[Contribution from the Chemical Laboratories of Northwestern University]

A New Synthesis and the Stereochemistry of Some 2,3-Disubstituted Dioxanes

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Received February 11, 1957

A new synthesis of dioxanes involving the condensation of a diene, a mercuric salt and a glycol has been developed. The product from butadiene, mercuric nitrate and ethylene glycol, after precipitation as the halide and replacement of the halomercuri group with iodine, yielded a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxanes. Nitric acid oxidation of the *trans*-bis-(iodomethyl) compound produced the *trans*-dicarboxylic acid in good yields and without isomerization. The anhydride of the *trans*-acid was converted to the *cis*-anhydride by extended refluxing in acetic anhydride, and hydrolysis of the *cis*-anhydride yielded the *cis*-diacid. The facts that *trans*-diacid could be partially resolved, but that *cis*-diacid could not, were used for definite assignment of configuration. Oxidation of the *cis*-2,3-bis-(iodomethyl)-*p*-dioxane failed to produce a diacid but did produce *cis*-3-hydroxymethyl-2-*p*-dioxanecarboxylic lactone. When *cis*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane, which had been formed from the glycol obtained by the reduction of dimethyl *cis*-2,3-*p*-dioxanedicarboxylate, was treated with sodium iodide, the *cis*-bis-(iodomethyl)-*p*-dioxane was obtained, thus relating the latter to the *cis*-diacid. In the original synthesis, equilibration conditions produced predominantly the *trans* compound, indicating it to be more stable than the *cis* isomer.

Introduction

For several years a great deal of study has been devoted to the structures, configuration, properties and theoretical treatment of cyclohexane derivatives. It would seem desirable to have considerable similar information for comparison purposes concerning six-membered ring compounds containing hetero atoms such as dioxanes.

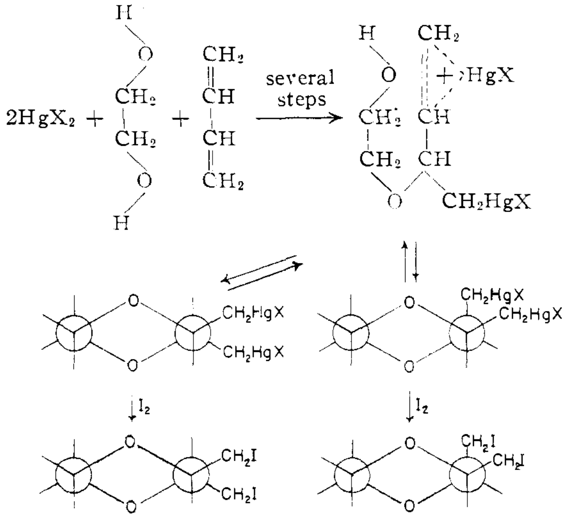
The structures and configuration of several 2,5- and 2,6-disubstituted dioxanes have been definitely established.[1,2] Although a number of 2,3-disubstituted dioxanes have been reported, and a very few speculative assignments of configuration have been made[3-5] on the basis of the meager available evidence, the configuration of no 2,3-disubstituted dioxane is known with certainty. Most of the 2,3-disubstituted dioxanes that have been prepared were not suitable for such studies, either because both members of a pair of isomers were not available, or because the isomers contained no convenient reactive functional group. We therefore decided to attempt the synthesis of appropriate pairs of isomeric, 2,3-disubstituted dioxanes and the determination of their configuration by conclusive chemical means.

We have recently proposed a mechanism[6] to account for the products and isomer ratios when aqueous mercuric salt solutions are used to cyclize allyl alcohol and allyl ether. The same mechanism may be used to explain the recent similar synthesis of dioxanes from allyl ethers of polyols by Werner and Scholz.[7] On the basis of this mechanism it seemed that a new synthesis of dioxanes involving the mercuric salt condensation of dienes with glycols might prove feasible. Furthermore, these seemed to be a good chance of obtaining the desired pairs of *cis* and *trans* isomers, as both the meso and racemic isomers had been formed in good yields when butadiene was condensed[8] with methanolic solutions of mercuric salts.

Discussion

Mercuric nitrate dissolved in aqueous ethylene glycol was observed to condense readily with 1,3-butadiene to form 2,3-disubstituted dioxanes which, after the appropriate sequence of reactions, yielded a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxanes. When the condensation reaction was conducted in the presence of added strong acid, the proportion of *trans* isomer was increased as was the total yield of dioxane compound.

The *trans* isomer I was isolated easily by simple recrystallization, since it was formed in the larger proportion from the acid synthesis and since it was slightly less soluble than the *cis* compound. The *cis* isomer II was isolated by slowly growing crystals from a methanolic solution of both isomers. Rhombic crystals of I and rod-shaped crystals of II formed and were separated by hand picking. The crystals of II were collected and again subjected to the same procedure. The rod-shaped crystals melted at 83.5–84° in a capillary tube, but on a Fisher–Johns block the compound melted at 77–84°.



I (*trans*) II (*cis*)

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[1] R. K. Summerbell and James R. Stephens, This Journal, **76**, 731, 6401 (1954); **77**, 6080 (1955).

[2] E. Augdahl, *Acta Chem. Scand.*, **9**, 1237 (1955).

[3] N. Stumpf, *Z. Elektrochem.*, **57**, 690 (1953).

[4] R. K. Summerbell and B. Nelson, This Journal, **77**, 544 (1955).

[5] J. Boeseken, F. Tellegen and P. C. Henriquez, *Rec. trav. chim.*, **54**, 733 (1935).

[6] R. K. Summerbell, Gregory J. Lestina and Hal Waite, This Journal, **79**, in press (1957).

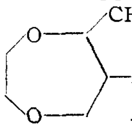
[7] L. H. Werner and C. R. Scholz, *ibid.*, **76**, 2701 (1954).

[8] J. R. Johnson, W. H. Jobling and G. W. Bodamer, *ibid.*, **63**, 131 (1941).

Early experimental results were difficult to interpret until it was realized that we were dealing with two crystalline modifications, IIa and IIb, which were readily interconvertible.

