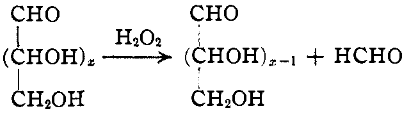
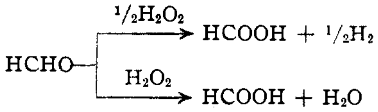
compounds. The liberation of hydrogen is characteristic, although the quantities formed were relatively small. *d*-Glucose is likewise only slowly oxidized by the hydrogen peroxide. There is some indication that the hydrogen peroxide is stabilized by the glucose.

The reaction with sucrose is characterized by a much greater speed than with *d*-arabinose, or *d*-glucose. Hydrogen is evolved likewise in much greater quantities. A darkening of the reaction mixture occurred when low concentrations of hydrogen peroxide were used. This was not true at higher concentrations. No doubt the fructose portion of the molecule is more susceptible to attack than the glucose portion.

The evidence presented here indicates that the liberation of hydrogen is characteristic of the action of hydrogen peroxide on carbohydrates. The origin of the hydrogen in the formaldehyde produced by scission or in the last step of the degradation offers a satisfactory mechanism based on previous evidence that hydrogen is not set free from the peroxide itself, from the aldehyde group, or from carbon atoms in the alpha position to the aldehyde group. The scission reaction would proceed according to the general scheme

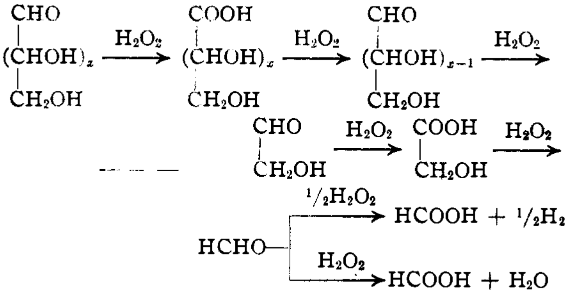


$$\begin{array}{c}CHO\\|\\(CHOH)_x\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2} \begin{array}{c}CHO\\|\\(CHOH)_{x-1}\\|\\CH_2OH\end{array} + HCHO$$



$$HCHO \begin{cases} \xrightarrow{{}^1/_2H_2O_2} HCOOH + {}^1/_2H_2 \\ \xrightarrow{H_2O_2} HCOOH + H_2O \end{cases}$$

Stepwise degradation giving formaldehyde in the final step would be as follows



$$\begin{array}{c}CHO\\|\\(CHOH)_x\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2} \begin{array}{c}COOH\\|\\(CHOH)_x\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2} \begin{array}{c}CHO\\|\\(CHOH)_{x-1}\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2}$$

$$--- \begin{array}{c}CHO\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2} \begin{array}{c}COOH\\|\\CH_2OH\end{array} \xrightarrow{H_2O_2}$$

$$HCHO \begin{cases} \xrightarrow{{}^1/_2H_2O_2} HCOOH + {}^1/_2H_2 \\ \xrightarrow{H_2O_2} HCOOH + H_2O \end{cases}$$

Summary

A quantitative investigation of the action of hydrogen peroxide on glyceric aldehyde, erythritol, *d*-arabinose, *d*-glucose, and sucrose, shows that hydrogen is a characteristic reaction product in every case. A satisfactory reaction mechanism places the origin of the hydrogen in formaldehyde produced in the oxidative degradation of the compounds.

Glyceric aldehyde apparently undergoes a dismutation reaction in the presence of low concentrations of hydrogen peroxide.

HONOLULU, HAWAII RECEIVED JUNE 4, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WESTERN KENTUCKY STATE TEACHERS COLLEGE]

A Study of Certain Brominated Derivatives of Oxindole

BY WARD C. SUMPTER, MARION MILLER AND LAURA NELL HENDRICK

The bromination of certain N-substituted oxindoles has been investigated by Stollé and coworkers.[1] These investigators found that the bromination of N-substituted oxindoles in aqueous solution yielded derivatives with bromine substituted in position 5 when one molecular proportion of bromine was employed and in positions 5 and 7 when two molecular proportions of bromine were used. On the other hand, the bromination of the N-substituted oxindoles in anhydrous carbon tetrachloride gave the 3,3-dibromo derivatives of the oxindole employed.

No similar study of the bromination of oxindole itself has been reported. Baeyer and Knop[2] reported the preparation of a monobromoöxindole through the action of bromine water on an aqueous solution of oxindole and a tribromoöxindole through the action of excess bromine on an aqueous solution of oxindole. Baeyer and Knop reported the m. p. of their monobromoöxindole as 176°. The preparation was repeated by Henze and Blair,[3] who found the m. p. to be 220–221° but did not determine the structure of the compound. Baeyer and Knop reported that their tribromoöxindole did not melt but decomposed on heating without melting. That this observation was also in error will appear in the Experimental Part.

