

[CONTRIBUTION FROM THE LABORATORY FOR PURE RESEARCH OF MERCK AND CO., INC.]

DIASTEREOMERS OF $\alpha, \alpha', \beta, \beta'$ -TETRABROMOETHYL ETHER

BY WILLIAM L. RUGH AND RANDOLPH T. MAJOR

RECEIVED JUNE 3, 1931

PUBLISHED AUGUST 5, 1931

One of the products obtained by the bromination of paraldehyde is the so-called "Tetrabromobutyraldehyde" that was first obtained by Freundler.¹ Hibbert, Perry and Taylor² reported that this compound was identical with the product which they obtained by the bromination of divinyl ether. They offered further evidence to show that this compound was $\alpha, \alpha', \beta, \beta'$ -tetrabromoethyl ether, $\text{CH}_2\text{BrCHBrOCHBrCH}_2\text{Br}$, and that it was not tetrabromobutyraldehyde, $\text{CH}_2\text{BrCHBrCHBr}_2\text{CHO}$.

The divinyl ether obtained by Ruigh and Major³ was an apparently much purer product than that investigated by Hibbert, Perry and Taylor. From the description of the preparation of divinyl ether which was published by the latter authors the presence of acetaldehyde in their product was quite possible. It seemed desirable, therefore, to repeat and amplify the work of these authors and for the bromination of divinyl ether to use a product of known purity.

We have found that when pure divinyl ether was brominated in chloroform or carbon tetrachloride solutions *two* distinct crystalline products were obtained together with a small amount of a highly lachrymatory oil. When, however, the bromination was carried out in the presence of powdered calcium carbonate, using carbon tetrachloride as the solvent and carefully dried materials, a quantitative yield of the two solid products only was obtained. The oil obtained in the earlier brominations was probably a mixture containing bromination products of acetaldehyde, since divinyl ether is readily hydrolyzed to acetaldehyde in the presence of moisture and acids.

We were unable to effect a quantitative separation of the mixture obtained in these brominations; we were, however, able to isolate pure samples of the two products which formed this mixture. One of the products crystallized in the form of prisms, while the other formed long fine needles.

The identity of the prisms with the compound obtained by Freundler by the bromination of paraldehyde, was shown by a mixed melting point determination. This is in harmony with the view of Stepanov, Preobrashenski and Shchukina⁴ that Freundler's "tetrabromobutyraldehyde" was in reality $\alpha, \alpha', \beta, \beta'$ -tetrabromoethyl ether. Our analytical results

¹ Freundler, *Compt. rend.*, **140**, 1693 (1905); *Bull. soc. chim.*, [4] **1**, 66 (1907).

² Hibbert, Perry and Taylor, *THIS JOURNAL*, **51**, 1551 (1929).

³ Ruigh and Major, *ibid.*, **53**, 2662 (1931).

⁴ Stepanov, Preobrashenski and Shchukina, *Ber.*, **59B**, 2533 (1926).

confirmed the results of Hibbert, Perry and Taylor, which favored the latter structure. These authors also showed that the compound condensed with ethylene glycol to give bromoethylidene glycol, a fact which they presented as additional evidence in favor of the ether structure of the compound.

It was further found that acetaldehyde was formed when the compound was treated with sodium in xylene or zinc dust in acetic acid. By the action of *p*-nitrophenylhydrazine on the compound in acetic acid we obtained the *p*-nitrophenylosazone of glyoxal. The four carbon chain that is in tetrabromobutyraldehyde would not be expected to give a derivative of glyoxal under these conditions.⁵ Dworzak and Prodinger⁶ showed that $\alpha,\alpha',\beta,\beta'$ -tetrabromoisobutyl ether, obtained by the bromination of isobutyraldehyde, gave α -hydroxyisobutyraldehyde when treated with a dilute solution of sodium bicarbonate. When our prisms were treated in a similar manner we found that the resulting solution contained glycolaldehyde or possibly bromoacetaldehyde.

On the basis of the evidence outlined, there seems to be no reason to doubt that this compound has the structure $\alpha,\alpha',\beta,\beta'$ -tetrabromoethyl ether.

The other product of the bromination of divinyl ether which crystallized in the form of needles was obtained in pure form and free from the prisms only with great difficulty. Its melting point was only a few degrees below that of the prisms and the solubilities of the two compounds in various solvents were very much the same. The melting point of a mixture of the two compounds was considerably lower than that of either. The results obtained from analytical and molecular weight determinations of the needles corresponded with the values calculated for tetrabromoethyl ether. When treated with *p*-nitrophenylhydrazine in acetic acid, a quantitative yield of the *p*-nitrophenylosazone of glyoxal was obtained. By heating the needles above their melting point, they were converted into the isomeric prisms. This conversion also took place on long standing in solution in ether at room temperature. In petroleum ether, however, the needles were apparently perfectly stable.