Infrared spectrograms in carbon disulfide solution indicated that I and II were different compounds and that samples of each contained little if any of the other. However, IIa and IIb gave identical infrared spectrograms in carbon disulfide solution, but in potassium bromide pellets a small difference was observed in the region of 10.94 μ where IIa possessed a medium strong absorption which IIb did not have.

It seemed probable that I and II were dioxanes from the method of synthesis, since six-membered rings form more readily than seven-membered ones[9] and 1,4-additions of mercuric salts to butadiene have not been observed, even though carefully sought in a similar situation by McNeely and Wright.[10] If such an addition had occurred here, the product would be a dioxacycloheptane such as A. Chemical evidence supporting the *p*-dioxane structure of I was furnished by the hot concentrated nitric acid oxidation of the iodide I in good yield to a single dicarboxylic acid IV of appropriate empirical formula. Such a compound could hardly be formed by the oxidation of A. Later the smooth conversion of IV back to I afforded additional evidence that Compound I possessed a dioxane rather than a dioxacycloheptane structure.


A

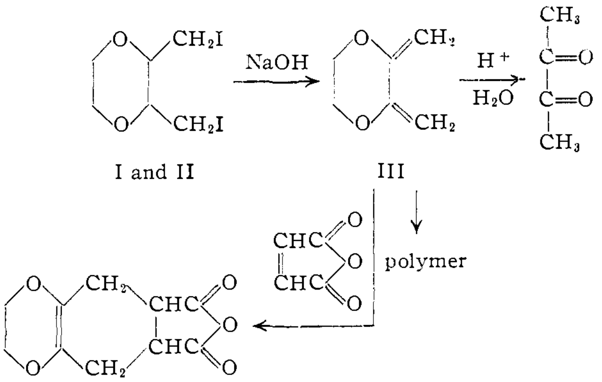
The presence of a dioxane nucleus in the lower melting iodide II was indicated by the conversion of the *cis*-dicarboxylic acid IX to the *cis*-diiodide II, thus eliminating A as a possible structure for II.

In a somewhat analogous case Johnson[8] and coworkers showed that the two forms of 1,4-diiodo-2,3-dimethoxybutane were diastereoisomers and not structural isomers, since both could be converted to 2,3-dimethoxy-1,3-butadiene by means of a base elimination of hydrogen iodide.

The application of this elimination reaction to 2,3-bis-(iodomethyl)-*p*-dioxane resulted in the formation of an easily polymerized diene which was characterized as 2,3-bis-(exomethylene)-*p*-dioxane (III). This diene readily underwent a Diels–Alder reaction with maleic anhydride to form a compound believed to be 5,8-dioxaoctalin-*cis*-2,3-dicarboxylic anhydride. Substance III was hydrolyzed in dilute hydrochloric acid and, upon treatment of the hydrolysate with phenylhydrazine, a compound was obtained which was identified as the phenylosazone of biacetyl.

The *trans*-iodide I was oxidized to *trans*-2,3-*p*-dioxanedicarboxylic acid (IV) in 73% yield by the action of hot, concentrated nitric acid.[1] The acid which was isolated was believed to be a pure compound and not a mixture of acids by virtue of its unique infrared spectrogram, neutral equivalent, combustion data and sharp melting point.

The *trans*-acid IV was converted to *trans*-2,3-*p*-dioxanedicarboxylic anhydride (V) by the action of refluxing acetic anhydride. The empirical formula was indicated by the combustion and neutral equivalent data. The monomeric nature of the anhydride was indicated by the molecular weight of a freshly prepared sample, but when the anhydride was allowed to stand at room temperature for a month, its molecular weight rose from the expected 158 units to 200 units. Upon hydrolysis of the anhydride V the acid IV was regenerated.



At one stage in our work, we became suspicious that epimerization might accompany nitric acid oxidation. To test this possibility, we applied our oxidation procedure to a much more sensitive case, the *meso* and racemic diiodo-2,3-dimethoxybutanes and obtained the appropriate corresponding dimethoxysuccinic acids without evidence of isomerization. Such chain compounds would probably be more easily isomerized than our ring compounds. This particular reaction had additional incidental interest in that it supplied chemical evidence to support the supposed configurations of the 1,4-diiodo-2,3-dimethoxybutanes which had been assigned previously on the basis of physical evidence only,[8] when attempted chemical proof by oxidation failed to yield significant products.

As a second test, the acid IV was converted to the iodide I from which it originally was derived by the following reactions which have been shown to proceed without isomerization[1,11] in similar cases. The *trans*-acid IV was esterified with diazomethane to yield dimethyl *trans*-2,3-*p*-dioxanedicarboxylate (VI) which was subsequently reduced with lithium aluminum hydride to an oil assumed to be *trans*-2,3-bis-(hydroxymethyl)-*p*-dioxane. This glycol was converted to *trans*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (VII) which was then treated with sodium iodide in acetone to yield the *trans*-iodide I.

By extended refluxing in acetic anhydride the *trans*-anhydride V was converted into a new compound which, because of its combustion and neutral equivalent data as well as its melting point, was assumed to be *cis*-2,3-*p*-dioxanedicarboxylic anhydride (VIII). The *cis*-anhydride was hydrolyzed in dilute hydrochloric acid to yield *cis*-2,3-*p*-dioxanedicarboxylic acid (IX). When a mixture of the *cis*-acid IX and the *trans*-acid IV was melted, the melting point of the mixture was considerably

