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PREPARATION OF BENZISOXAZOLES BY OXIDATIVE RING CLOSURE

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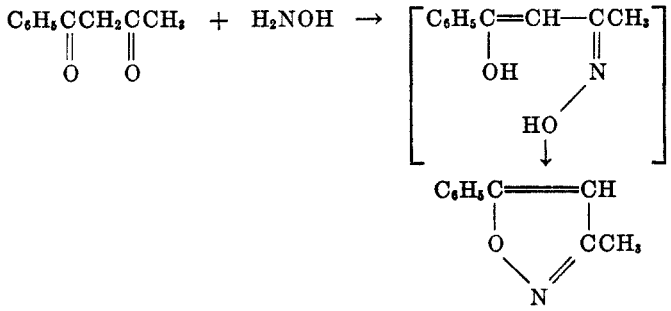
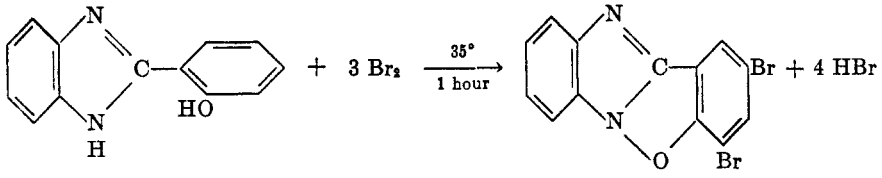
Methods for the preparation of isoxazoles are generally similar to that used by Claisen (1) who in 1888 formed an isoxazole from the reaction of hydroxylamine with benzoylacetone.



In the course of investigating the compound 2-(*o*-hydroxyphenyl)benzimidazole (I) as a reagent (2), we have found what we believe to be a novel method of formation of benzisoxazoles based on oxidative ring closure using bromine. Unlike the analogous 2-(*o*-hydroxyphenyl)benzoxazole which consumed two moles of bromine per mole to form the dibromo derivative (3), the benzimidazole (I) was found to take up 3 moles of bromine per mole. Analysis and molecular weight determination of the reaction product revealed that only two bromines were introduced in the molecule. A consideration of the structure of I led us to postulate that the third mole of bromine consumed by the benzimidazole might have served to oxidize the compound to yield the ring-closed product, II, a dibrominated benzimidazo-benzisoxazole:



I II

The product II was a crystalline solid (m.p. 182–185°) which failed to show either the enol test or the alkali solubility of the parent compound indicating loss of the phenolic function. A molecular weight determined cryoscopically by the Rast method was in accord with the postulated structure II.

To further test the validity of the postulated course of the reaction, it was decided to subject salicylamide (III), a compound analogous to I, to bromination

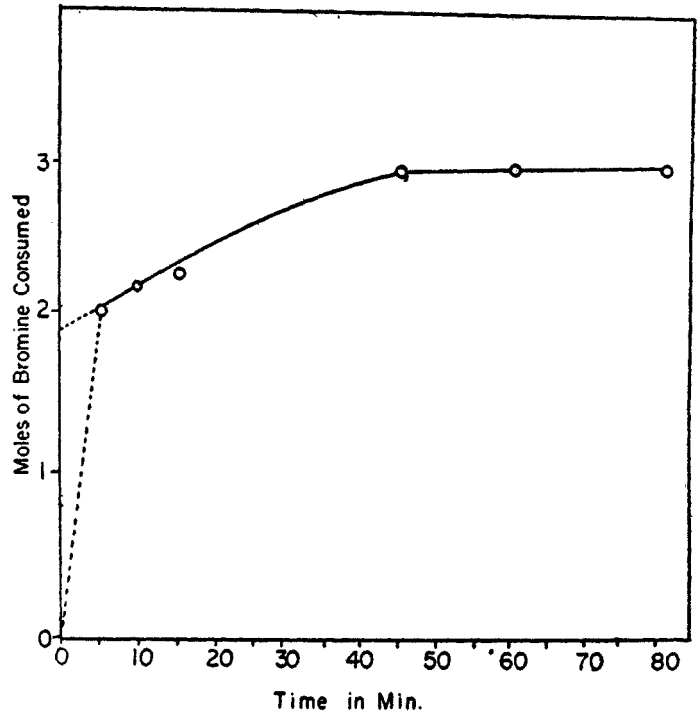
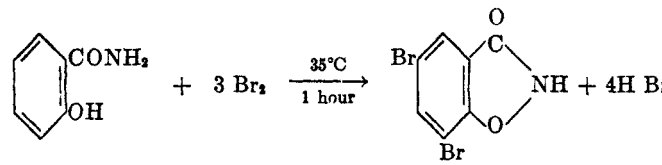


