

56. *Reactions of Benzthiazole Derivatives. Part III. The Interaction of 1-Thiolbenzthiazoles and Alcohols.*

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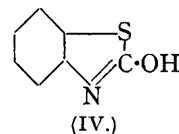
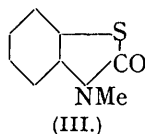
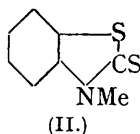
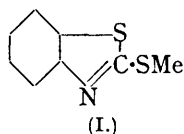
When heated with methyl or ethyl alcohol in the presence of catalysts, 1-thiolbenzthiazoles afford the benzthiazole derivatives (types I—IV) which it is suggested are derived by loss of H_2O , H_2S , or RSH from a labile hypothetical addition product (V) of the thiolbenzthiazole with the alcohol. The thermal isomerisation of 1-methoxybenzthiazole to 2-methylbenzthiazolone is not catalysed by iodine.

These observations are considered in relation to the reactions of benzthiazole derivatives recorded in Parts I and II.

It has previously been shown that methylation of 1-thiolbenzthiazole with methyl sulphate and aqueous sodium hydroxide gives mainly 1-methylthiobenzthiazole (I) and a small amount of 1-thio-2-methyl-1:2-dihydrobenzthiazole (II) (Reed, Robertson, and Sexton, J., 1939, 473). An investigation has now been made of the alkylation of 1-thiolbenzthiazoles with methyl and ethyl alcohol in the presence of catalysts at elevated temperatures under pressure.

No appreciable reaction occurred on prolonged heating of 1-thiolbenzthiazole with methyl alcohol. In the presence of catalysts, however, in addition to gaseous by-products, (I, II, III, and IV) were obtained, the proportions depending on the catalyst and on the reaction conditions. With iodine as catalyst, (I, II, and IV) were identified, with bromine (II and IV) were obtained, whereas a single

experiment with sulphuric acid gave a 43% yield of (IV). The reaction between 1-thiolbenzthiazole and ethyl alcohol at elevated temperatures in the presence of iodine gave the ethyl analogue of (II),



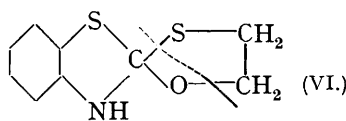
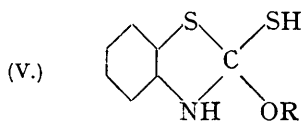
and (IV). 1-Thiol-4-methylbenzthiazole with methyl alcohol and iodine afforded 1-thio-2:4-dimethyl-1:2-dihydrobenzthiazole, and 4-chloro-1-thiolbenzthiazole under similar conditions gave 4-chloro-2-methylbenzthiazolone.

At the minimum temperature required for ensuring reaction in a reasonable time between 1-thiolbenzthiazole and methyl alcohol in the presence of iodine, a high proportion of (I) was formed. Increasing the temperature or the period of heating increased the proportion of (II) at the expense of (I) and it seems probable that (II) arises by the thermal rearrangement of (I) (Reed, Robertson, and Sexton, *loc. cit.*).

The formation of 1-hydroxybenzthiazole (IV) was less dependent on the reaction time and temperature. It was not formed by hydrolysis of the other products, since it could not be isolated from the reaction products of 1-thiolbenzthiazole, 1-methylthio-2-methyl-1:2-dihydrobenzthiazole (II) with water in the presence of iodine or from the reaction product of (I) with aqueous methyl alcohol containing iodine.

As the production of 1-alkoxybenzthiazoles might have been expected in this reaction, the thermal stability of 1-methoxybenzthiazole was examined. Oxidation of methyl phenylthioncarbamate with potassium ferricyanide by the method of Hunter and Parken (J., 1935, 1755) gave a mixture of unchanged ester and 1-methoxybenzthiazole. The latter was more conveniently obtained by treating 1-chlorobenzthiazole with alcoholic sodium methoxide (cf. Hofmann, *Ber.*, 1880, 13, 10) and its properties do not accord with those ascribed to 1-methoxybenzthiazole by Hunter and Parken (*loc. cit.*). Their proof of structure, namely, by bromination to 5-bromo-1-methoxybenzthiazole, is, however, invalid, since bromine might effect simultaneous oxidation and bromination of methyl phenylthioncarbamate itself to give 5-bromo-1-methoxybenzthiazole. Confirmation of the structure of our methoxybenzthiazole was afforded by its thermal isomerisation to 2-methylbenzthiazolone, which took place at a much lower temperature than that required for the corresponding thio-derivative (I). It therefore appears that, if methoxybenzthiazoles were formed in the reaction between thiolbenzthiazoles and methyl alcohol, they would be isomerised under the conditions of the reaction. No reaction took place when 1-hydroxybenzthiazole (IV) was heated with methyl alcohol in the presence of iodine.