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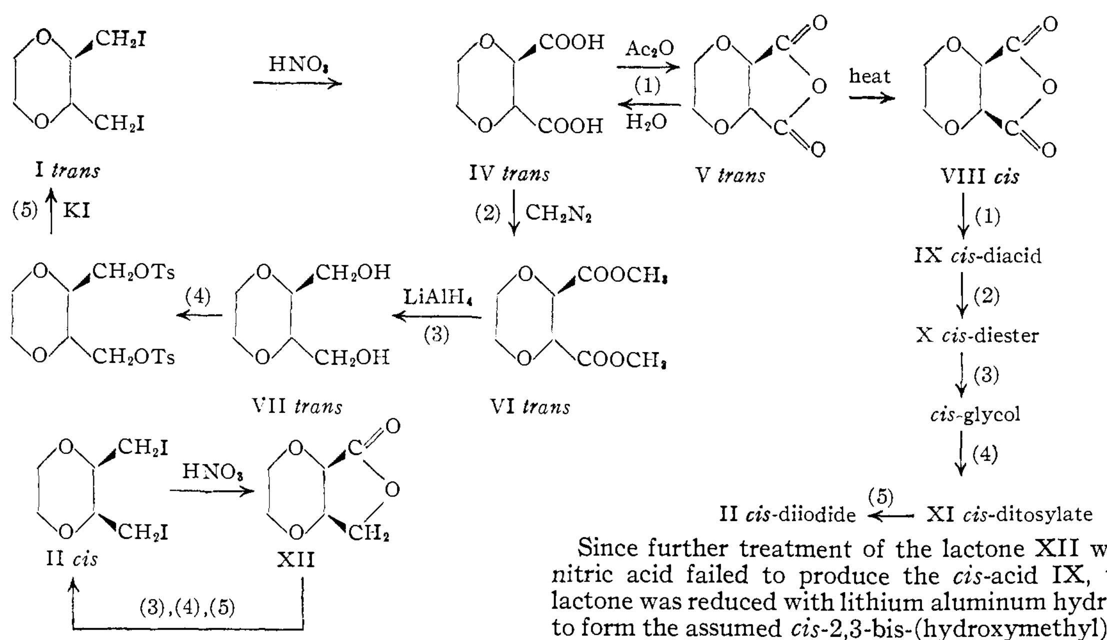
(9) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(10) K. H. McNeely and G. F. Wright, THIS JOURNAL, **77**, 2553 (1955).

(11) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).



lower than that of either pure isomer. The *cis*-acid IX readily was reconverted to the *cis*-anhydride VIII by the action of refluxing acetic anhydride.

The geometrical nature of the isomerism was indicated by the thermal conversion of the *trans*-anhydride V to the isomeric *cis* compound VIII. The conversion of the *cis*-acid IX to a mixture composed of 58 ± 10% *cis* and 42 ± 10% *trans* by means of aqueous potassium hydroxide, as well as the conversion of the *trans*-acid to a mixture composed of 27 ± 10% *cis* and 73 ± 10% *trans* by the same means, further substantiates the belief that *cis–trans* isomerism rather than skeletal rearrangement is involved.

The relationship between the *cis*-acid IX and the *cis*-iodide II was shown by the following series of reactions, all of which are known to proceed with lack of isomerization.[1,11] The *cis*-acid was esterified with diazomethane to yield dimethyl *cis*-2,3-*p*-dioxanedicarboxylate (X) which was subsequently reduced with lithium aluminum hydride to an oil assumed to be the *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane. This glycol was converted to *cis*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (XI) which was treated with sodium iodide in acetone to form the *cis*-iodide II.

When the *cis*-iodide II was treated with concentrated nitric acid in an attempt to form the *cis*-acid IX, a solid was obtained which, when purified, dissolved in water to give a solution neutral to litmus, although its infrared spectrogram indicated the presence of a carbonyl group (strong absorption at 5.6–5.7 μ) and which gave a melting point and combustion analysis different from any of the acids or anhydrides in the dioxane series. The possibility of having formed *cis*-3-hydroxymethyl-2-*p*-dioxanecarboxylic lactone (XII) seemed credible since five-membered rings fused in a *cis* manner to six-membered rings form quite readily.[12]

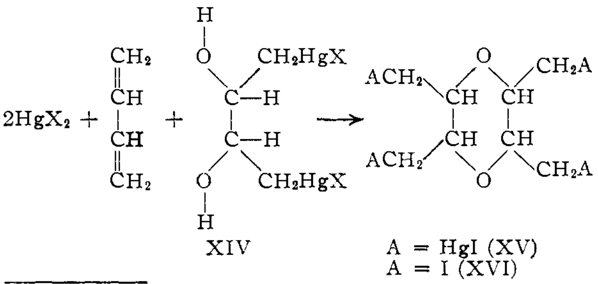
Since further treatment of the lactone XII with nitric acid failed to produce the *cis*-acid IX, the lactone was reduced with lithium aluminum hydride to form the assumed *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane which was then converted to the now known *p*-toluenesulfonate ester (XI).

The *trans*-2,3-*p*-dioxanedicarboxylic acid is the racemic modification and hence should be resolvable into its optical antipodes, whereas the *cis*-acid is the *meso* form and hence would be non-resolvable.

It was found experimentally that the acid IV could be resolved partially, whereas no resolution could be effected with the acid IX. Hence IV was assigned the *trans* configuration and IX was designated the *cis* isomer.

Chemical evidence already mentioned is consistent with this assignment; for example, thermal conversion of the *trans*-anhydride V to the *cis*-anhydride VIII, since one would expect the *trans*-anhydride to be the less stable compound.[13] The behavior of the two methiodides toward nitric acid, where one (I) produces a dibasic acid and the other (II) a lactone, is also pertinent, since the *cis*-lactone would be quite stable in contrast to a *trans*-lactone which, even if formed,[12] would probably be easily hydrolyzed and oxidized further to the *trans*-diacid.

If butadiene is allowed to react with an aqueous mercuric nitrate solution in the absence of an alcohol, 1,4-dinitratomercuri-2,3-dihydroxybutane (XIV) would be the expected product.[14] Our ideas of the mechanism of this reaction[6] suggested that this compound, a glycol, could condense with



XIV

A = HgI (XV)
A = I (XVI)

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[12] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 621 622.

[13] A. Baeyer, *Ann.*, **258**, 213 (1890).