This investigation was undertaken with the end in view of determining the structure of the two derivatives prepared by Baeyer and Knop and of determining whether the bromine atoms could be directed to the benzene or to the pyrrole ring by choice of solvent in the manner accomplished by Stollé and his co-workers in the case of the N-substituted oxindoles.

To this end a solution of oxindole (I) in water was treated with a solution of one molecular proportion of bromine in aqueous potassium bromide. The product was the monobromoöxindole, m. p. 220–221°, described by Henze and Blair. That this compound is 5-bromoöxindole (II) was shown

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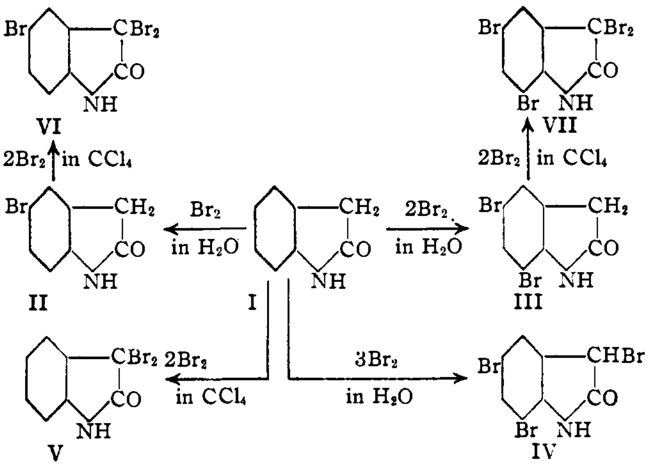
[1] Stollé, Bergdoll, Luther, Auerhahn and Wacker, *J. prakt. Chem.*, **128**, 1 (1930).

[2] Baeyer and Knop, *Ann.*, **140**, 1 (1866).

[3] Henze and Blair, THIS JOURNAL, **55**, 4621 (1933).



by conversion to 5-bromoisatin-β-oxime through treatment with nitrous acid and to 5-bromoisatin-β-phenylhydrazone by coupling with benzenediazonium chloride. Identification of the 5-bromoisatin oxime and of the 5-bromoisatin phenylhydrazone was accomplished by comparison with authentic samples by melting point methods.

A similar procedure employing two molecular proportions of bromine yielded 5,7-dibromooxindole (III). The structure of this compound was established by conversion to 5,7-dibromoisatin-β-phenylhydrazone through coupling with benzenediazonium chloride. Utilization of three molecular proportions of bromine gave a product identical with the tribromoöxindole prepared by the procedure of Baeyer and Knop. (Baeyer and Knop did not crystallize their product from acetic acid.) This substance was obtained as colorless needles, m. p. 210°. Identification of this derivative as 3,5,7-tribromoöxindole (IV) was accomplished by refluxing a solution of the substance in alcohol with phenylhydrazine. The product was 5,7-dibromoisatin-β-phenylhydrazone identified by comparison with an authentic sample.

Bromination of oxindole with two molecular proportions of bromine in anhydrous carbon tetrachloride yielded 3,3-dibromoöxindole (V). The structure of this compound was established by its conversion to isatin-β-phenylhydrazone through the action of phenylhydrazine. This reaction proved that the bromine atoms in V were in the 3,3-position. Similarly bromination of II in carbon tetrachloride yielded 3,3,5-tribromooxindole (VI) while similar treatment of III yielded 3,3,5,7-tetrabromoöxindole (VII). Treatment of VI with phenylhydrazine gave 5-bromoisatin-β-phenylhydrazone while treatment of VII with the same reagent gave 5,7-dibromoisatin-β-phenylhydrazone.

Experimental

5-Bromoöxindole (II)-A.—The compound was prepared as described by Baeyer and Knop[2] and Henze and Blair[3]; colorless prisms, m. p. 220–221°.

B.—Oxindole (0.05 mole) was dissolved in 200 cc. of hot water. A solution of 8 g. of bromine (0.05 mole) in 25 cc. of water containing 12 g. of potassium bromide was slowly added to the hot solution. Nine and nine-tenths grams of colorless crystalline material separated. The crude product was crystallized from alcohol; colorless prisms, m. p. 220–221°. The product was identical with that obtained by procedure A.

5-Bromoisatin-β-oxime.—5-Bromoöxindole (0.01 mole) was dissolved in 100 cc. of glacial acetic acid and 1.73 g. (0.025 mole) of sodium nitrite added. The yellow product which separated slowly was collected and crystallized from ethyl alcohol; yellow needles, m. p. 273°.[4] A mixture with an authentic sample of 5-bromoisatin-β-oxime prepared from 5-bromoisatin showed no depression in m. p.

