and melted at 90–91°. The pure amide VII, after repeated recrystallization from benzene, melted at 95°.

Anal. Calcd. for $C_8H_{11}NO_3S$: C, 47.75; H, 5.50; N, 6.96. Found: C, 48.25; H, 5.70; N, 6.79.

N,N,N′,N′-Tetramethyl-α,β-diphenoxyethane-4,4′-disulfonamide (III).—4-Hydroxybenzenesulfondimethylamide (VII) (1.00 g., 0.005 mole) and potassium hydroxide (0.30 g., 0.00535 mole) were dissolved in ethanol (25 cc.). Ethylene dibromide (0.47 g., 0.0025 mole) was added and the mixture was refluxed three hours, diluted to 200 cc. with water and filtered. The product (0.193 g., 18% yield) melted at 192–196°. When it was mixed with a sample of the same material, m. p. 198–198.5°, prepared by Procedure A (above), the mixture melted at 195–197°.

Summary

1. A series of seventeen N-substituted α,β-diphenoxyethane-4,4′-disulfonamides has been prepared.

2. A series of ten other derivatives of α,β-diphenoxyethane has been prepared; six of these are water-soluble.

3. The orientation of the groups entering α,β-diphenoxyethane on treatment with chlorosulfonic acid has been established as 4 and 4′.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

Some Bromination Products of the Fluorophenols[1]

BY L. CHAS. RAIFORD AND ARTHUR L. LEROSEN[2]

We have studied the bromination of the three isomeric fluorophenols under various conditions and have prepared the following new derivatives: 2-fluoro-4,6-dibromophenol, 2,4,5,6-tetrabromo-3-fluorophenol, and 2,4,6-tribromo-3-fluorophenol bromide. We have repeated the preparation of some others already reported by Hodgson and Nixon.[3]

The 2,4,6-tribromo-3-fluorophenol bromide was of special interest, and consequently was studied in more detail than the other compounds.

The isomeric fluorophenols differed considerably from each other in their reactions with bromine as shown below.

When a glacial acetic acid solution of *o*-fluorophenol was treated with slightly more than two moles of bromine, 2-fluoro-4,6-dibromophenol was obtained. This structure was assumed from the fact that the hydroxyl group directs much more strongly[4] to the 4 and 6 positions than the fluorine atom does to the 3 and 5 positions. With a large excess of bromine an unidentified oil was obtained.

p-Fluorophenol was brominated according to the directions given by Hodgson and Nixon[3] to yield 2,6-dibromo-4-fluorophenol. An excess of bromine in glacial acetic acid oxidized *p*-fluorophenol to tetrabromoquinone.[5]

The bromination products of *m*-fluorophenol depended to some extent on the solvent. In water solution both the tribrominated phenol and the phenol bromide were formed. Bromination in glacial acetic acid produced the same compounds, even under the conditions that caused oxidation or decomposition of *p*- and *o*-fluorophenol. In carbon tetrachloride the highest brominated derivative was a dibromo compound, *viz.*, 3-fluoro-4,6-dibromophenol; however, if solid sodium bicarbonate was added to the reaction mixture, the phenol bromide was formed. Tribromophenol bromide[6,7] could also be prepared by this method.

When 2,4,6-tribromo-3-fluorophenol bromide was heated in concentrated sulfuric acid, it rearranged to give 2,4,5,6-tetrabromo-3-fluorophenol. Benedict[6] observed an analogous behavior of tribromophenol bromide.

Reduction with zinc and hydrochloric acid, or treatment with phenylhydrazine converted 3-fluorotribromophenol bromide into 2,4,6-tribromo-3-fluorophenol.

Since there has been considerable discussion concerning the relative merits of the quinoid and hypobromite structures for the phenol bromides,[8,9,10] an attempt was made to replace some of the bromine in 3-fluorotribromophenol bromide by fluorine through the use of silver fluoride. When this reaction was carried out in acetone at room temperature it was possible to isolate a small amount of bright yellow crystals, m. p. 169°. Analysis for fluorine indicated the composition $(C_6HOBr_3F)_2$. A second treatment at the boiling point of acetone gave some 2,4,6-tribromo-3-fluorophenol as the only product isolated.

Thiele and Eichwede treated tribromophenol bromide with lead acetate in glacial acetic acid and obtained 2,6-dibromobenzoquinone. When 3-fluorotribromophenol bromide was treated in the same way, a white granular solid, practically insoluble in all solvents, appeared (m. p. 162°). This substance possessed the formula $(C_6HOBr_3F)_2$ on the basis of its bromine content, it readily

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[1] From a thesis submitted by Arthur L. LeRosen in partial fulfillment of the requirements for the degree of Doctor of Philosophy, to the Graduate College of the State University of Iowa, June, 1940.