[14] A. N. Nesmeyanov and I. F. Lutsenko, *Bull. acad. sci. U.S.S.R classe sci. chim.*, 366 (1942).

more butadiene and mercuric salt to form a tetrasubstituted dioxane (XV), which would probably react with iodine to form 2,3,5,6-tetra-(iodomethyl)-*p*-dioxane (XVI). Furthermore, our mechanism implies that if XIV were treated with strong acid, part of it should be decomposed, regenerating the requisite butadiene and mercuric salt to react with the portion that was not decomposed. When this series of reactions was attempted, a small amount of a compound of the correct analysis and molecular weight for 2,3,5,6-tetra-(iodomethyl)-*p*-dioxane was obtained.

We have previously reported the properties of a number of 2,5- and 2,6-disubstituted dioxanes and explained them in terms of a chair conformation and the equatorial–axial concept of Becket, Pitzer and Spitzer.[15] Assuming a chair conformation, the equatorial–axial isomer, the *cis*-2,5- and the *trans*-2,6-, was found to have a lower melting point and to be less stable than its corresponding more symmetrical isomer. In the present series of 2,3-disubstituted dioxanes, the *cis* compounds would be expected to have the lower melting points and the lesser stabilities. Some of the melting points conform to this prediction and some do not, but this is not particularly serious, since as yet only a few compounds have been made, and since in the related cyclohexane compounds, occasional anomalies in melting points have been observed.[11,16] That the *trans* isomer is the more stable one is indicated quite definitely by our original synthesis, since the yield and proportion of that isomer were increased by equilibration conditions of high acidity and long reaction time. In previous work,[6] the same conditions were found to favor the *trans*-2,5- and the *cis*-2,6-isomers.

The assumption of a chair form for most dioxanes would seem to follow current trends. For instance, Brown, Brewster and Schechter[17] have brought together a large amount of evidence indicating that " . . . an oxygen atom in a ring system can result in the same type of conformational effects as a methylene group." They cite several examples involving two oxygens in the ring.

On the other hand, Kumler and Huitric[18] point out: "When heteroatoms . . . replace CH_2 groups in the cyclohexane ring, the energies of the flexible forms are going to be less, due to fewer intereactions between consecutive CH_2 groups and to more favorable angles in the rings." In our studies thus far, the behavior of dioxane derivatives has paralleled that of cyclohexanes very closely.

Acknowledgments.—We wish to express our gratitude to the Abbott Foundation of Northwestern University for a grant of financial aid and to the Allied Chemical and Dye Corporation for a Fellowship held by G.J.L.

TABLE I

MELTING POINTS OF DIOXANE DERIVATIVES

	2,3-*cis*	2,3-*trans*	2,5-*cis*	2,5-*trans*	2,6-*cis*	2,6-*trans*
Diacid	183.5	176	178	275	178	162
Dimethylester of diacid	63.5	59	92	143	103	89
Diacid anhydride	116.5	201.5	75	..	106	..
Bis-iodomethyl	77.5 + 84	90	97	158	92	70
Bis-*p*-toluenesulfonatomethyl	97	105	88	205		

Experimental

A. The Formation of 2,3-Bis-(iodomethyl)-*p*-dioxane. 1. The Preparation of 2,3-Bis-(nitratomercurimethyl)-*p*-dioxane.—To 243.0 g. (1.12 moles) of mercuric oxide was added a solution of 300 ml. of concd. (sp. gr. 1.42, 4.7 moles) nitric acid and 150 ml. of water. When solution was complete, there was put in an additional 100 ml. of water and 500 ml. of freshly distilled ethylene glycol. The mixture was cooled to 20°, and 1,3-butadiene was bubbled through the solution at a rate of 2 bubbles/second. The reaction was assumed to be complete when after 3 hr. a 0.5-ml. aliquot no longer gave a precipitate of mercuric oxide when added to a 10% sodium hydroxide solution. The mixture was cooled to −5°, and the precipitate of 2,3-bis-(nitratomercurimethyl)-*p*-dioxane which had formed during the reaction was collected by suction filtration.

2. The Preparation of 2,3-Bis-(iodomercurimethyl)-*p*-dioxane.—The precipitate described in the preceding section was dissolved in a 2-liter solution of 10% sodium hydroxide. There was a slight liberation of free mercury accompanying this solution. To this mixture was added a solution of 133 g. (0.801 mole) of potassium iodide dissolved in 500 ml. of water. A precipitate of 2,3-bis-(iodomercurimethyl)-*p*-dioxane formed. After the solution had been tested for completeness of precipitation, the precipitate was collected by suction filtration. After drying for 24 hr. at 45°, there was obtained 276 g. (0.359 mole), m.p. 196–198°.[19]

3. The Preparation of 2,3-Bis-(iodomethyl)-*p*-dioxane. a. The Isolation of *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I).—To a mixture of 800 ml. of chloroform and 200 ml. of water containing 183 g. (0.718 mole) of iodine there was added the substance described in the previous section. The mixture was vigorously stirred and refluxed for 12 hr. When the contents of the flask had cooled, the excess iodine was removed by washing the mixture with a 10% solution of sodium thiosulfate. The mercuric iodide was removed by solution in aqueous potassium iodide. The chloroform layer was separated and evaporated under reduced pressure and the residue dissolved in boiling methanol and filtered. When the solution was cooled slowly, there was obtained 77.0 g. (0.209 mole) of I, m.p. 89–90°, which upon further recrystallization from methanol, deposited rhombic crystals, m.p. 89.5–90°.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71; mol. wt., 368. Found: C, 19.69; H, 2.71; mol. wt., Rast method, 369.

Evaporation of the methanolic mother liquor deposited 42.0 g. (0.114 mole) of crystals, m.p. 57–70°, which, by virtue of the absorbancies in its infrared spectrogram, was adjudged to be a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxane.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71. Found: C, 19.52; H, 2.53.

