

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Dioxadiene

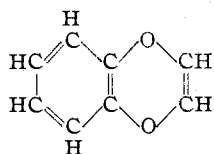
BY R. K. SUMMERBELL AND R. R. UMHOEFER

I. Introduction

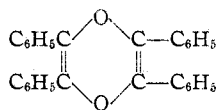
The synthesis of dioxene¹ and the subsequent investigation of its properties has shown this compound to differ in many respects from dioxane. Thus while dioxane is soluble in all proportions with water, dioxene is insoluble. The boiling point of dioxene is seven degrees below that of dioxane. Also the ability to form the unique addition products characteristic of dioxane is no longer evident. Consideration of the contrast in properties of these compounds has led us to synthesize dioxadiene (I), a compound with two double bonds.

Dioxadiene, although hitherto unknown, has long been listed in chemical abstracts under the name of Dioxin. It is used as the fundamental or parent nucleus for the cataloging of dioxane, dioxene, and their derivatives. The term dioxadiene has been proposed previously to designate the compound discussed here.^{2,3}

Condensed forms of the dioxadiene nucleus such as benzodioxadiene (II)⁴ and dibenzodioxadiene (III) is the only non-condensed derivative of dioxadiene that has been prepared and studied thus far.³ The presence of so many phenyl groups, raising the molecular weight and modifying the properties of the double bonds, limits the usefulness of such compounds as material for the study of the dioxadiene nucleus.



II



III

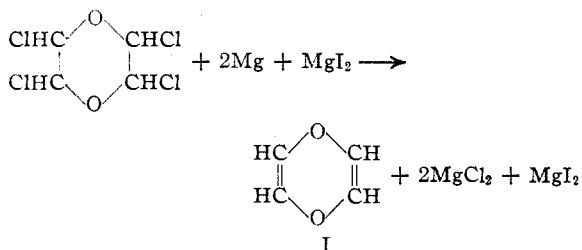
II. Synthesis of Dioxadiene

A new synthesis of dioxene from 2,3-dichlorodioxane using a mixture of magnesium and magnesium iodide in ethyl ether as a dehalogenating reagent has been reported.⁶ An obvious exten-

sion of the method to the synthesis of dioxadiene would be the application of the same dehalogenating reagent to 2,3,5,6-tetrachlorodioxane.

Although dioxene is readily prepared from 2,3-dichlorodioxane, there is a considerable difference in reactivity of 2,3-dichlorodioxane and 2,3,5,6-tetrachlorodioxane. The dichlorodioxane is easily hydrolyzed in ten to fifteen minutes by heating with water, while the tetrachloro compound requires three or four hours for hydrolysis. No reaction could be observed when the symmetrical tetrachlorodioxane was treated with magnesium iodide dissolved in ethyl ether.

The reaction was modified by using the higher boiling *n*-butyl ether as a solvent. Because of the possibility that the dioxadiene would be polymerized at the high temperature required for the reaction, the apparatus was so arranged that the dioxadiene would distil from the reaction mixture as it was formed. The method produced yields of dioxadiene as high as 64% of the theoretical.



III. Physical Properties

An interesting physical property of dioxadiene is the boiling point, 75°, which is 26° less than that of dioxane. This large difference is found also in the furan series, where the boiling point of furan is 33° less than that of tetrahydrofuran. Vinyl ether shows a much smaller decrease in boiling point compared with ethyl ether. Correspondingly, a large difference exists between the calculated and observed values of the molar refractivity of both dioxadiene and furan. On the basis of these comparisons the unsaturation of dioxadiene is nearer to that of furan than that of vinyl ether.

Dioxadiene is insoluble in water. This may be explained by assuming that resonance involves the electron pairs of the oxygen so that they are

(1) Summerbell and Bauer, *THIS JOURNAL*, **57**, 2364 (1935).

(2) Footnote by Hurd, Suter and Summerbell, *THIS JOURNAL*, **57**, 2364 (1935).

(3) Madelung and Oberwegner, *Ann.*, **490**, 201 (1931); *ibid.*, **526**, 195 (1936).

(4) Moureu, *Compt. rend.*, **128**, 559 (1889).

(5) Ullmann and Stein, *Ber.*, **39**, 622 (1906).

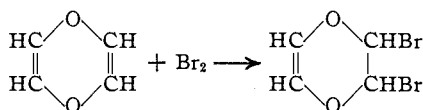
(6) Summerbell and Umhoefer, *THIS JOURNAL*, **61**, 3016 (1939).

not available for hydrogen bond formation with the solvent.

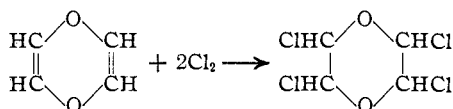
IV. Chemical Properties

The chemical properties of dioxadiene in general are those of an unsaturated ether. However, it shows a greater stability toward dilute acid solutions than other unsaturated ethers such as dioxene and vinyl ether.