[2] This paper was prepared after the death of Dr. Raiford.

[3] H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1085 (1930); 273 (1932).

[4] C. K. Ingold, *J. Chem. Soc.*, 1329 (1926).

[5] K. Auwers and G. Büttner, *Ann.*, **302**, 142 (1898).

[6] R. Benedict, *Ann.*, **199**, 127 (1879).

[7] J. Thiele and H. Eichwede, *Ber.*, **33**, 673 (1900).

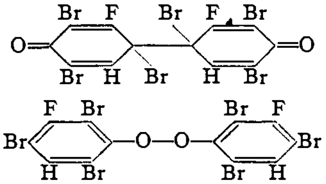
[8] J. H. Kastle, A. S. Loevenhart, R. Speyer and J. W. Gilbert, *Am. Chem. J.*, **27**, 31 (1902).

[9] W. M. Lauer, THIS JOURNAL, **48**, 422 (1926).

[10] I. Suknevich and S. Budnitzkii, *J. prakt. Chem.*, **138**, 18 (1933).

liberated iodine from potassium iodide in the cold. There was no indication of the formation of 2,6-dibromo-3-fluoro-1,4-benzoquinone, m. p. 150°, which had been prepared by Hodgson and Nixon.[11]

The formulas below illustrate two arrangements of the C_6HOBr_3F units which were assigned to the products resulting from the action of silver fluoride and lead acetate on the phenol bromide:



It is tentatively suggested that the yellow compound has the partially quinoid structure while the colorless substance possesses the peroxide formula.

Experimental[12]

Starting Materials.—The fluorophenols used in these experiments were prepared by the fluoborate method of Schiemann.[13]

2-Fluoro-4,6-dibromophenol.—A solution of 5.6 g. of *o*-fluorophenol in 10 ml. of glacial acetic acid was treated with 6 ml. of bromine. After an hour the reaction mixture was poured into water giving an oil that did not solidify on standing. The product was washed with sodium bisulfite solution in order to remove an excess of bromine. This treatment caused the oil to solidify. The crude substance was purified by treating its solution in dilute sodium hydroxide with charcoal and filtering. This filtrate was acidified with dilute sulfuric acid precipitating the brominated phenol. Several crystallizations from petroleum ether gave 5.2 g. (38%) of colorless needles, m. p. 35°.

Anal. Calcd. for $C_6H_3Br_2FO$: Br, 59.43. Found: Br, 59.25.

Action of Excess Bromine on *o*-Fluorophenol.—A solution of 1.1 g. (10 m.mol.) of *o*-fluorophenol in glacial acetic acid was treated with 2.6 g. (40 + m.mol.) of bromine and the reaction mixture was poured into water. The product, a reddish oil, was subjected to a second bromination without showing any visible change. It was not identified and attempts to isolate identifiable products from it were unsuccessful.

2,6-Dibromo-4-fluorophenol.—A solution of 5.6 g. of *p*-fluorophenol in 125 ml. of water was brominated as directed by Hodgson and Nixon.[3] After crystallization from petroleum ether the product melted at 56°, whereas the authors mentioned reported the melting point as 48°.

In a second preparation 5.6 g. of the phenol in 20 ml. of glacial acetic acid was treated with 5.3 ml. of bromine. The mixture was poured into water after standing for a short time. In this way 5.93 g. (44%) of pure product was obtained.

Action of Excess Bromine on *p*-Fluorophenol.—Five and six-tenths grams (50 m.mol.) of *p*-fluorophenol in 20 ml. of glacial acetic acid was treated with 12 ml. (200 m.-mol.) of bromine for thirty minutes. The reaction mixture was poured into water yielding an oil from which crystals were precipitated on standing. On recrystallization from benzene they were obtained as yellow platelets melting at 295°. Auwers and Büttner[5] give the same melting point for tetrabromo-*p*-quinone. The oily residue from the crystals was treated with a second portion of bromine to give more of the quinone. The total yield was 69%.

Anal. Calcd. for $C_6Br_4O_2$: Br, 75.43. Found: Br, 75.46.

3-Fluoro-4,6-dibromophenol.—*m*-Fluorophenol was brominated in carbon tetrachloride to give 3-fluoro-4,6-dibromophenol (84%), m. p. 46°. Hodgson and Nixon[3] reported the melting point, 45°. Even when a large excess of bromine was used only this product was isolated.

Anal. Calcd. for $C_6H_3Br_2OF$; Br, 59.43. Found: Br, 59.36.