Thus there was obtained a total of 119 g. (0.323 mole) of 2,3-product for a yield of 56% based on the number of moles of mercuric salt used in the initial reaction. In a similar sequence of reactions, 32 g. (0.1 mole) of mercuric acetate without the addition of any strong acid was treated with excess 1,4-butadiene. There was obtained, after the appropriate sequence of reactions, 7.5 g. (0.02 mole) of 2,3-product, m.p. 64–72°, for a yield of 40%.

b. The Isolation of *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II).—The lower melting crops, when dissolved in methanol and allowed to stand in beakers, slowly deposited crystals of the *cis* and *trans* isomers. The *cis* isomer appeared as rod-shaped crystals which could be separated from the rhombic crystalline *trans* isomer by hand picking. The

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[15] C. W. Becket, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947); see also S. Siegel, *ibid.*, **75**, 1317 (1953).

[16] L. N. Owen and Robis, *J. Chem. Soc.*, 320 (1949).

[17] H. C. Brown, J. H. Brewshter and H. Schecter, THIS JOURNAL, **76**, 467 (1954).

[18] W. D. Kumler and A. C. Huitric, *ibid.*, **78**, 3369 (1956).

[19] All melting points were taken on a Fisher-Johns block unless otherwise indicated.

crystals of the *cis* isomer so obtained were recrystallized from methanol and from hexane. Although its melting point was not sharp, it was assumed to be free of the *trans* isomer because of the lack of the strong *trans* absorption at 10.6 μ in its infrared spectrogram.

When this substance was dissolved in boiling hexane and slowly cooled, needle-shaped crystals (IIa) appeared, m.p. 77–77.5°. The compound was dried at 30° and 0.1 mm. for 12 hr. and the melting point remained unchanged.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71; mol. wt., 368. Found: C, 19.72; H, 2.58; mol. wt., Rast method, 368.

When IIa was melted in a capillary or when melted on a steam-bath and suddenly cooled, the melting point rose to 83.5–84° (IIb). A mixed melting point with the 77.5° isomer melted at 83–84°.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71. Found: C, 19.48; H, 2.64.

Both forms depress the *trans* isomer in a mixed melting point determination.

TABLE II

MIXED MELTING POINTS OF THE 2,3-DIIODIDES

Components	M.p., °C.
I and IIa	60–70
I and IIb	63–73
IIa and IIb	83–84

When IIb was dissolved in hot hexane and the solution allowed to cool slowly, there were obtained fine needles, m.p. 77–77.5°. When IIa was melted at 80° on the Fisher–Johns block and the liquid seeded with a crystal of IIb, the liquid slowly solidified and melted at 83.5–84°.

In carbon disulfide solution, forms IIa and IIb gave identical infrared spectrograms. In a 2% mixture of the iodides in potassium bromide, form IIb had a medium strong absorption at 10.94 which form IIa did not possess. The pellets weighed *ca.* 60 mg. and were formed under 6000 p.s.i.

B. The Synthesis of 2,3-Bis-(exomethylene)-*p*-dioxane (III). 1. The Preparation of III.—In a 1-liter claisen flask fitted with an addition funnel and a condenser there was placed 100 ml. of carbitol and 44 g. (1.1 moles) of sodium hydroxide dissolved in 50 ml. of water. The temperature of the heating bath was kept between 200–210° so that a slow distillation occurred. By means of the addition funnel 110 g. (0.3 mole) of 2,3-bis-(iodomethyl)-*p*-dioxane suspended in 200 ml. of an equivolume water-carbitol mixture was added in small portions. Each addition was followed by the sudden ebullition of vapor which condensed to give a milky liquid composed of water and III which was collected in a receiver immersed in an ice–salt-bath and under an atmosphere of nitrogen. When the addition of the iodide was completed, 50 ml. of a water-carbitol mixture was added and the heating continued until the distillate became clear. The distillate separated into two layers, the upper layer of water and the lower layer of III. Substance III was removed and dried by means of anhydrous sodium carbonate and stored at −78° under a nitrogen atmosphere. Compound III was considerably soluble in water, hence there was obtained only 14 g. (0.12 mole) of diolefin for a 40% yield, $n^{20}D$ 1.4922.

2. The Polymerization of III.—Substance III, when allowed to stand at 25°, polymerizes noticeably within 5 minutes. At the end of 24 hr. a white, glass-like polymer was obtained which did not melt at 240°.

3. The Hydrolysis of III.—To 40 ml. of water containing two drops of 12 *N* hydrochloric acid 1.0 g. (0.009 mole) of III was added. The mixture was warmed gently for 15 minutes and then allowed to stand overnight. Upon standing, the solution assumed a canary-yellow color. The phenylosazone of biacetyl was prepared according to the method listed by Shriner and Fuson.[20,21] There was obtained 0.75 g. (0.0028 mole) of substance which was assumed to be the phenylosazone of biacetyl, m.p. 243–244° (lit. m.p. 242–243°).[21] There was no depression in the melting point when this osazone was mixed with an authentic sample of the phenylosazone of biacetyl.

Anal. Calcd. for $C_{16}H_{18}N_4$: N, 21.04. Found: N, 21.22.

4. The Reaction of III with Maleic Anhydride.—To 30 ml. of benzene containing 2.0 g. (0.020 mole) of maleic anhydride and 0.5 g. of hydroquinone under a nitrogen atmosphere there was added 2.0 g. (0.018 mole) of III. The ensuing reaction was exothermic so that cooling became necessary. After the mixture was allowed to stand overnight, the benzene was removed under reduced pressure. The residue was extracted twice with 10 ml. of ethyl ether to remove the hydroquinone. The resulting solid was recrystallized from a hexane–benzene mixture to yield 2.22 g. (0.0105 mole) of 5,8-dioxaoctalin-*cis*-2,3-dicarboxylic anhydride, m.p. 81.5–82°, for a 58.3% yield.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79; neut. equiv., 105. Found: C, 57.36; H, 4.67; neut. equiv., 108.

5. The Reaction of III with Mercuric Acetate in Ethylene Glycol.—To a solution of 200 ml. of ethylene glycol and 10 ml. of acetic acid containing 64 g. (0.036 mole) of mercuric acetate there was added 4.0 g. (0.036 mole) of III. After 4 hr., a yellow gelatinous precipitate formed which was removed by filtration. This precipitate did not dissolve in aqueous sodium hydroxide but did take up iodine in the replacement reaction. There was obtained 0.15 g. of substance, m.p. 118–118.5°, which smelled similar to iodoform and which did not depress authentic iodoform in a mixed m.p. determination.