Dioxadiene polymerizes in two to three weeks to a hard colorless solid which does not melt below 250°. The polymer is insoluble in water, benzene, dioxane and camphor and hence its molecular weight has not been determined. The polymerized material gave a slight reaction with bromine water. Dioxadiene reacts vigorously with bromine. When brominated in carbon tetrachloride solution, a solid crystalline product, containing two atoms of bromine, was obtained with practically no evolution of hydrogen bromide. The reaction is probably one of addition of bromine to only one of the double bonds. Dioxadiene



reacts with chlorine to form the symmetrical tetrachlorodioxane. This reaction is of importance, as it is an excellent proof of the structure of dioxadiene, since the derivative obtained by this reaction was one of the known isomers.



Hydrogen chloride adds to dioxadiene to form the 2,5-dichlorodioxane. Dioxadiene reacts readily with a solution of mercuric chloride to yield an amorphous solid of unknown structure. Analysis indicates the product to be a dimercury derivative. Slight color changes of doubtful significance were observed when dioxadiene was treated with maleic anhydride and with picric acid; however, no compounds could be isolated.

In all of the above reactions, dioxadiene has behaved in a manner to be expected of an unsaturated aliphatic compound where the unsaturation is conjugated to a limited extent. The name dioxadiene seems more appropriate than dioxin.

Attempts to prepare dioxadiene from more available intermediates were unsuccessful. These included the treatment of diglycolic acid anhy-

dride and glycolide with zinc dust and the pyrolysis of the acetate of dimeric glycol aldehyde.

Experimental

Dioxadiene.—To 23 g. of magnesium turnings in 500 cc. of dry *n*-butyl ether in a one-liter, three-necked flask equipped with an efficient mercury-sealed stirrer connected with a condenser by a bent tube of large diameter, 80 g. of iodine was added in small portions. After all the iodine had reacted, the flask was immersed in an oil-bath and the latter heated to 140°. With good stirring, 35.5 g. of 2,3,5,6-tetrachlorodioxane (m. p. 141–142°) was added in 1–2 g. lots. The reaction was accompanied by vigorous ebullition of the mixture, resulting in the distillation of the dioxadiene along with a considerable amount of *n*-butyl ether. After about 100 cc. of distillate had been collected, 100 cc. of *n*-butyl ether was added to the reaction flask. When all the tetrachlorodioxane had reacted, the bath temperature was raised to 155° and an additional 25 cc. of distillate collected; time, one and one-half hours. The distillate (300 cc.), slightly colored with iodine, was distilled from an ordinary distilling flask and the low boiling fraction (up to 115°) was fractionated through a 40-cm. Podbielniak type column. An 8.4 g. (64%) fraction was obtained, b. p. 73–78°. In another preparation of dioxadiene under the same conditions, a 48% yield was obtained. However, all the material distilled at a constant boiling point of 75° at 746 mm.; d_4^{20} , 1.115; n_D^{20} , 1.4350; *MR*, calcd. 20.84; found, 19.66.

Anal. Calcd. for $\text{C}_4\text{H}_4\text{O}_2$: C, 57.12; H, 4.76. Found: C, 57.18; H, 4.94.

Reaction of Dioxadiene with Bromine.—To a solution of 1.18 g. (0.0142 mole) of dioxadiene in 15 cc. of dry carbon tetrachloride at 0° was added slowly 2.28 g. (0.0142 mole) of bromine dissolved in 10 cc. of carbon tetrachloride. The dioxadiene readily reacted with the bromine. No further reaction of the dioxadiene with bromine occurred when an additional small quantity of the bromine solution was added. This was indicated by the persistence of the bromine color. The carbon tetrachloride was removed in a vacuum desiccator, and the crystalline residue was recrystallized from petroleum ether as needles, m. p. 55–57°; yield 2.98 g. (87%). After another recrystallization from petroleum ether, the material melted at 58°. The compound decomposed over a period of several weeks when exposed to the atmosphere.

Anal. Calcd. for $\text{C}_4\text{H}_4\text{O}_2\text{Br}_2$: Br, 65.55. Found: Br, 65.97.

Symmetrical Tetrachlorodioxane.—A solution of 1.3 g. of dioxadiene in 40 cc. of dry carbon tetrachloride was saturated with chlorine at room temperature. After evaporation of the carbon tetrachloride from a water-bath, the residue (0.5 g.) was crystallized three times from methyl alcohol: needles, m. p. 139–140°. A mixed melting point with 2,3,5,6-tetrachlorodioxane (m. p. 142–143°) melted at 139–140.5°.

Anal. Calcd. for $\text{C}_4\text{H}_4\text{O}_2\text{Cl}_4$: Cl, 62.81. Found: Cl, 62.35.