The two α -carbon atoms of $\alpha,\alpha',\beta,\beta'$ -tetrabromoethyl ether are asymmetric and theoretically there should exist two inactive forms, the meso and the racemic. On the basis of the evidence here presented, it appears that the two bromination products of divinyl ether are diastereomeric forms of $\alpha,\alpha',\beta,\beta'$ -tetrabromoethyl ether. Although it is possible that the needles are also a product of the bromination of paraldehyde, we have not been able to isolate it from the products of this reaction.

⁵ Chattaway and Irving, *J. Chem. Soc.*, 87 (1930); Chattaway and Farinholt, *ibid.*, 94 (1930).

⁶ Dworzak and Prodinger, *Monatsh.*, 53/54, 588 (1929).

A study of the quantitative bromination of divinyl ether by the method of McIlhiney⁷ was undertaken. The amount of bromine absorbed represented about 95% of that theoretically required. However, when the iodate correction was applied, the amount of bromine added to the unsaturated groups varied from 76 to 82% of the theoretical requirements. Buckwalter and Wagner⁸ have recently shown that the McIlhiney method for the determination of the amount of unsaturation in organic compounds gives erratic and erroneous results. The method developed by these authors is not applicable to a determination of the amount of unsaturation in divinyl ether due to the low boiling point of the ether.

Experimental Part

Bromination of Divinyl Ether.—Five grams of pure divinyl ether in 20 g. of chloroform was chilled to -15° and 22.8 g. of bromine in 50 g. of chloroform was slowly added with stirring. All but about 0.5 cc. of the bromine solution was absorbed before a slight permanent yellow color appeared. This color was removed by the addition of a drop of divinyl ether. The solution was evaporated down to an oil (37.1 g.), which was mixed with an equal volume of petroleum ether. The solid which crystallized out was filtered off; the filtrate when chilled yielded more solid. The total yield of solid was 21.7 g. or 78% of the theoretical amount of $\alpha,\alpha',\beta,\beta'$ -tetrabromoethyl ether. When 50 g. of divinyl ether was brominated in carbon tetrachloride, 222.3 g. or an 80% yield of the solid was obtained. The highly lachrymatory oil which remained after the solid products of the reaction had been removed was not investigated.

The solid from the reaction consisted of a mixture of prisms and needles. It was not possible to effect a quantitative separation but apparently about 20% of the solid consisted of the needles. When 10 g. of divinyl ether was brominated with 46 g. of bromine at -20° in the presence of an excess of calcium carbonate (precipitated chalk) in dry carbon tetrachloride solution, a quantitative yield of the mixed forms was obtained. No oil was formed in this experiment. Under these conditions, by inspection under the microscope, the needles formed about 50% of the total solid.

The prisms were fairly readily obtained when the mixture slowly crystallized from petroleum ether. The first fraction consisted of the practically pure prisms.

The needles, however, were obtained in a pure condition only with great difficulty. In order to do this the needles were allowed to grow rapidly and the ligroin solution, which was supersaturated with respect to the prisms, was decanted. Five grams of the pure needles was obtained in this manner.

In ethyl ether a slow isomerization of the needle to the prism form took place, which was complete after the mixture had stood for three weeks at room temperature. Solutions of the bromination products in acetone gradually decomposed after several days and gave a black tar. The compounds appeared to be quite stable, however, in petroleum ether.

The prisms melted at $65-66^{\circ}$; a mixture of these crystals with the compound obtained by Freundler by the bromination of paraldehyde also melted at $65-66^{\circ}$.¹

Anal. Calcd. for $C_4H_6Br_4O$: C, 12.32; H, 1.56; Br, 82.02. Found: C, 12.47, 12.23, 12.38; H, 1.61, 1.67, 1.26; Br, 82.21, 82.47.

⁷ Hans Meyer, "Analyse und Konstitutionsermittlung organischen Verbindungen," Verlag von Julius Springer, Berlin, 1916, p. 960.

⁸ Buckwalter and Wagner, THIS JOURNAL, 52, 5241 (1930).

The needles melted at 62–63°; a mixture of the needles and prisms melted at 45–57°.

Anal. Calcd. for $C_4H_6Br_4O$: C, 12.32; H, 1.56; Found: C, 12.41, 12.48; H, 1.37, 1.41.

Mol. wt. Calcd. for $C_4H_6Br_4O$, 389.7. Found: 376.3, 378.2 (Menzies–Wright ebullioscopic method).