Aqueous potassium iodide was added to the filtrate of the reaction mixture and a precipitate formed. This precipitate was treated with excess iodine in chloroform for 2 hr. Upon evaporation of the chloroform under reduced pressure there was obtained 0.56 g. (0.0013 mole) of compound which, after crystallization from methanol, melted at 136° and was assumed to be 4a,8a-bis-(iodomethyl)-1,4,5,8-tetroxadecalin.

Anal. Calcd. for $C_8H_{12}O_4I_2$: C, 22.55; H, 2.83. Found: C, 22.66; H, 2.87.

C. The Oxidation of *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I). 1. The Formation of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV).—To 2 liters of concd. (sp. gr. 1.42) nitric acid there was added 161 g. (0.44 mole) of I. The mixture was heated on a steam-bath until only a solid remained. There was obtained 56.5 g. (0.32 mole) of impure IV for a 73% yield. The acid was recrystallized by dissolving it in boiling acetone, adding hexane until a slight cloudiness developed and then allowing the mixture to cool slowly to room temperature. Crystals of IV were thus obtained melting at 175–176°.

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.57; neut. equiv., 88.1. Found: C, 40.95; H, 4.50; neut. equiv., 88.9.

2. *trans*-2,3-*p*-Dioxanedicarboxylic Anhydride (V).—A sample, 17.6 g. (0.10 mole), of IV was refluxed in 100 ml. of acetic anhydride for 1 hr. After one-half of the solvent was distilled under reduced pressure, the mixture was allowed to cool to room temperature. Crystals formed which, after collection by filtration, weighed 10.8 g. (0.068 mole) for a 68% yield of impure V. Further crystallization from acetic anhydride produced the solid, m.p. 201–201.5°.

Anal. Calcd. for $C_6H_6O_4$: C, 45.57; H, 3.83; neut. equiv., 79; mol. wt., 158. Found: C, 45.72; H, 3.75; neut. equiv., 79.6; mol. wt., Rast method, 165; mol. wt., Rast method after one month, 200.

3. The Hydrolysis of V.—To 10 ml. of water containing 2 drops of 12 *N* hydrochloric acid there was added 1.0 g. (0.0063 mole) of V, and the mixture was heated for 1 hr. on a steam-bath. When the excess solvent was removed under reduced pressure, there was obtained 0.82 g. (0.0047 mole), yield 74%, of IV which, after recrystallization from acetone–hexane, melted at 175–176° and did not depress the melting point of authentic IV in a mixed m.p. determination.

D. The Conversion of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV) to *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I). 1. The Formation of Dimethyl *trans*-2,3-*p*-Dioxanedicarboxylate (VI).—To 100 ml. of ethyl ether containing a suspension of 3.0 g. (0.017 mole) of IV there was added an ethereal solution of diazomethane[22] until the yellow color of the diazomethane persisted. The ether solution was allowed to

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(20) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 117.

(21) R. W. Balcom, THIS JOURNAL, **39**, 315 (1917).

(22) F. Arndt, *Org. Syntheses*, **15**, 4 (1935).

stand for 24 hr. and was then filtered. The filtrate was evaporated to dryness by heating and a colorless oil remained which solidified on standing. After recrystallization from ethyl ether there was obtained 2.5 g. (0.012 mole) of VI, m.p. 59°, for a 71% yield.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.05; H, 5.92. Found: C, 47.34; H, 5.60.

2. **The Reduction of VI with Lithium Aluminum Hydride.**—To 150 ml. of anhydrous ethyl ether containing a suspension of 2.0 g. (0.052 mole) of lithium aluminum hydride there was added slowly 2.34 g. (0.0115 mole) of VI dissolved in 50 ml. of ethyl ether. The reaction was mildly exothermic. The mixture was refluxed for 4 hr., and then 2 ml. of methyl alcohol was added to destroy the excess anhydride reagent. To this mixture was added 9 ml. of water and the reaction was allowed to stand overnight. The hydroxides were precipitated in the form of pellets which could be removed easily by filtration. This hydroxide precipitate was extracted in a Soxhlet apparatus for three days. Upon evaporation of the combined ether solvents there was obtained *ca.* 1.4 g. of a colorless oil which was assumed to be the *trans*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

3. **The Preparation of *trans*-2,3-Bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (VII).**—The *p*-toluenesulfonate derivative was made from the oil from the previous experiment according to the method of Tipson.[23] There was obtained 1.26 g. (0.0025 mole) of VII which, after repeated recrystallization from acetone-hexane, melted at 105° for an overall yield of 24% from the dimethyl ester.

Anal. Calcd. for $C_{20}H_{24}O_8S_2$: C, 52.61; H, 5.29. Found: C, 52.53; H, 5.05.

4. **The Conversion of VII to I.**—To 30 ml. of anhydrous acetone[24] containing 2.0 g. (0.013 mole) of anhydrous sodium iodide there was added 0.46 g. (0.001 mole) of VII. The solution was refluxed for 6 hr. during which time a precipitate formed. The acetone was evaporated by means of an air jet, and water was added to the residual solid. The insoluble material (I) was collected by filtration. There was obtained 0.36 g. (0.0098 mole) of compound for a 98% yield. The substance was recrystallized from methanol to yield crystals, m.p. 89.5-90°, which gave no depression with authentic I in a mixed m.p. determination. The infrared spectrogram of this compound was identical to that of authentic I.

E. **The Formation of *cis*-2,3-*p*-Dioxanedicarboxylic Anhydride (VIII).** 1. **The Isomerization of V.**—A mixture of 70 ml. of acetic anhydride and 10.0 g. (0.068 mole) of the *trans*-anhydride V was refluxed for 9 hr. During this time the reaction mixture turned dark brown. The solvent was distilled at reduced pressure until 60 ml. had been collected. The reaction mixture was cooled in an ice-salt-bath and crystals slowly formed. There was collected 1.18 g. (0.0075 mole) of VIII which upon further recrystallization from acetic anhydride melted at 116-116.5° for an 11.8% yield.