5-Bromoisatin-β-phenylhydrazone.—To a solution of 0.01 mole of 5-bromoöxindole in 100 cc. of ethyl alcohol was added one of 10 g. of sodium acetate in 25 cc. of water and the mixture cooled to 0°. A solution of benzenediazonium chloride (from 1.0 g. of aniline) was added. The precipitate, which separated almost immediately, was collected and crystallized from alcohol; orange yellow needles, m. p. 271–272°. A mixture with an authentic sample of 5-bromoisatin-β-phenylhydrazone exhibited the same m. p.

5,7-Dibromoöxindole (III).—A solution of 8 g. (0.05 mole) of bromine in 25 cc. of water containing 12 g. of potassium bromide was added to a boiling solution of 3.33 g. (0.025 mole) of oxindole in 100 cc. of water. The colorless product was collected and purified by crystallization from glacial acetic acid. The yield of crude product was 7.1 g. The substance was obtained as colorless needles, m. p. 260°.

Anal. Calcd. for $C_8H_5Br_2ON$: Br, 54.95; N, 4.81. Found: Br, 55.08; N, 4.87, 4.95.

5,7-Dibromoisatin-β-phenylhydrazone from III.—A solution of 20 g. of sodium acetate in 25 cc. of water was added to a solution of 2.91 g. (0.01 mole) of 5,7-dibromoöxindole in 250 cc. of ethyl alcohol and the mixture cooled to 0°. A solution of benzenediazonium chloride (from 1.0 g. of aniline) was added. The orange yellow precipitate was collected and purified by crystallization from glacial acetic acid; orange needles, m. p. 301–302°. The m. p. was unchanged when mixed with an authentic sample of 5,7-dibromoisatin-β-phenylhydrazone prepared from 5,7-dibromoisatin.

3,5,7-Tribromoöxindole (IV). **A.**—The substance was prepared as described by Baeyer and Knop; crystallized from glacial acetic acid it separated as colorless needles, m. p. 210°.

B.—A solution of 12 g. (0.075 mole) of bromine in 50 cc. of water containing 18 g. of potassium bromide was added to a boiling solution of 3.33 g. (0.025 mole) of oxindole in 200 cc. of water. Eight grams of nearly colorless product separated. Crystallized from glacial acetic acid the substance separated as colorless needles, m. p. 210°.

Anal. Calcd. for $C_8H_4Br_3NO$: Br, 64.84; N, 3.78. Found: Br, 65.01; N, 3.85, 4.05, 4.06.

5,7-Dibromoisatin-β-phenylhydrazone from IV.—One gram of 3,5,7-tribromoöxindole (IV) was dissolved in 20 cc. of ethyl alcohol and a solution of 3 g. of phenylhydrazine in 5 cc. of glacial acetic acid added and the mixture heated for two hours at reflux temperature. The product was collected and crystallized from glacial acetic acid; m. p. 301–302° alone and when mixed with an authentic sample of 5,7-dibromoisatin-β-phenylhydrazone.

3,3-Dibromoöxindole. **(V).**—A solution of 16 g. (0.1 mole) of bromine in 400 cc. of anhydrous carbon tetrachloride was added slowly to a boiling solution of 6.65 g. (0.05 mole) of oxindole in 200 cc. of anhydrous carbon tetrachloride. The boiling was continued until no further evolution of hydrogen bromide took place. Most of the solvent was removed by distillation, the concentrate

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[4] Baeyer and Knop (ref. 2) reported decomposition at 240°

treated with Norite, filtered and allowed to cool. The product which separated was purified by crystallization from glacial acetic acid; colorless prisms, m. p. 165°.

Anal. Calcd. for $C_8H_5Br_2NO$: N, 4.81; Br, 54.95. Found: N, 4.86, 5.18; Br, 55.14.

Isatin-β-phenylhydrazone from V.—A solution of 5 g. of phenylhydrazine in 5 cc. of glacial acetic acid was added to a solution of 1.5 g. of V in 25 cc. of ethyl alcohol and the mixture heated at reflux temperature for one hour. The product, which separated on cooling, was crystallized from ethyl alcohol; yellow needles, m. p. 210°. A mixture with an authentic sample of isatin-β-phenylhydrazone exhibited the same m. p.

3,3-Diphenyloxindole from V.—To a solution of 1.5 g. of V in 20 cc. of dry benzene, 3 g. of anhydrous aluminum chloride was added in small portions. The mixture was heated for two hours at 60° and the benzene then removed under reduced pressure. Ice and then water were added, the solid residue collected and crystallized from benzene; colorless needles, m. p. 225–226°. Mixed with an authentic sample of 3,3-diphenyl-oxindole prepared similarly from 3,3-dichlorooöxindole and benzene the m. p. was unchanged.

