

THE REDUCTION OF BENZOXAZOLES AND BENZOTHAZOLES IN LIQUID AMMONIA¹

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Received October 6, 1941

The available information relative to the behavior of oxazoles, thiazoles, and related compounds towards reducing agents is quite limited. The only conclusive studies recorded are those of the reduction of 2-phenyloxazoline (1), 2,5-diphenyloxazole (2), and 2,4-dimethylthiazole (3), all of which were reduced with rupture of the heterocyclic rings by the use of sodium and alcohol. In the present paper there is described the reduction of benzoxazole, 2-phenylbenzoxazole, benzothiazole, and 2-chlorobenzothiazole. Reduction was effected through the use of sodium in liquid ammonia (method 1), and nascent hydrogen generated by the interaction of ammonium bromide and sodium in liquid ammonia (method 2). The effectiveness of these unusually strong reducing agents in the reduction of a variety of organic substances has been demonstrated previously (4-7).

EXPERIMENTAL

Methods and materials. All reduction reactions were carried out under strictly anhydrous conditions in liquid ammonia at -33.5° in an apparatus similar to that described by Johnson and Fernelius (8). Benzoxazole was prepared by the method of Niementowski (9) and 2-chlorobenzothiazole was prepared as described by Scott and Watt (10).

Preparation of 2-phenylbenzoxazole. This compound was prepared by a method which was suggested by Wheeler (11) but which has not been described. Benzamide (187 g.) and *o*-aminophenol (168 g.) were refluxed for six hours, during which ammonia and water were eliminated. Distillation of the reaction mixture followed by treatment with "Norit", recrystallization from alcohol, and final recrystallization from concentrated hydrochloric acid yielded 280 g. (80% yield) of colorless crystalline 2-phenylbenzoxazole, m.p. 103° .² This melting point is in agreement with that reported by Ladenberg (12) for 2-phenylbenzoxazole prepared by the condensation of *o*-aminophenol and phthalic anhydride.

Preparation of benzothiazole. The method of Hofmann (13) as modified by Kiprianov and co-workers (14) was found to be impractical for the preparation of appreciable quantities of benzothiazole. Consequently, this material was prepared by an adaptation of the method of Möhlau and Krohn (15) as modified by Mills (16). Dimethylaniline and sulfur were refluxed for eighteen hours, the resulting mixture was distilled and the fraction distilling over the range $200-260^{\circ}$ was collected and dissolved in an equal volume of concentrated hydrochloric acid. The by-product "benzothiazolemethenesulfide" (17), $C_6H_7NS_2$, was precipitated by dilution with water and removed by filtration. Addition of an excess of aqueous ammonium nitrate solution to the filtrate resulted in the precipitation of benzothiazole nitrate, which was separated by filtration, washed with a small quantity of ammo-

¹ This work was supported in part by a grant from the University Research Institute (Project No. 25).

² All melting points reported in this paper are corrected.

nium nitrate solution, and thereafter dissolved in water. Benzothiazole was liberated by addition of aqueous ammonia, dried, and distilled; b.p. 131°/34 mm.; n_D^{20} 1.6379; d_4^{20} 1.246. The following physical constants have been recorded for benzothiazole: b.p. 227–228°/765 mm. (18); n_D^{24} 1.6370 (19); d_4^{24} 1.244(18). Yield data together with information concerning the influence of variation in the dimethylaniline/sulfur ratio are shown in Table I.

Determination of reaction ratios. The ratio of moles of the oxazole or thiazole to gram-atoms of sodium was determined by dissolving a weighed quantity of oxazole or thiazole in liquid ammonia and adding sodium in small pieces until a permanent blue coloration was

TABLE I
PREPARATION OF BENZOTHAZOLE

DIMETHYLANILINE (G.)	SULFUR (G.)	C ₆ H ₇ NS ₂ (G.)	BENZOTHAZOLE YIELD	
			(g.)	(%)
500	650	60	50	9
500	750	50	75	13.5
500	800	0	113	20

TABLE II
REACTION RATIOS (METHOD 1)