2,5-Dichlorodioxane.—Approximately 0.35 mole of dry hydrogen chloride was passed into a solution of 4.9

g. of dioxadiene and 5 cc. of dry carbon tetrachloride. Some solid separated during the reaction. After the carbon tetrachloride was removed in a vacuum desiccator, the residue was warmed with petroleum ether and the solution decanted from some insoluble material. The petroleum ether solution on cooling deposited needle-like crystals of 2,5-dichlorodioxane, m. p. 117-118°. The material decomposed on standing. It was readily hydrolyzed by water and the solution yielded the *p*-nitrophenylosazone of glycol aldehyde when treated with *p*-nitrophenylhydrazine; m. p. 300° (uncorr.).

Mercuration of Dioxadiene.—A solution of 1 g. of dioxadiene in 5 cc. of alcohol was added to 71.5 cc. of a cold solution which contained 3.22 g. of mercuric chloride and 6.23 g. of sodium acetate-3H₂O. A white precipitate formed immediately. After standing overnight in a re-

(7) 2,5-Dichlorodioxane, needles, m. p. 118-119°, has been isolated as a product of the chlorination of dioxane by L. Roehen of this Laboratory. It is an unstable solid easily hydrolyzed by water.

frigerator, the solid was filtered and washed with water several times. The material after air drying weighed 3.28 g. The theoretical yield for a disubstituted compound is 3.30 g. The product showed no definite melting point, and was insoluble in alcohol, dioxane, benzene or a mixture of alcohol and acetic acid. The material was washed several times more with water and dried in a desiccator.

Anal. Calcd. for C₄H₂O₂Hg₂Cl₂: Hg, 72.39. Found: Hg, 71.56, 70.11.

Summary

1. Dioxadiene has been prepared for the first time.
2. The physical and chemical properties have been studied. These indicate that the unsaturation is modified to a marked extent by conjugation with the ether oxygens.

EVANSTON, ILLINOIS

RECEIVED JUNE 17, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXV. Cholesterol Derivatives

BY RUSSELL E. MARKER AND EWALD ROHRMANN

The present work is a continuation of a previously reported investigation¹ on 7-keto-cholesterol derivatives. In the previous work it was observed that 7-ketocholesteryl chloride upon catalytic hydrogenation in acetic acid solution gave a mixture of products from which cholesteryl chloride was isolated. Indications of the presence of 7-hydroxycholesteryl chloride were also obtained.

We have now observed that when the hydrogenation of $\Delta^{5,6}$ -unsaturated 7-keto compounds is conducted in a neutral medium with Adams catalyst the essential product is a saturated 7-keto compound. This selective reduction of the ethylenic linkage most probably is due to the slightly hindered nature of the carbonyl group at C-7.

The catalytic hydrogenation of 7-ketocholesteryl chloride in neutral solution with Adams catalyst yielded 7-ketocholesteryl chloride identical with that prepared previously by the oxidation of crude 7-hydroxycholesteryl chloride.¹ A similar reduction of 7-ketocholesteryl acetate gave 7-ketocholesteryl acetate evidently identical with the product which Windaus and Kirchner² obtained by the hydrogenation of 7-ketocholesteryl acetate with palladium catalyst in an acidic medium. When the hydrogenation of 7-ketocholesteryl

acetate was carried out in acetic acid solution with Adams catalyst followed by alkaline hydrolysis of the reduction products, 7-hydroxycholestanol was obtained. This was identical with the product obtained by the reduction of 7-ketocholestanol with aluminum isopropylate. Mild oxidation of this diol with chromic anhydride yielded 7-ketocholestanone first reported by Windaus and Kirchner.²

Dimroth and Trautmann³ reported the preparation of $\Delta^{5,6}$ -cholestenol-7 by the reduction of $\Delta^{5,6}$ -cholestenone-7 with aluminum isopropylate. No analytical data were given on their product which melted at 93-94°. The substance was reported to yield a benzoate, m. p. 108-109°. We have prepared $\Delta^{5,6}$ -cholestenol-7 by the reduction of 7-hydroxycholesteryl chloride with sodium and amyl alcohol. The product, m. p. 106°, gave a benzoate, m. p. 147°. Bromination of the substance followed by mild oxidation with chromic anhydride and subsequent debromination gave $\Delta^{5,6}$ -cholestenone-7 of m. p. 126°, while catalytic hydrogenation in neutral medium gave cholestanol-7.

It is improbable that our $\Delta^{5,6}$ -cholestenol-7 differs from that of Dimroth and Trautmann in the configuration of the hydroxyl group as in both

(1) Marker, *et al.*, *THIS JOURNAL*, **59**, 619 (1937).

(2) Windaus and Kirchner, *Ber.*, **53**, 614 (1920).

(3) Dimroth and Trautmann, *ibid.*, **69**, 669 (1936).