3,3,5-Tribromoöxindole (VI).—A solution of 8 g. (0.05 mole) of bromine in 100 cc. of anhydrous carbon tetrachloride was added slowly to a boiling mixture of 5.3 g. (0.025 mole) of 5-bromoöxindole and 300 cc. of anhydrous carbon tetrachloride. Heating was continued until there was no further evolution of hydrogen bromide. The resulting solution was concentrated and the product purified by crystallization from carbon tetrachloride or glacial acetic acid; colorless prisms. When heated in the usual way in a capillary tube the substance does not melt but begins to darken at about 190° and gradually decomposes by 250–260°. However, if the capillary tube is introduced into the heating bath at 235° or above the substance melts with decomposition.

Anal. Calcd. for $C_8H_4Br_3NO$: Br, 64.84; N, 3.78. Found: Br, 64.82; N, 3.70.

5-Bromoisatin-β-phenylhydrazone from VI.—A mixture of 1.5 g. of VI, 3 g. of phenylhydrazine and 20 cc. of ethyl alcohol was heated at reflux temperature for one hour. The product, which separated on cooling, was crystallized from ethyl alcohol; orange yellow needles, m. p. 271–272° alone and when mixed with an authentic sample of 5-bromoisatin-β-phenylhydrazone.

3,3,5,7-Tetrabromoöxindole (VII).—A solution of 6.4 g. (0.04 mole) of bromine in 100 cc. of anhydrous carbon tetrachloride was added slowly to a boiling solution of 5.82 g. (0.02 mole) of 5,7-dibromoöxindole in 400 cc. of anhydrous carbon tetrachloride. Heating was continued until there was no further evolution of hydrogen bromide. The resulting solution was concentrated and the product which separated on cooling purified by crystallization from glacial acetic acid; nearly colorless prisms, darkening at about 235° and melting at 250° (dec.).

Anal. Calcd. for $C_8H_3Br_4NO$: Br, 71.27; N, 3.12. Found: Br, 71.31; N, 3.00, 3.01.

5,7-Dibromoisatin-β-phenylhydrazone from VII.—A mixture of 0.6 g. of VII with 30 cc. of ethyl alcohol and 2 g. of phenylhydrazine was heated at reflux temperature for one hour. The product which separated was purified by crystallization from glacial acetic acid; m. p. 301–302° alone and when mixed with an authentic sample of 5,7-dibromoisatin-β-phenylhydrazone.

This work has been supported by a research grant (A.A.A.S.) received through the Kentucky Academy of Science.

Summary

1. The monobromoöxindole and the tribromooxindole of Baeyer and Knop have been shown to be 5-bromoöxindole and 3,5,7-tribromoöxindole, respectively.

2. Bromination of oxindole in aqueous solution yields 5-bromoöxindole, 5,7-dibromoöxindole and 3,5,7-tribromoöxindole, respectively, as one, two and three molecular proportions of bromine are employed.

3. Bromination of oxindole and of nuclear substituted oxindole derivatives in anhydrous carbon tetrachloride yields the corresponding 3,3-dibromo derivatives.

BOWLING GREEN, KENTUCKY RECEIVED MAY 21, 1945

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Some N-Methylbenzylamines and Derivatives

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[1]

In a previous communication[2] directions for preparing N-methylbenzylamine in excellent yields were described. It was of interest to prepare certain N-methylbenzylamines containing hydroxy and methoxy groups on the benzene ring from the corresponding aldehydes. These secondary amines were desired for the preparation of various derivatives of possible pharmacological value.

The N-methylbenzalimines were obtained in good yields from the reactions of aqueous methylamine with salicylaldehyde, *p*-hydroxybenzaldehyde, *o*-methoxybenzaldehyde, and anisaldehyde. These imines were readily reduced, catalytically, to the secondary amines, (V), (VII), (VIII) and (XI) in good yields. The purification of the free base of (V) was difficult because of the relative ease with which this compound lost methylamine and gave, apparently, a phenol–formaldehyde type of condensation product. Heating the free base of (VII) also caused self-condensation with loss of methylamine and formation of a resin. The lability of these C–N bonds will be discussed in a future communication.

The N-benzoyl derivatives of the free base of (V), (VIII) and (XI) were obtained in excellent yields. It had been hoped that the *p*-aminobenzenesulfonamides of the *s*-amines might be prepared. Although (XI) gave a good yield of N-(*p*-acetylaminobenzene-sulfonyl)-N-methyl-*p*-methoxybenzylamine (XIV), it was not possible to hydrolyze this product in the usual way to the sulfanilamido derivative.

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[1] Part of the experimental work described was done under a Parke, Davis and Company Research Fellowship, 1943–1944.

[2] Cromwell, Babson and Harris, THIS JOURNAL, **65**, 313 (1943).