SUBSTANCE	WT. OF SUBSTANCE (G.)	WT. SODIUM REQUIRED (G.)	GRAM-ATOMS Na/GRAM-MOLE OF SUBSTANCE
Benzoxazole.....	5.69	2.15	1.95
2-Phenylbenzoxazole.....	10.00	2.20	1.86
Benzothiazole.....	7.02	2.39	2.00
2-Chlorobenzothiazole.....	1.08	0.54	3.70

TABLE III
REACTION RATIOS (METHOD 2)

SUBSTANCE	WT. OF SUBSTANCE (G.)	WT. Na (G.)	VOL. H ₂ (CC.)	G.-ATOMS Na (AND/OR H)/MOLE OF SUBSTANCE
Benzoxazole.....	2.59	1.69	224	2.46
2-Phenylbenzoxazole.....	1.76	1.06	156	3.55
Benzothiazole.....	1.52	0.97	147	2.56
2-Chlorobenzothiazole.....	1.08	0.89	106	4.57

produced (method 1). Although the detection of the "end-point" was in some cases rendered difficult by the formation of colored reduction products, reproducible values could be obtained. These data are given in Table II.

A second procedure involved the addition of an excess of sodium, followed by addition of ammonium bromide and collection of the hydrogen thereby liberated (method 2). From the weights of materials involved and the weight of hydrogen liberated, the quantity of sodium utilized in the reduction of the oxazole or thiazole was calculated. The values listed in Table III were obtained by method 2 and represent the average of two closely agreeing results in each case.

IDENTIFICATION OF REDUCTION PRODUCTS

The only difference between the reactions carried out for the purpose of determining reaction ratios and those described in this section lies in the fact that for purposes of purification and identification of products, it was frequently necessary to effect reactions on a relatively larger scale. Without exception, the primary reduction products were unstable under ordinary atmospheric conditions. Hydrolysis or neutralization of the primary products resulted in the formation of substances which, in general, showed a pronounced tendency towards oxidation and decomposition leading to the production of dark-colored, tarry, resinous materials.

Reduction of benzoxazole by sodium. After evaporation of the solvent ammonia following the reduction of 8.01 g. of benzoxazole by 3.29 g. of sodium, the crude product was extracted with 10% sodium hydroxide solution. The resulting solution was treated with an excess of benzoyl chloride and cooled. The white crystals of dibenzoyl-*o*-aminophenol which separated were recrystallized once from alcohol and once from a mixture of benzene and petroleum ether, m.p. 180–182°.

Anal. Calc'd for $C_{20}H_{15}NO_3$: N, 4.42. Found: N, 4.29.

A mixture with an authentic sample of dibenzoyl-*o*-aminophenol (20) showed no depression in melting point. The material which was insoluble in sodium hydroxide consisted of a black tar which oxidized readily and which could not be identified.

In another experiment, the primary reduction product (a brick-red precipitate) obtained by addition of 3.18 g. of sodium to 21.10 g. of benzoxazole dissolved in 300 cc. of liquid ammonia was treated with a large excess (65 g.) of ethyl bromide. The solvent was evaporated and the residue extracted with anhydrous ether. Distillation of this extract yielded 25.1 g. of a colorless viscous oil which darkened upon exposure to air, and which had the following physical constants: B.p. 79–85°/1 mm., 200–205°/754 mm.; n_D^{20} 1.5330; d_4^{20} 1.015. M. [assuming the product to be N-(*o*-ethoxyphenyl)propylideneimine], Calc'd, 53.86; Found, 54.52.

Anal. Calc'd for $C_{11}H_{14}NO$: C, 74.50; H, 8.47; N, 7.92. Found: C,³ 72.33; H, 8.68; N, 7.84.

Molecular weight determinations (ebullioscopic in acetone) were inconclusive. The weight of product obtained corresponds to an 80% yield of N-(*o*-ethoxyphenyl)propylideneimine. The synthesis of this compound (which has not been described previously) from propanal and *o*-phenetidine by a method similar to that of Knoevenagel (21) was attempted but without success.

Reduction of benzoxazole by hydrogen. Benzoxazole (2.14 g.) was dissolved in liquid ammonia containing an excess of dissolved ammonium bromide. To this solution was added in small pieces 1.90 g. of sodium. Of the 0.0833 g. of hydrogen produced by the interaction of sodium and ammonium bromide, 0.0203 g. was collected as molecular hydrogen. From these data it was calculated that 0.0630 g. of hydrogen was utilized in the reduction of the oxazole and that the ratio of gram-atoms of hydrogen/gram-moles of oxazole was 3.47.

