hydrogen sulphide. The reaction also proceeds satisfactorily with 2-chloro-1-methylbenzimidazole, an illustration of the considerable nucleophilic power of the SH^- ion, since chlorine is not displaced from this compound by the action of sodium hydroxide solution.[1] However, 2-chlorobenzimidazole could not be converted into benzimidazoline-2-thione by treatment with sodium hydrogen sulphide solution. Thus, although the SH^- ion is a weaker base than the OH^- ion, it must convert 2-chlorobenzimidazole largely into the unreactive anion.

Benzimidazoline-2-thiones may be used as nucleophiles for the displacement of chlorine from 2-chlorobenzimidazoles. Interaction of these compounds in boiling dry ethanol usually resulted in the precipitation of the crude hydrochloride of a dibenzimidazol-2-yl sulphide. As expected, this reaction was favoured by electron-releasing substituents in the thione and by electron-attracting substituents in the chloro-compound. Thus, 5-nitrobenzimidazoline-2-thione and 2-chloro-5-methylbenzimidazole failed to react appreciably, but 5-methylbenzimidazoline-2-thione and 2-chloro-5-nitrobenzimidazole rapidly formed the hydrochloride of 5-methylbenzimidazol-2-yl 5-nitrobenzimidazol-2-yl sulphide. It is noteworthy that Watt[10] observed no reaction between 2-chlorobenzothiazole and benzothiazoline-2-thione under similar conditions to those used here. This suggests that benzothiazoline-2-thione is a weaker nucleophile than benzimidazoline-2-thione since Scott and Watt[9] obtained an " addition compound " (probably the hydrochloride of the mixed sulphide) from the reaction of the latter thione with 2-chlorobenzothiazole.

Benzimidazol-2-yl phenyl sulphides were isolated in good yields from the reactions of thiophenol with both 2-chlorobenzimidazole and 2-chloro-5-methylbenzimidazole, but not with those chloro-compounds containing nitro-substituents. Since the latter are normally particularly susceptible to nucleophilic attack, it seems probable that further reaction may have occurred. A more detailed investigation of these reactions is planned. Solutions of sodium thiophenoxide in ethanol also converted 2-chlorobenzimidazole and 2-chloro-5-methylbenzimidazole into benzimidazol-2-yl phenyl sulphides, a result compatible with the low basic strength (pK_a ~6·5) of the thiophenoxide ion.

[8] F. J. Wolfe, R. M. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 2266.
[9] W. Scott and G. W. Watt, *J. Org. Chem.*, 1937, **2**, 148.
[10] G. W. Watt, *J. Org. Chem.*, 1939, **4**, 436.
[11] R. D. Desai, R. F. Hunter, and A. Rahman Khan Khalidi, *J.*, 1934, 1186.
[12] A. W. Hofmann, *Ber.*, 1887, **20**, 1788.

Experimental

2-Chloro-1-methyl-5,6-dinitrobenzamidazole.—2-Chloro-5,6-dinitrobenzimidazole (0·5 g.) in 5% aqueous sodium hydroxide (20 ml.) formed a clear red solution to which dimethyl sulphate (1 ml.) was added slowly with stirring, the mixture being cooled throughout in a bath of cold water. After 1 hr. the yellow solid was collected, washed with water (4 × 25 ml.), and dried, giving the *1-methyl derivative* (0·4 g.), as pale yellow leaflets from aqueous acetone, m. p. 194—196° (Found: C, 37·0; H, 2·1; Cl, 14·1; N, 22·2. $C_8H_5ClN_4O_4$ requires C, 37·4; H, 2·0; Cl, 13·8; N, 21·8%).

Other 2-chlorobenzimidazoles were prepared by published methods.[1,4]

Reactions of 2-Chlorobenzimidazoles with Thiourea.—A solution of 2-chlorobenzimidazole (1 g.) and thiourea (0·5 g.) in ethanol (50 ml.) was boiled under reflux for 1 hr. and then evaporated to dryness. Treatment of the residue with 2% aqueous sodium carbonate (50 ml.), vigorous agitation, and cautious acidification with 4N-hydrochloric acid after 1 hr., afforded benzimidazoline-2-thione (0·90 g.), m. p. ~305° from aqueous ethanol (lit., 290°,[13] 312—313° [14]). By mixed m. p. and ultraviolet spectrum it was shown to be identical with an authentic sample prepared from *o*-phenylenediamine and thiourea. The 1-acetyl derivative had m. p. 201—202° (lit.,[15] 200°).