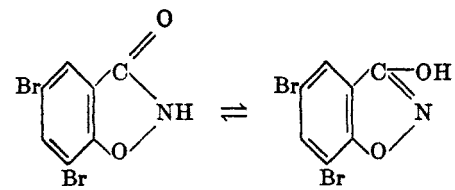
FIGURE 1. RATE OF BROMINATION OF SALICYLAMIDE

under the same conditions. We found that, as with I, three moles of bromine were consumed per mole of III, and again only two atoms of bromine were introduced into the product (IV). On the basis of the stoichiometry of the reaction we may represent the bromination by the following equation:



III IV

The compound IV, a dark brown solid (m.p. 154–158°) gave a positive enol test which may be explained on the basis of the following equilibrium:



IV

Since it was of interest to know whether the bromination or the ring closure was the first step in the reaction a kinetic study of the reaction of salicylamide with bromine was carried out. The results, shown in Figure 1, reveal a very rapid consumption of the first two moles of bromine with a relatively slow reaction with the third. This indicates that the salicylamide is first brominated to dibromosalicylamide (V) which then undergoes the ring closure. This was confirmed by brominating salicylamide with the bromate-bromide equivalent to a little more than two moles of bromine to one of salicylamide. Exactly two moles of bromine were consumed in the reaction in which dibromosalicylamide was produced.

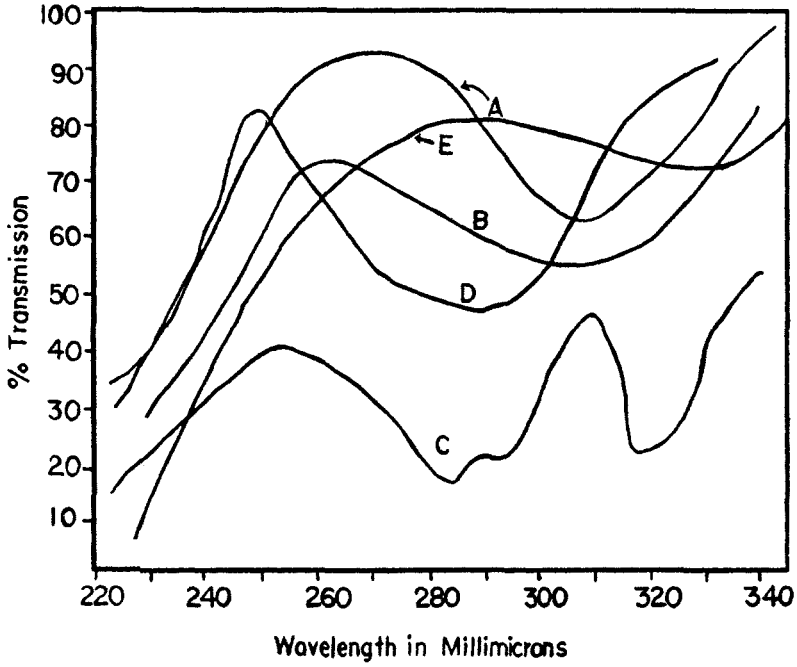


FIGURE 2. ABSORPTION SPECTRA OF COMPOUNDS (1×10^{-5} *M*) IN ABSOLUTE ALCOHOL. A, 3,5-Dibromosalicylamide; B, brominated 2-(*o*-hydroxyphenyl)benzimidazole; C, 2-(*o*-hydroxyphenyl)benzimidazole; D, salicylamide; E, dibromobenzisoxazolone (IV).

To further characterize the bromination products II, IV, and V, their ultraviolet absorption spectra in absolute ethanol along with those of the parent compounds I and III, were determined. As can be seen from Figure 2, the spectra of II and IV resemble each other while differing from those of I, III, and V.

The bromination of anthranilic acid, in the attempt to produce another benzisoxazole, resulted in the formation of tribromoaniline.

EXPERIMENTAL

REAGENTS. *Bromate-bromide mixture.* To make a 0.1 *N* bromate-bromide solution, 2.780 g. of C.P. potassium bromate and 10.00 g. of C.P. potassium bromide was dissolved in about 500 cc. of distilled water and diluted to a liter in a volumetric flask.

Standard thiosulfate solution. Analytical Reagent grade sodium thiosulfate (24.82 g.) was weighed into a liter volumetric flask and the volume was brought up to a 1000 ml. with distilled water. This solution was standardized against the bromate-bromide solution.