2,4,6-Tribromo-3-fluorophenol.—*m*-Fluorophenol was brominated in aqueous solution to give the tribromo derivative (95%), m. p. 94°. Hodgson and Nixon[3] recorded 90°.

Anal. Calcd. for $C_6H_2Br_3OF$: Br, 68.75. Found: Br, 68.97.

3-Fluoro-2,4,6-tribromophenol Bromide.—A solution of 11.2 g. of *m*-fluorophenol in 175 ml. of water was slowly dropped into 250 ml. of stirred bromine-potassium bromide solution (2.5 *M* Br_2 in 2 *M* KBr). After twenty minutes the product was filtered off and dried. The yield was 40 g. (94%).

A second method of preparation was as follows: slightly more than 4 moles of bromine were slowly added to a carbon tetrachloride solution of *m*-fluorophenol. A vigorous evolution of hydrogen bromide occurred. Sodium bicarbonate was then added slowly in excess of the amount necessary to react with all of the hydrogen bromide evolved. The mixture was warmed and the liquid was decanted from a solid residue. The product precipitated on cooling. It was filtered off and the residue in the reaction flask was repeatedly extracted with the filtrate until no more product crystallized out on cooling. The product was recrystallized from carbon tetrachloride, bright yellow platelets (m. p. 152°, with evolution of bromine).

Anal. Calcd. for C_6HBr_4OF; Br, 74.73. Found: Br, 74.47.

Tribromophenol Bromide.—Nine and four-tenths grams of phenol in 150 ml. of carbon tetrachloride containing 40 g. of solid sodium bicarbonate was treated with 30 ml. of bromine under reflux. The product was worked up as in the preceding experiment yielding 30 g. (75%) of tribromophenol bromide which decomposed at 128° with evolution of bromine.

Anal. Calcd. for $C_6H_2OBr_4$: Br, 78.03. Found: Br, 78.60.

Bromination of *m*-Fluorophenol in Glacial Acetic Acid.—A solution of 2.22 g. of *m*-fluorophenol in 8 ml. of acetic acid was treated with 5.2 ml. of bromine (5 + m.mol. bromine per mole of the phenol). After an hour the reaction mixture was poured into water and the precipitated solid was filtered off. After reprecipitation from glacial acetic acid by addition of water, the product was extracted with a mixture of 60 ml. of ether and 20 ml. of petroleum ether. This treatment left 2.2 g. (51%) of an insoluble, cream colored residue that melted with decomposition at 153° and which was identified as 3-fluoro-2,4,6-tribromophenol bromide. The substance soluble in the extract was precipitated by the addition of more petroleum ether and recrystallized from petroleum ether. It was identified by its melting point and mixed melting point as 3-fluoro-2,4,6-tribromophenol.

3-Fluoro-2,3,4,5-tetrabromophenol.—Fifteen grams of 3-fluoro-2,4,6-tribromophenol bromide was heated with 150 ml. of concentrated sulfuric acid with stirring. At 75° there was evidence of reaction and at 105° the reaction mixture was clear and colored reddish-brown. An oil was precipitated during the reaction. The cooled reaction mixture was poured into a beaker full of chipped ice. The separated solid was collected, dried, and crystallized from ether–petroleum ether to give 13.5 g. (90%) product. This material was purified by solution in dilute sodium hydroxide, treatment with charcoal, filtration, and acidifi-

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[11] H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1871 (1930).

[12] Melting points are uncorrected. For analysis the samples were decomposed in the Parr bomb; the bromine was estimated volumetrically by the Volhard method and the fluorine was determined as lead chlorofluoride (Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley & Sons, New York, N. Y., 1929, p. 603).

[13] G. Schiemann, *Z. physik. Chem.*, **156**, 414 (1931); *J. prakt. Chem.*, **143**, 23 (1935).

cation of the filtrate. The precipitate was recrystallized from petroleum ether to give colorless needles (m. p. 114°).

Anal. Calcd. for C_6HOBr_4F: Br, 74.73. Found: Br, 74.47.

The Reduction of 3-Fluoro-2,4,6-tribromophenol Bromide.—This bromide was reduced with zinc and hydrochloric acid. The product was isolated by steam distillation after dilution with some water. Upon crystallization from petroleum ether, the product melted at 94° and showed no depression with a sample of 3-fluoro-2,4,6-tribromophenol.

Anal. Calcd. for $C_6H_2OBr_3F$: Br, 68.75. Found: Br, 68.82.