Anal. Calcd. for $C_6H_6O_4$: C, 45.57; H, 3.83; neut. equiv., 79.4; mol. wt., 158. Found: C, 45.88; H, 3.86; neut. equiv., 79.4; mol. wt., Rast method, 164.

2. **From IX.**—A mixture of 15 ml. of acetic anhydride and 1.15 g. (0.0065 mole) of *cis*-diacid IX was refluxed for 1 hr The solvent was then distilled under reduced pressure, and there was obtained on cooling 0.72 g. (0.0046 mole) of substance which upon recrystallization from acetic anhydride melted at 116-116.5° and which did not depress the melting point of VIII in a mixed m.p. determination.

F. **The Formation of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX).**—To 25 ml. of water containing 2 drops of concd. hydrochloric acid there was added 1.0 g. (0.0063 mole) of VII. The mixture was heated for 2 hr. on a steam-bath and then the solvent was evaporated at 25° and reduced pressure. There was obtained 0.94 g. (0.0053 mole) of IX, m.p. 177-180°, for an 84% yield. The substance was recrystallized from an acetone-hexane mixture as described in section C to yield crystals, m.p. 182.5-183.5°, which in a mixed m.p. determination with IV melted at 150-163°.

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.57; neut. equiv., 88.1. Found: C, 41.15; H, 4.54; neut. equiv., 88.6.

G. **The Conversion of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX) to *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II).** 1. **The Preparation of Dimethyl *cis*-2,3-*p*-Dioxanedicarboxylate (X).**—The conversion of IX to II was performed in exactly the same manner as that of V to I. The diester was prepared in 83% yield and after recrystallization from ethyl ether melted at 63-63.5°. A mixed melting point with the *trans*-diester melted at 45-55°.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.05; H, 5.92. Found: C, 47.31; H, 5.69.

2. **The Reduction of X with Lithium Aluminum Hydride.**—After the reduction procedure there was obtained *ca.* 0.7 g. of a clear viscous liquid assumed to be the *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

3. **The Formation of *cis*-2,3-Bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (XI).**—The *p*-toluenesulfonate derivative was made from the oil obtained in the previous experiment according to the method of Tipson.[23] Substance XI was obtained in 38% yield from the diester and after recrystallization from acetone-hexane melted at 97°.

Anal. Calcd. for $C_{20}H_{24}O_8S_2$: C, 52.61; H, 5.29. Found: C, 52.35; H, 5.03.

4. **The Formation of II from XI.**—After the appropriate reaction there was obtained a compound in 83% yield which after recrystallization from methanol melted at 82-83.5° and which did not depress authentic II in a mixed melting point determination. The infrared spectrogram in carbon disulfide solution was identical to that of authentic II.

H. **The Interconversions of the 2,3-*p*-Dioxanedicarboxylic Acids.** 1. **IV to IX.**—To 50 ml. of water containing 12 g. of potassium hydroxide there was added 1.0 g. of IV. The mixture was heated for 12 hr. on a steam-bath, cooled to 0°, acidified with 6 *N* hydrochloric acid to *p*H 2 and evaporated to dryness by heating on a steam-bath. The residue was pulverized and extracted three times with 30-ml. portions of acetone. The acetone was evaporated to dryness by heating and there was obtained 0.92 g., m.p. 130-138°, for a 92% recovery. The recovered substance had a neutral equivalent of 90 compared to the theoretical value of 88 for the diacids. The mixture contained 73 ± 10% *trans*-acid and 27 ± 10% *cis*-acid as determined by infrared analysis.

2. **IX to IV.**—A solution of 50 ml. of water containing 6.0 g. of potassium hydroxide and 0.5 g. of IX was heated for 12 hr. on a steam-bath. The product was isolated as described in the previous section. There was obtained upon evaporation of the acetone extract 0.33 g., m.p. 140-145°, for a 66% recovery. The recovered substance had a neutral equivalent of 91 as compared to a theoretical value of 88 for the diacids. The mixture contained 58 ± 10% *cis*-acid and 42 ± 10% *trans*-acid as determined by infrared analysis.

3. **Infrared Analysis.**—The analyses were performed by preparing a 2% mixture of the acids in potassium bromide. Pellets of the order of 65 mg. were analyzed on the Baird infrared recording spectrophotometer. The *cis*-acid absorbed at 11.1 and at 11.4 μ, whereas the *trans* isomer absorbed at 11.4 μ. The concentrations were determined by comparing the relative absorptions at 11.1 and 11.4 μ with known mixtures.

The known mixtures were prepared by weighing the appropriate amounts of pure acids, dissolving them in acetone and boiling the acetone to dryness. The resulting solid was pulverized with an agate mortar and pestle and its spectrogram determined in the same manner as the unknown acid mixtures.

I. **The Partial Resolution of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV).**—To 2 liters of acetone containing 2.37 g. (0.0060 mole) of brucine there was added 1.0 g. (0.0057 mole) of IV dissolved in 50 ml. of acetone. The solution was

TABLE III

FRACTIONAL CRYSTALLIZATION OF *trans*-ACID BRUCINATE

Fraction	Yield, g.	M.p., °C.	$\alpha^{25}{}_D$[a]
1	1.8	242-243	+0.37°[b]
2	0.34	230-232	−1.0
3	.24	225-230	−0.65
4	.20	232-234	− .60
5	.20	218-223	− .63

[a] Defined as the optical rotation after the removal of brucine. [b] Defined as the rotation observed from the acid obtained from 0.30 g. of brucinate.

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[23] R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

[24] K. Shipsey and E. A. Werner, *J. Chem. Soc.*, **103**, 1255 (1913).

boiled for 15 minutes and allowed to cool. Overnight some crystals were formed which were removed by filtration. The remainder of the solution was allowed to stand in a 3-liter beaker at room temperature. From time to time crystals of the brucinate salt were deposited and collected.