Bromination of 2-(o-hydroxyphenyl)benzimidazole (I). In a typical run, about 150 mg. of 2-(o-hydroxyphenyl)benzimidazole was weighed into an iodine flask and dissolved in about 50 ml. of hot glacial acetic acid. The flask was cooled to room temperature and 50 ml. of the bromate-bromide mixture was pipetted into the flask. The iodine flask was immediately stoppered and a few milliliters of potassium iodide solution (6% W/V KI) was added to the flask reservoir to prevent any loss of bromine. The flask was immersed in a water-bath kept at approximately 35° and the reaction was allowed to proceed for 1–1½ hours. Then 25 ml. of 6% W/V potassium iodide solution was added to the reaction mixture and the iodine thus liberated was titrated with standard 0.1 *N* sodium thiosulfate using a dead-stop indicator apparatus (2). A blank was run by following this procedure omitting the organic

TABLE I

BROMINATION DATA

COMPOUND	SAMPLE WEIGHT, g.	A NET VOLUME OF THIOSULFATE	MOLES OF BROMINE CONSUMED PER MOLE
2-(o-Hydroxyphenyl)-benzimidazole	0.1616	48.9	3.1
	.1220	35.0	3.0
Salicylamide	0.0906	38.5	2.9
	.0891	38.7	3.0
	.0879	40.0	3.1
Anthranilic acid	0.0900	40.0	3.0
	.0891	39.4	3.0

compound. The results, summarized in Table I, were calculated with the aid of the following equation:

$$\text{Moles of Bromine consumed per mole} = \frac{\text{A} \times N_{S_2O_3^{=}} \times \text{M.W.}}{\text{sample wt.} \times 2000}$$

where A is difference between the volume of thiosulfate used for the blank and that used for the sample and M.W. signifies the molecular weight of the benzimidazole.

Bromination product of I. The yellow-brown crystalline precipitate formed during the bromination of I was filtered and, after recrystallization from alcohol-water, had m.p. 182–185° (corr.). The crystals gave no enol test with ferric chloride and were insoluble in dilute (3 *M*) sodium hydroxide.

Anal. Calc'd for (II) $C_{13}H_8Br_2N_2O$: Br, 43.7; M.W. 366.

Found: Br, 44.1; M.W. (Rast), 361.

Bromination of salicylamide and anthranilic acid. The brominations of salicylamide and anthranilic acid were carried out exactly as was the bromination of I described above. The results, calculated similarly, are also summarized in Table I. It may be noted that each of the three compounds consumed 3 moles of bromine per mole.

The conditions under which the kinetic study of salicylamide bromination was made closely approximated the same conditions with the sole exception of reaction time as noted in the Figure.

In a separate set of brominations in which the amount of bromate-bromide solution

used (30 ml. which required 30.3 ml. of $Na_2S_2O_3$ solution) represented only a small excess over a 2:1 mole ratio of bromine to salicylamide the following results were obtained

SAMPLE WEIGHT, g.	A	MOLES OF BROMINE CONSUMED PER MOLE
0.0944	28.3	2.0
.0916	28.8	2.1
.0818	22.7	1.9

Bromination product of salicylamide. The bromination mixture was extracted with ethyl ether. The ether extract was treated with sodium bicarbonate to remove acetic acid, washed, dried, and finally allowed to evaporate on a watch glass to give a dark brown solid melting at 154–158°. Ferric chloride gave a purple enol test.

Anal. Calc'd for $C_7H_3Br_2NO_2$: Br, 54.7. Found: Br, 53.8.

If to the bromination mixture an excess of thiosulfate was added and the mixture was allowed to stand after some hours a white crystalline precipitate formed which, after recrystallization from alcohol-water, was found to melt at 182–183° (corr.). Spilker (4) gives m.p. 183° for dibromosalicylamide.

Anal. Calc'd for $C_7H_7Br_2NO_2$: Br, 54.3. Found: Br, 54.5.

Bromination product of anthranilic acid. A pale pink crystalline precipitate formed during the bromination. Upon recrystallization from alcohol-water the crystals melted at 119–120° (corr.); reported for tribromoaniline, 120°.

Anal. Calc'd for $C_6H_4Br_3N$: Br, 72.7. Found: Br, 73.0.

The *bromine analyses* were carried out by Mr. George Stragand of the University's Organic Microanalytical Laboratory.

Ultraviolet absorption spectra shown in Figure 2 were obtained using a Beckman Model DU ultraviolet spectrophotometer with a 1-cm. cell.

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PITTSBURGH, PA.

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