The evidence suggests that the various products are formed from a labile addition product (V) of 1-thiolbenzthiazole and the alcohol ROH by loss of H_2O , H_2S , or RSH, together with the isomerisation



known to be possible under the experimental conditions. Such a mechanism also explains the thermal conversion of 1- β -hydroxyethylthio-2-methyl-1:2-dihydrobenzthiazole into 1-hydroxybenzthiazole (Sexton, J., 1939, 470), the first step being the formation of an unstable intermediate (VI).

Although 1-methoxybenzthiazole is readily isomerised by heat, this reaction is not catalysed by iodine, in contrast to the isomerisation of the analogous thio-derivatives (Reed, Robertson, and Sexton, *loc. cit.*). This suggests that the action of iodine or methyl iodide as catalyst in the isomerisation of the thio-compounds proceeds by addition first to the sulphur atom of the alkylthio-group, giving a sulphonium compound, which eliminates the catalyst after rearrangement to a quaternary ammonium salt (compare Parts I and II).

EXPERIMENTAL.

(1) *Reaction of 1-Thiolbenzthiazole with Methyl Alcohol.*—The reaction mixtures were extracted with aqueous sodium hydroxide to remove 1-thiolbenzthiazole (m. p. 179°) and 1-hydroxybenzthiazole (IV) (m. p. 138°), which were liberated on acidification. Treatment of the alkali-insoluble material with concentrated hydrochloric acid (4—5 vols.) extracted 1-methylthio-2-methyl-1:2-dihydrobenzthiazole (I) (m. p. 50°), which was isolated after basification, and left the 1-thio-2-methyl-1:2-dihydrobenzthiazole (II) (m. p. 90°), which has no basic properties. In all cases, the yields given are of unpurified fractions obtained in this way, though these were purified when it was necessary to ensure their identity. Identification was by mixed m. p. with authentic materials prepared by the methods described in Parts I and II.

(a) *Without catalyst.* 1-Thiolbenzthiazole (16.7 g.) and methyl alcohol (8 c.c.) were heated in a sealed tube at 210—215° for 10 hours. 1-Thiolbenzthiazole (14.7 g.), m. p. 172—176°, was recovered.

(b) *With iodine as catalyst.* 1-Thiolbenzthiazole (334 g.), methyl alcohol (128 g.), and iodine (0.8 g.) were stirred in an electrically heated autoclave. The results are summarised below:

Temp.	Time, hours.	Products.					
		(I.)		(II.)		(IV.)	
		Wt., g.	M. p.	Wt., g.	M. p.	Wt., g.	M. p.
150°*	3	143	34—36°	—	—	—	—
150	10	273	43—48	—	—	57	115—125°
175	3	224	32—34	53.2	84—86°	35.7	126—128
175	10	116	semi-solid	115	75—82	45.7	122—133
200	4	80	semi-solid	166	50—68	55	127—129
225	3	40	semi-solid	204.5	48—51	36.5	114—128

* In this experiment alone, 1-thiolbenzthiazole (181 g.) was recovered unchanged.

After 1-thiolbenzthiazole (334 g.) had been heated with methyl alcohol (96 g.) and iodine (0.8 g.) in the autoclave for 10 hours at 150°, the products were (I) (239 g.), m. p. 39—42°, (II) (19.4 g.), m. p. 86—90°, and (IV) (61 g.), m. p. 118—128°. From a mixture of 1-thiolbenzthiazole (167 g.), methyl alcohol (128 g.), and iodine (0.8 g.) heated at 150° for 10 hours, the products obtained were (I) (109 g.), m. p. 38—45°, and a mixture of (IV) with unchanged 1-thiolbenzthiazole (47.2 g.) which was not separated.

(c) *With bromine as catalyst.* In a sealed tube at 200° 1-thiolbenzthiazole (22.2 g.), methyl alcohol (8.6 g.), and bromine (0.2 g.) afforded after 10 hours 1-thio-2-methyl-1 : 2-dihydrobenzthiazole (II) (5.0 g.), m. p. 82—85°, and 2-methylbenzthiazolone (III) (10.0 g.), m. p. 74—76° after one crystallisation from methyl alcohol.

(d) *With sulphuric acid as catalyst.* Under the same conditions as (c), 1-thiolbenzthiazole (22.2 g.), methyl alcohol (8.6 g.), and sulphuric acid (a few drops) gave 1-hydroxybenzthiazole (IV) (8.1 g.), m. p. 130—135° after one crystallisation from methyl alcohol. 1-Methylthiobenzthiazole was isolated from the residue after separation of the alkali-soluble material. The products were not further examined.

(e) *Miscellaneous experiments bearing on the mechanism.* The reactants were heated in sealed tubes at 210—215° for 10 hours: the products were isolated as before.

(i) From 1-hydroxybenzthiazole (10 g.), methyl alcohol (5.4 c.c.), and a trace of iodine, 1-hydroxybenzthiazole (9.5 g.), m. p. 125—134°, was recovered.