To each set of crystals was added 1 ml. of concd. ammonium hydroxide. To the mixture containing precipitated brucine there was added 2 ml. of chloroform with vigorous shaking. The resulting two-liquid layers were separated and the ammoniacal layer was extracted twice with chloroform, filtered and put in a one-decimeter polarimeter tube. The magnitude of its optical rotation was measured with an Aminco photomultiplier microphotometer whose accuracy was estimated at ±0.03.

J. The Attempted Resolution of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX).—To 1.5 liters of acetone containing 0.48 g. (0.0012 mole) of brucine there was added 0.200 g. (0.0011 mole) of IX in 50 ml. of acetone. The solution was boiled for 15 minutes and allowed to stand. Over the period of a month crystals were deposited and collected.

TABLE IV

FRACTIONAL CRYSTALLIZATION OF *cis* ACID BRUCINATE

Fraction	Yield, g.	M.p., °C.	$\alpha^{25}\text{D}^{a}$
1	0.19	214–215	+0.03°
2	.13	214–215	0°
3	.23	213–215	0°
4	.10	210–214	+0.03°

[a] Defined as optical rotation after the removal of brucine.

The acids were liberated from the brucine and the optical rotations measured in the same manner as described in the previous section.

K. The Oxidation of *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II). 1. The Formation of *cis*-3-Hydroxymethyl-2-*p*-dioxanecarboxylic Lactone (XII).—To 15 ml. of concd. (sp. gr. 1.42) nitric acid there was added 2.0 g. (0.0054 mole) of II. The mixture was heated on a steam-bath for 10 hr. A clear oil was obtained which solidified on standing. The resulting solid, after drying on a clay plate, weighed 0.55 g. (0.0038 mole) for a 70% yield of XII. When it was recrystallized from carbon tetrachloride the substance melted at 86–86.5°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.99; H, 5.39.

An infrared spectrogram of this compound was obtained from a 2% mixture in potassium bromide. The compound possessed a strong absorption at 5.62 μ which was attributed to the carbonyl group.

A neutral equivalent was attempted by titrating the sodium salt of the acid with 0.1 *N* hydrochloric acid. When the reaction was followed potentiometrically, no break was observed in the titration curve.

2. The Conversion of XII to XI. a. The Reduction of XII with Lithium Aluminum Hydride.—To 100 ml. of anhydrous ethyl ether containing 0.60 g. (0.015 mole) of lithium aluminum hydride there was added 0.80 g. (0.0056 mole) of XII. The mixture was refluxed for 6 hr. and then hydrolyzed by the addition of 1 ml. of methanol followed by the addition of 3 ml. of water. The mixture was allowed to stand overnight. The hydroxide precipitate was collected by filtration and extracted in a Soxhlet apparatus for 4 days. Upon evaporation of the ether there was obtained *ca.* 0.70 g. of an oil which was assumed to be *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

b. The Formation of XI.—The *p*-toluenesulfonate derivative was made from the oil isolated in the previous experiment according to the method of Tipson.[21] There was obtained 0.70 g. (0.0015 mole) of XI which, after recrystallization from methanol, melted at 96–97° for a 27% yield from the lactone. A mixed m p. with authentic XI gave no depression (m.p. 96–97°).

L. The Oxidation of 2,3-Dimethoxy-1,4-diiodobutane. 1. The Formation of *meso*-α,α′-Dimethoxysuccinic Acid (XIII).—To 60 ml. of concd. (sp. gr. 1.42) nitric acid there was added 5.35 g. (0.0144 mole) of *meso*-2,3-dimethoxy-1,4-diiodobutane.[8]

The mixture was heated on a steam-bath until a heavy oil remained. There was obtained 1.80 g. (0.0101 mole) of XIII which, after recrystallization from an acetone–hexane mixture, melted at 160–161.5° (lit.[25] m.p. 161°) for a 65.8% yield.

2. The Formation of *rac.*-α,α′-Dimethoxysuccinic Acid (XIV).—To a 20 ml. of concd. (sp. gr. 1.42) nitric acid there was added 1.5 g. (0.0041 mole) of *rac.*-2,3-dimethoxy-1,4-diiodobutane.[8] The mixture was allowed to react and was worked up as described in the previous section. There was obtained 0.22 g. (0.0012 mole) of XIV which, after recrystallization from acetone–hexane, melted at 168–169° (lit.[26] m.p. 168–171°) for a 29% yield. In a mixed m.p. determination with XIII the mixture melted at 140–150°.

M. The Formation of 2,3,5,6-Tetra-(iodomethyl)-*p*-dioxane (XVI).—A solution of 114 g. (0.35 mole) of mercuric nitrate dissolved in 200 ml. of water containing 30 ml. of concd. nitric acid was prepared and 1,4-butadiene was bubbled through at a rate of 2 bubbles/second. The reaction was assumed complete when a 0.5-ml. portion no longer gave a mercuric oxide precipitate when added to a 10% sodium hydroxide solution. During the course of the reaction a precipitate was formed which was removed by filtration and suspended in 50 ml. of 6 *N* nitric acid for 24 hr. The mixture was then added to a liter of 1 *N* sodium hydroxide. A slight liberation of free mercury accompanied this solution. A solution of 40 g. (0.24 mole) of potassium iodide dissolved in 200 ml. of water was added with vigorous stirring. A precipitate formed which was collected and then treated with 25 g. (0.1 mole) of iodine in a water–chloroform mixture. Upon evaporation of the chloroform by an air jet, a solid remained which was recrystallized from methanol to yield 2.0 g. (0.0031 mole) of compound assumed to be XVI, m.p. 206–206.5°.

Anal. Calcd. for $C_8H_{12}O_2I_4$: C, 14.83; H, 1.87; mol. wt., 648. Found: C, 14.87; H, 1.78; mol. wt., Rast method, 654.

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(25) T. S. Patterson and D. S. Patterson, *J. Chem. Soc.*, **107**, 155 (1915).

(26) H. Wren and K. Hughes, *ibid.*, **125**, 1742 (1924).