In a similar reaction involving 6.34 g. of benzoxazole, 20.91 g. of ammonium bromide, and 4.30 g. of sodium, the crude product was extracted with boiling benzene. From this solution, by concentrating and cooling, 5.2 g. (79% yield) of *o*-methylaminophenol, m.p. 86–87° (22) was obtained. The monobenzoyl derivative was prepared in benzene and recrystallized from a mixture of alcohol and water, m.p. 157–159° (23).

Anal. Calc'd for $C_{14}H_{13}NO_2$: N, 6.19. Found: N, 6.02.

Reduction of 2-phenylbenzoxazole by sodium. The reduction of this compound by means of either sodium or hydrogen yields tarry resinous products which are very susceptible to atmospheric oxidation. Despite repeated and varied methods of attack, no success at-

³ Duplicate analyses for carbon were made on independently prepared samples. These analyses led to results which were in close agreement but which were uniformly low.

tended efforts at isolation and identification of the reduction products. 2-Phenylbenzoxazole is only slightly soluble in liquid ammonia at -33.5° .

Reduction of benzothiazole by sodium. Benzothiazole (13.5 g.) was reduced by addition of 2.37 g. of sodium. The solvent was evaporated from the resulting red solution and the reduction product was hydrolyzed by water. The red alkaline aqueous solution was subjected to distillation with steam. No benzothiazole (which is readily volatile with steam) was found to be present. The solution was acidified with acetic acid, buffered with sodium acetate solution, and treated with an excess of aqueous lead acetate solution. A tan colored solid separated, which was insoluble in all common organic solvents and which was purified by extraction with acetone, alcohol, and ether, m.p. $> 275^{\circ}$.

Anal. Calc'd for $C_6H_7NS \cdot Pb(C_2H_3O_2)_2$ (a 1:1 double salt of *o*-aminothiophenol and lead acetate): N, 3.11; S, 7.11.

Found: N, 3.14; S, 7.18.

This compound has not been reported previously.

In a similar experiment, 5.87 g. of benzothiazole was reduced by 2.00 g. of sodium, and the primary reduction product was neutralized by ammonium bromide. After evaporation of the ammonia, the residue was extracted with alcohol. To this solution was added

TABLE IV
REDUCTION OF BENZOTHAZOLE BY SODIUM

BENZOTHAZOLE (G.)	SODIUM (EQUIVALENTS)	BENZOTHAZOLE RECOVERED (%)	Hg SALT (G.)	BENZOTHAZOLE ACCOUNTED FOR (%)
5.10	1	46.4	3.97	91.0
5.87	2	0	8.58	83.5
5.26	3	0	7.87	85.5

an alcoholic solution of mercuric cyanide, resulting in the precipitation of the golden-yellow mercuric salt of N-(*o*-mercaptophenyl)methylideneimine. The salt was purified by recrystallization from a mixture of carbon disulfide and ether, m.p. $> 120^{\circ}$ (decomp.).

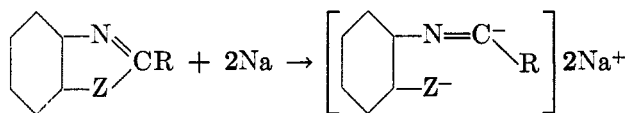
Anal. Calc'd for $C_{14}H_{12}HgN_2S_2$: N, 5.92. Found: N, 5.90.

A series of reactions was effected in order to determine the influence of variation in the sodium/benzothiazole ratio. Two reactions corresponding to each ratio were carried out. The product of one reaction was subjected to steam distillation to separate unchanged benzothiazole, which was identified as the picrate (24), m.p. 167° . The product of the other reaction was used in the formation of the mercuric salt of N-(*o*-mercaptophenyl)methylideneimine, the weight of which serves as a measure of the quantity of benzothiazole reduced. The results of these experiments are given in Table IV.