(ii) From 1-methylthiobenzthiazole (10 g.), water (2 c.c.), and a trace of iodine, 1-thio-2-methyl-1 : 2-dihydrobenzthiazole (2.5 g.), m. p. 86—90°, was formed and 1-methylthiobenzthiazole (5.8 g.), m. p. 36—42°, was recovered. No appreciable amount of alkali-soluble solid was isolated.

(iii) From 1-methylthiobenzthiazole (10 g.), methyl alcohol (1.2 c.c.), water (0.8 c.c.), and a trace of iodine, 1-thio-2-methyl-1 : 2-dihydrobenzthiazole (1.2 g.), m. p. 82—87°, was formed and 1-methylthiobenzthiazole (6.4 g.), m. p. 40—50°, was recovered. No appreciable amount of alkali-soluble material was isolated.

(iv) 1-Thio-2-methyl-1 : 2-dihydrobenzthiazole (9 g.), after being heated with water (2 c.c.) and a trace of iodine, was recovered (8.8 g.), m. p. 89—90°.

(v) From 1-thiolbenzthiazole (16.7 g.), water (5 c.c.), and a trace of iodine, the initial material was recovered (15.6 g.), m. p. 173—177°.

(2) *Reaction of 1-Thiolbenzthiazole with Ethyl Alcohol.*—1-Thiolbenzthiazole (22.4 g.), ethyl alcohol (12.6 g.), and iodine (0.07 g.) were heated in a sealed tube at 230° for 10 hours. The products, separated as in the experiments with methyl alcohol, were 1-hydroxybenzthiazole (5.3 g.), m. p. 100—110°, raised to 139—140° by two crystallisations from alcohol, and 1-thio-2-ethyl-1 : 2-dihydrobenzthiazole (15.5 g.), m. p. 76° after one crystallisation from alcohol.

In a second experiment with double the quantity of iodine, the yield of 1-thio-2-ethyl-1 : 2-dihydrobenzthiazole was 18.5 g., and of 1-hydroxybenzthiazole 2.8 g.

(3) *Reaction of Substituted 1-Thiolbenzthiazoles with Methyl Alcohol.*—(a) *4-Chloro-1-thiolbenzthiazole.* The thiol (20.2 g.) was heated in a sealed tube with methyl alcohol (6.5 g.) and iodine (0.1 g.) for 10 hours at 230°. The product was partly liquid and partly a reddish-brown solid. The latter, after being washed with dilute sodium hydroxide solution and crystallised from alcohol, was identified by m. p. 109—110° and mixed m. p. as 4-chloro-2-methylbenzthiazolone.

(b) *1-Thiol-4-methylbenzthiazole.* Treated as in (a), this gave a solid product only, which after crystallisation from alcohol was identified by m. p. 190° and mixed m. p. as 1-thio-2 : 4-dimethyl-1 : 2-dihydrobenzthiazole.

(4) *1-Methoxybenzthiazole.*—(a) Methyl phenylthioncarbamate (4.3 g.), dissolved in 30% aqueous sodium hydroxide (37 c.c.) containing methyl alcohol (5 c.c.), was diluted with water (87 c.c.) and added in 10 c.c. portions at 5-minute intervals to a stirred solution of potassium ferricyanide (30 g.) in water (140 c.c.) at 80—85°. After a further 10 minutes' stirring, the oil was separated, dissolved in a little light petroleum (b. p. 40—60°), and filtered from insoluble red tar. The solvent was removed, and the residual reddish oil crystallised from a little methyl alcohol with good cooling. The product, m. p. 31—33°, had a characteristic

odour of wintergreen. Treatment of the alkaline aqueous layer with ether extracted crude methyl phenylthioncarbamate, m. p. 82—90° (mixed m. p. with an authentic specimen 89—93°). Hunter and Parken (*loc. cit.*) give the m. p. of "1-methoxybenzthiazole" as 88—89° (the m. p. of pure methyl phenylthioncarbamate is 93°).

(b) 1-Chlorobenzthiazole (16.9 g.) was added to a solution of sodium methoxide (sodium 2.4 g., in methyl alcohol, 40 c.c.), the mixture boiled for 3 hours and poured into water, and the solid obtained crystallised from methyl alcohol with good cooling; it had m. p. 34—35°; yield, 11 g. (Found: C, 58.0; H, 4.1; N, 8.4; S, 19.5. C_8H_7ONS requires C, 58.2; H, 4.3; N, 8.5; S, 19.4%). The substance had the same wintergreen type of smell as the product obtained in (a) and the mixed m. p. of the two products was 32—34°.

(5) *Isomerisation of 1-Methoxybenzthiazole.*—After heating for 3 hours at 150°, with or without a trace of iodine, unchanged material, m. p. 33—35°, was recovered. After heating at 175—180° for 3 hours, the product (in absence of iodine) readily solidified on cooling to give 2-methylbenzthiazolone, m. p. and mixed m. p. 74—75°; in presence of a trace of iodine, the product was a mixture of oil and 2-methylbenzthiazolone, m. p. and mixed m. p. 73—75°.

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