Table 1 gives details of other benzimidazoline-2-thiones prepared by the same method. Aqueous ethanol was used for recrystallisation except in the case of 1-methyl-5,6-dinitrobenzimidazoline-2-thione which required a mixture of water, ethanol, and acetone.

Table 1

Benzimidazoline-2-thiones prepared from 2-chlorobenzimidazoles and thiourea

Benzimidazoline-2-thione	Yield (g.) *	M. p.	Lit. M. p.	Found (%)				Calc. for or requires (%)				Formula
				C	H	N	S	C	H	N	S	
5-Methyl	0·40	285—286° (decomp.)	284° [13]; 285 [16]; >295 [14]	58·8	4·9	16·7	19·3	58·5	4·9	17·1	19·5	$C_8H_8N_2S$
5-Nitro	0·50	274 (decomp.)	282 [3]	43·2	3·0	21·2	16·3	43·1	2·6	21·5	16·4	$C_7H_5N_3O_2S$
5,6-Dinitro	0·42	260—261	—	35·5	2·1	23·3	12·8	35·0	1·7	23·3	13·3	$C_7H_4N_4O_4S$
1-Methyl	0·45	192—193	191 [17] 200—200·5 [14]	58·2	4·8	17·4	19·9	58·5	4·9	17·1	19·5	$C_8H_8N_2S$
1-Isopropyl	0·45	146—147	—	62·2	6·0	14·5	16·6	62·5	6·3	14·6	16·7	$C_{10}H_{12}N_2S$
5,6-Dinitro-1-methyl	0·50	253—254 (decomp.)	—	38·0	2·2	21·6	12·0	37·8	2·4	22·0	12·6	$C_8N_6N_4O_4S$

* From 0·5 g. of chloro-compound.

Reactions of 2-Chlorobenzimidazoles with Sodium Hydrogen Sulphide.—A solution of sodium hydrogen sulphide (~1M) in dimethylformamide was prepared as described by Cheeseman.[18] To this solution (10 ml.) was added 2-chloro-1-methylbenzimidazole (0·5 g.), and the mixture boiled under reflux for 90 min. Addition of water (250 ml.) and 4N-hydrochloric acid precipitated crude 1-methylbenzimidazoline-2-thione (0·45 g.), shown by its infrared spectrum to be identical with the product prepared by use of thiourea, but contaminated with sulphur which was not easily removed. 2-Chlorobenzimidazole did not react under these conditions.

Reactions of 2-Chlorobenzimidazoles with Benzimidazoline-2-thiones.—2-Chlorobenzimidazole (1 g.) and the benzimidazoline-2-thione (1 g.) in ethanol (30 ml.) were heated under reflux for 6 hr. or until solid began to separate from the hot solution. Collection of this solid (the hydrochloride of the required sulphide), dissolution in 4N-sodium hydroxide followed by cautious addition of 4N-hydrochloric acid precipitated the *sulphide*, which was recrystallised from

[13] E. Lellmann, *Annalen*, 1883, **221**, 9.
[14] W. G. Bywater, D. A. McGinty, and N. D. Jenesel, *J. Pharmacol.*, 1945, **85**, 14.
[15] T. N. Ghosh and P. C. Guha, *J. Indian Chem. Soc.*, 1929, **6**, 181.
[16] O. Billeter and A. Steiner, *Ber.*, 1887, **20**, 231.
[17] K. Futaki, *J. Pharm. Soc. Japan*, 1954, **74**, 1365.
[18] G. W. H. Cheeseman, *J.*, 1960, 242.

aqueous ethanol. Where the amount of sulphide obtained in this way was small, water was added to the alcohol filtrate after removal of the hydrochloride. This precipitated more of the sulphide together with unchanged chloro-compound and thione. Efficient separation of this