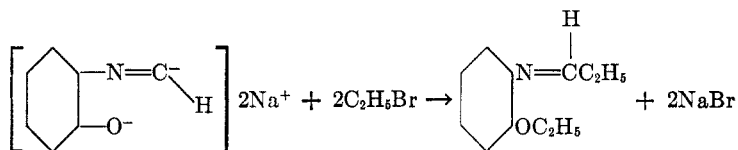
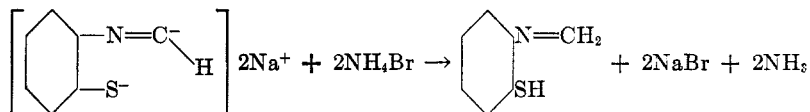
Reduction of 2-chlorobenzothiazole by sodium. The reduction of this compound was carried out primarily to secure essential information concerning reaction ratios. Although not investigated extensively, the ultimate products of these reactions appeared to be essentially the same as those obtained by the reduction of benzothiazole.

DISCUSSION OF RESULTS

The data of Tables II and IV indicate that benzoxazoles and benzothiazoles are reduced by sodium in liquid ammonia as shown by the equation,

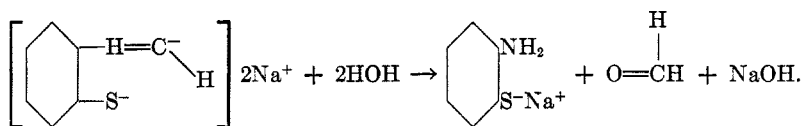
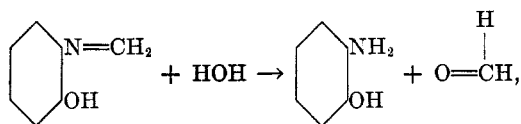


where R may be H or C₆H₅, and Z may be O or S. When R is Cl, the sodium / thiazole ratio is increased from two to four. Since the sodium salts are unstable, the character of the products ultimately isolated and identified depends upon the treatment of the primary products. When the sodium salts are neutralized by ammonium bromide or are treated with ethyl bromide, the corresponding Schiff bases are formed,



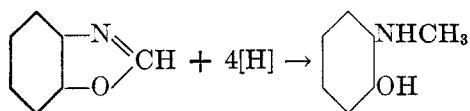
This view is supported by the isolation of the mercuric salt of N-(*o*-mercapto-phenyl)methylideneimine and N-(*o*-ethoxyphenyl)propylideneimine, although the identity of this latter compound cannot presently be said to be finally established.

If, on the other hand, either the sodium salts or the Schiff bases are subjected to conditions favoring hydrolysis, the corresponding aminophenols or thiophenols are produced.



This has been shown by the isolation of dibenzoyl-*o*-aminophenol and the lead acetate double salt of *o*-aminothiophenol. In this connection it is significant that neither the sodium salts nor the Schiff bases showed any tendency towards ammonolysis (25).

That reduction by hydrogen is more extensive than reduction by sodium is shown by the isolation of a high yield of *o*-methylaminophenol from the products of the reduction of benzoxazole by hydrogen.



This conclusion is also indicated by the reaction ratio data obtained by method 2. An inspection of the data of Table III shows that the reaction ratios are uniformly low, but approach integral values greater than those obtained by method 1; the quantity of hydrogen collected was always less than that anticipated. This discrepancy is undoubtedly due in part to the solubility of hydrogen in the water over which the gases were collected, but probably due in larger measure to participation of the liberated hydrogen in a more extensive reduction. This situation is analogous to that encountered by Cappel and Fernelius (5) in their study of the reduction of 1,2,3-benzotriazole. In contrast with their results, however, the present study provided no indication of hydrogenation of the atomatic ring.

As has already been suggested, a major source of difficulty encountered throughout this investigation involved the marked instability and ease of oxidation and polymerization of the reduction products. That this behavior is generally characteristic of aminophenols and aminothiophenols has been demonstrated by earlier workers (26-29).

SUMMARY

1. A method for the preparation of 2-phenylbenzoxazole and an improved procedure for the preparation of appreciable quantities of benzothiazole in a high state of purity have been described.

2. Certain experiments on the reduction of benzoxazole, 2-phenylbenzoxazole, benzothiazole, and 2-chlorobenzothiazole by means of sodium and hydrogen ($\text{Na} + \text{NH}_4\text{Br}$) in liquid ammonia have been described and a possible interpretation of the results of these experiments has been suggested.

3. Evidence that reduction by hydrogen is more extensive than reduction by sodium has been presented.

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