Behavior of 3-Fluoro-2,4,6-tribromophenol Bromide toward Phenylhydrazine.—Some 3-fluoro-2,4,6-tribromophenol bromide was dissolved in dioxane and poured into a solution containing an excess of phenylhydrazine in a mixture of dioxane and glacial acetic acid. After purification by sublimation the product melted at 94° and showed no depression with 3-fluoro-2,4,6-tribromophenol.

Action of Silver Fluoride on 3-Fluoro-2,4,6-tribromophenol Bromide.—Ten grams of this compound was mixed with 10 g. of solid silver fluoride, suspended in 250 ml. of acetone, and stirred for several hours. The silver bromide was filtered off and the filtrate was diluted with water to a volume of 1200 ml. A small amount (less than a gram) of bright yellow platelets, m. p. 169° precipitated and was filtered off.

Anal. Calcd. for $(C_6HOB_3F)_2$: F, 5.46. Found: F, 5.5.

Action of Lead Acetate on 3-Fluoro-2,4,6-tribromophenol Bromide.—A mixture of 4.3 g. of the bromide and 15 g. of lead acetate trihydrate in glacial acetic acid was stirred and kept at 70° for four hours and then allowed to stand for twelve hours. The solution was decanted from the lead bromide, diluted with water and extracted with ether. The ether solution was washed with very dilute sodium hydroxide to remove acetic acid, then with water, and finally was dried over calcium chloride. Most of the ether was distilled off and the rest removed under vacuum. The viscous residue was dissolved in ether then precipitated with petroleum ether as a white granular solid, almost insoluble in all of the common solvents. Upon heating it became slightly pink at about 140° and melted to a red oil at 162° with decomposition. It liberated iodine from potassium iodide in the cold.

Anal. Calcd. for $(C_6HOBr_3F)_2$: Br, 68.97. Found: Br, 69.27.

Summary

The preparation of 2,6-dibromo-3-fluorophenol, 2,4,6-tribromo-3-fluorophenol and 2,6-dibromo-4-fluorophenol had been repeated. The following new compounds have been obtained: 2-fluoro-4,6 - dibromophenol, 2,4,5,6 - tetrabromo - 3 - fluorophenol, and 2,4,6-tribromo-3-fluorophenol bromide. The bromination of the three fluorophenols with an excess of bromine has been studied and an attempt has been made to elucidate the structure of 3-fluorotribromophenol bromide.

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[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH]

The Vitamin B_6 Group. I. Formation of Additional Members from Pyridoxine and Evidence Concerning their Structure

BY ESMOND E. SNELL

Evidence for the occurrence in natural materials of one or more substances tentatively called "pseudopyridoxine" has been presented in detail.[1] The existence of such a substance was discovered because on suitable pyridoxine-free media, natural extracts were much more active in promoting growth of various lactic acid bacteria than could be explained by their pyridoxine content, as determined by other methods. Behavior on fractionation indicated that the substance was chemically similar to pyridoxine. Metabolic experiments with rats and human beings demonstrated that pyridoxine was partially converted into "pseudopyridoxine" by the animal organism. Experiments with *Streptococcus lactis* R[2] (*Streptococcus fecalis* R) showed that almost no pyridoxine was absorbed from media in which the concentration of this substance appeared to limit growth. It was assumed that the organism transformed only a minute amount of the pyridoxine present to the more active "pseudopyridoxine," and that the latter was the substance absorbed and utilized for growth purposes.

It was later shown[3] that the activity of pyridoxine for this organism was greatly increased by autoclaving with the basal medium used for assay. This increased activity was traced to interaction of pyridoxine with the amino acids of the medium. This explained why growth of *S. fecalis* R ceased even though pyridoxine was still present; the substance promoting growth was the product formed by autoclaving pyridoxine with amino acids and this was formed in very low yield by the procedure used. This production from pyridoxine by purely chemical means of a substance with heightened growth-promoting activity suggested that other more effective procedures for producing the transformation might be found, and that this approach to the problem might be more economical than direct isolation of the active substance from natural materials.

The activity of two synthetic compounds, pyridoxamine and pyridoxal, structures for which were suggested by this approach, has been briefly described.[4] The present paper describes work

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[1] Snell, Guirard and Williams, *J. Biol. Chem.*, **143**, 519 (1942).

[2] Niven and Sherman (*J. Bact.*, **47**, 335 (1944)) have shown that this organism is actually an enterococcus, physiologically and serologically identical with *Streptococcus fecalis*. The older designation is used here for purposes of continuity. Henceforward, this organism will be designated as *Streptococcus fecalis* R.

[3] Snell, *Proc. Soc. Exptl. Biol. Med.*, **51**, 356 (1942).

[4] Snell, *J. Biol. Chem.*, **154**, 313 (1944).