Action of Zinc Dust and Acetic Acid on the Prisms.—About 0.5 g. of the prisms was dissolved in 15 cc. of dilute acetic acid and several grams of zinc dust was added in small portions while the reaction mixture was warmed on the water-bath. The solution was filtered, diluted with water to a volume of about 50 cc., just neutralized with sodium carbonate and distilled. The distillate reduced Tollens' reagent. A small portion of the distillate when treated with *p*-nitrophenylhydrazine gave the *p*-nitrophenylhydrazone of acetaldehyde; m. p. 128–129°. A mixture of this material with the *p*-nitrophenylhydrazone of acetaldehyde melted at 128–129°.⁹

Action of Sodium on the Prisms.—In a 50-cc. flask were placed 10 g. of the prisms, 4 g. of sodium and 25 cc. of dry xylene. An 8-mm. bent glass tube served as a condenser and the receiver was a flask cooled with a solid carbon dioxide–acetone mixture. The xylene was heated just to the boiling point and after about half an hour about 0.5 cc. of liquid had collected in the receiver. The distillate had a strong odor of acetaldehyde, reduced Tollens' reagent and gave the *p*-nitrophenylhydrazone of acetaldehyde; m. p. 128–129°. A mixture of this material with the *p*-nitrophenylhydrazone of acetaldehyde melted at 128–129°.⁹

Hydrolysis of Prisms.—One gram of the prisms and 100 cc. of a 2% solution of sodium bicarbonate were warmed until the prisms melted. After the mixture had been shaken for about forty-five minutes, practically all of the solid material had disappeared. The solution was then cooled and saturated with carbon dioxide. A portion of this solution reduced Fehling's solution rapidly at room temperature, a red precipitate being formed after four minutes. The solution also gave the *p*-nitrophenyllosazone of glyoxal, m. p. 309–310°, when it was treated with *p*-nitrophenylhydrazine in acetic acid. When equal quantities of this solution and a 50% solution of potassium hydroxide were warmed, a yellow color developed.¹⁰

Action of *p*-Nitrophenylhydrazine on Prisms and Needles.—A solution of 0.5 g. of the prisms and 1 g. of *p*-nitrophenylhydrazine in about 50 cc. of 50% acetic acid was warmed on the water-bath for an hour. After the solution had been cooled the precipitate was removed by filtration; yield, 0.49 g. The crude product was dissolved in 40 cc. of hot pyridine from which red needles separated on cooling; m. p. 309–310°. It gave a deep blue color with a concentrated solution of potassium hydroxide to which had been added a few drops of alcohol. These facts together with the analysis identified this compound as the *p*-nitrophenyllosazone of glyoxal.¹¹

Anal. Calcd. for $C_{14}H_{12}N_6O_4$: N, 25.61. Found: N, 25.63.

A quantitative yield of 0.09 g. of the *p*-nitrophenyllosazone of glyoxal was obtained when 0.1 g. of the needles was warmed in a 50% acetic acid solution of *p*-nitrophenylhydrazine for several hours at 50–60°.

Transformation of the Prismatic to the Needle-like Form of Tetrabromoethyl Ether.—Two-tenths of a gram of the needles was heated in a test-tube for four minutes at 100°. A slight decomposition accompanied by the evolution of hydrogen bromide took place. This was shown by the white fumes produced when a stopper wet with ammonia was held near the mouth of the test-tube used. The product obtained was

⁹ E. Hyde, *Ber.*, **32**, 1813 (1899).

¹⁰ Fischer and Landsteiner, *ibid.*, **25**, 2552 (1892).

¹¹ Dakin and Dudley, *Biochem. J.*, **15**, 127 (1913).

recrystallized from ligroin; yield, 0.15 g. of the prisms. Evaporation of the mother liquor yielded a mixture of both needles and prisms. The crude prisms after one crystallization from ligroin melted at 64–65°. A mixture of this product with another sample of the prisms melted at 65°.

Titration of Divinyl Ether by Means of Bromine.—Samples of divinyl ether were enclosed in sealed glass bulbs and broken in the presence of a standard solution of bromine in stoppered flasks chilled on ice. The flasks were kept at 0° for an hour in the dark and then allowed to stand at the temperature of the laboratory. For analyses "A" and "B" of Table I the flasks stood for twenty-four hours before the addition of the solution of potassium iodide and the titration with sodium thiosulfate, while analyses "C" and "D" stood for two hours before the titration.

The results given in Line 1 of Table I express the percentage of the theoretical amount of bromine required by divinyl ether used that was actually absorbed. Line 2 gives the results in percentage of the theoretical amount of bromine actually absorbed after the iodate correction had been made.

TABLE I
EXPERIMENTAL DATA

	A	B	C	D
1	95.5	93.0	96.6	95.0
2	76.3	78.5	67.7	82.1

We are greatly indebted to Mr. Douglass Hayman, who made most of the analyses recorded in this paper.

Summary

1. It has been shown that the bromination of pure divinyl ether gives two distinct crystalline compounds. Evidence is given to show that these compounds are diastereomers of $\alpha, \alpha', \beta, \beta'$ -tetrabromoethyl ether.

2. The prismatic form of $\alpha, \alpha', \beta, \beta'$ -tetrabromoethyl ether has been shown to be identical with the bromination product of paraldehyde that was first obtained by Freundler and that was called by him "tetrabromo-butylaldehyde."

RAHWAY, NEW JERSEY