TABLE 2

Dibenzimidazol-2-yl sulphides

Substituent in the 2-chloro-benzimid-azole	Substituent in the benzimid-azoline-2-thione	Time of heat-ing (hr.)	Sulphides								
				Found (%)				Required (%)				
			M. p.	C	H	N	S	C	H	N	S	Formula
—	—	¾	250°	63·1	3·8	20·7	11·9	63·1	3·8	21·0	12·0	$C_{14}H_{10}N_4S$
5-Methyl	5-Methyl	4	240—241	65·1	4·5	19·2	10·8	65·3	4·8	19·0	10·9	$C_{16}H_{14}N_4S$ [a]
5-Nitro	5-Nitro	1½	273—274	47·3	2·3	23·4	8·8	47·2	2·3	23·6	9·0	$C_{14}H_8N_6O_4S$ [b]
1-Methyl	1-Methyl	6	180—181	65·6	5·1	19·3	11·0	65·3	4·8	19·0	10·9	$C_{16}H_{14}N_4S$ [a, c]
5-Methyl	—	3	252—253	63·9	4·3	20·1	11·7	64·2	4·3	20·0	11·4	$C_{15}H_{12}N_4S$
1-Methyl	5-Methyl	1½	199	64·8	4·9	19·5	11·3	65·3	4·8	19·0	10·9	$C_{16}H_{14}N_4S$
5,6-Dinitro	—	½	242—243	45·3	2·8	22·5	8·7	45·0	2·7	22·5	8·6	$C_{14}H_8N_6O_4S,H_2O$
5-Nitro	5-Methyl	½	220	55·4	3·3	21·2	10·1	55·4	3·4	21·5	9·9	$C_{15}H_{11}N_5O_2S$
5-Methyl	5-Nitro	6	No sulphide isolated									

[a] Insoluble in dilute alkali. [b] Purified by reprecipitation from alkaline solution. [c] Also prepared from Me_2SO_4 and dibenzimidazol-2-yl sulphide in aqueous sodium hydroxide.

mixture was not possible in all cases, hence yields are not included in Table 2 which gives details of the sulphides prepared by this method.

Reactions of 2-Chlorobenzimidazoles with Thiophenol.—2-Chlorobenzimidazole (1·0 g.) and thiophenol (5 ml.) in ethanol (25 ml.) were boiled under reflux for 1 hr. Concentration and dilution with water gave some of the product together with unchanged thiophenol, which was extracted with ether (2 × 25 ml.). Neutralisation of the aqueous solution with ammonia gave *benzimidazol-2-yl phenyl sulphide* (0·80 g.), as white leaflets (from aqueous ethanol), m. p. 201—202° (Found: C, 69·4; H, 4·5; N, 12·3; S, 13·8. $C_{13}H_{10}N_2S$ requires C, 69·0; H, 4·5; N, 12·4; S, 14·2%). By the same method 2-chloro-5-methylbenzimidazole gave *5-methylbenzimidazol-2-yl phenyl sulphide* (1·05 g.), m. p. 157—158° (Found: C, 69·6; H, 5·3; N, 11·5; S, 13·0. $C_{14}H_{12}N_2S$ requires C, 69·9; H, 5·0; N, 11·7; S, 13·3%).*

Reactions of 2-Chlorobenzimidazoles with Sodium Thiophenoxide.—To a solution of sodium (0·50 g.) in ethanol (40 ml.) was added thiophenol (5 ml.) and 2-chlorobenzimidazole (1·0 g.). The mixture was boiled under reflux for 2 hr., and benzimidazol-2-yl phenyl sulphide (0·80 g.) was isolated as described above. 2-Chloro-1-methylbenzimidazole treated in the same way afforded none of the required 1-methylbenzimidazol-2-yl phenyl sulphide. Attempts to prepare this compound by the action of dimethyl sulphate on a solution of benzimidazol-2-yl phenyl sulphide in aqueous sodium hydroxide also failed, possibly due to steric hindrance.

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* In the preparation of benzimidazol-2-yl phenyl sulphides by this method, some product may be dissolved by the ether used to extract the unreacted thiophenol.