[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Stereochemistry of Diphenyls. XXXVII. The Resolution of Certain Substituted Diphenylbenzenes[1]

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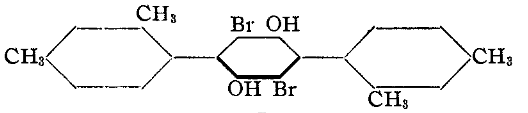
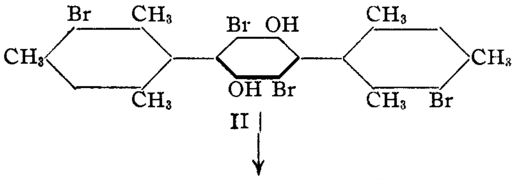
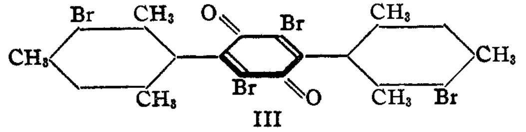
In establishing the fact that properly substituted diphenylbenzenes with two points of restricted rotation gave rise to two diastereoisomeric forms, the *cis* and *trans* (I) forms of 3,6-di-(2,5-dimethylphenyl)-2,5-dibromohydroquinone[2] and the *cis* and *trans* (II) forms of 3,6-di-(3-bromo-2,4,6 - trimethylphenyl) - 2,5 - dibromohydroquinone[3] were synthesized. The former pair (I) yielded the same quinone on oxidation which, in turn, on reduction resulted in a mixture of the original hydroquinones. Each of the latter pair (II), however, gave a well-defined individual series of compounds; especially may be mentioned the corresponding quinone (III) and from this the tetrahydroxybenzene (IV) as illustrated by the *trans* modification (II).



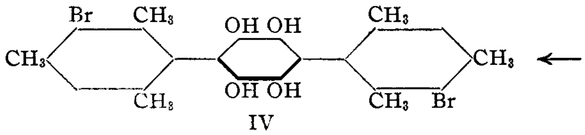
I



II



III

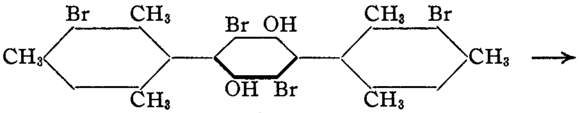


IV

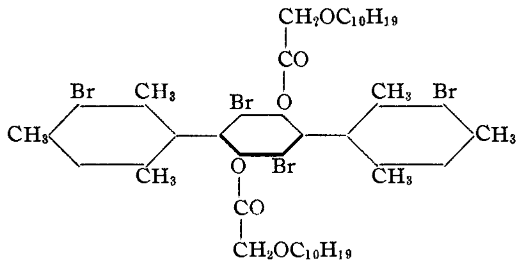
At the time of these investigations just mentioned it was assumed that the higher-melting, less-soluble isomers were *trans* modifications, which from a stereochemical standpoint would be meso, and they were designated as α-forms. The lower-melting, more-soluble isomers were assumed to be *cis* or racemic and were called β-forms. Many attempts to confirm experimentally the individual *cis* and *trans* forms by resolution of the racemic modification resulted in failure owing to the difficulty of introducing satisfactory salt-forming groups.

Resolution of the more soluble β-form (V) of 3,6 - di - (3 - bromo - 2,4,6 - trimethylphenyl) - 2,-5-dibromohydroquinone has now been accomplished, while a similar attempt to resolve the less-soluble α-form (II) resulted in failure. The dimenthoxyacetates of each form were synthesized from the hydroquinone and menthoxyacetyl chloride. From the β-form (V) two diastereoisomeric esters (VI) were produced which could be separated by crystallization from acetone.

By hydrolysis of these two products the two active forms of the hydroquinone (V) were obtained. By oxidation of the active forms the corresponding active quinones were synthesized which had opposite signs of rotation from the hydroquinones. These quinones were readily reduced to the original active hydroquinones.



V



VI. Two diastereoisomers

The α- or *trans* form (II) gave a dimenthoxyacetate which existed in two crystalline modifications, one m. p. 146–147° and one m. p. 167–168°. They were observed during the crystallization from either alcohol or acetone, when two types of crystals separated, small round opaque clusters of tiny crystals and large transparent crystal clusters. The former were the low-melting form, the latter the high-melting form. If

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[1] For the last paper in this series see Chang and Adams, THIS JOURNAL, **56**, 2089 (1934); also Adams and Yuan, *Chem. Rev.*, **12**, 261 (1933).

[2] Browning and Adams, *ibid.*, **52**, 4098 (1930).

[3] Shildneck and Adams, *ibid.*, **53**, 343, 2203 (1931).

petroleum ether was used as a solvent, only the high-melting form was obtained. It was observed that the low-melting form upon melting resolidified and again melted at 167–168°. Moreover, the recrystallization of either modification from alcohol or acetone resulted in the production of the two crystalline forms. The optical rotation of both forms was the same, and on decomposition to the corresponding hydroquinones, inactive material, the α-form of the hydroquinone, always resulted. It is obvious that two crystalline modifications of a single compound and not two diastereoisomers had been isolated.

A similar attempt to resolve the *cis* and *trans* forms of 3,6-di-(2,4-dimethyl)-2,5-dibromohydroquinone was not successful. The dimenthoxyacetate of the *trans* modification melted sharply and was, presumably, the derivative of the meso form. The ester from the *cis* modification or racemic form always melted over a rather wide range, but no satisfactory procedure was discovered for obtaining the individual diastereoisomers.

Experimental

Dimenthoxyacetate of *Cis* 2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone (VI).—A mixture of 20 g. of *cis* 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone[3] (m. p. 285°), 20 cc. of *l*-menthoxyacetyl chloride and 300 cc. of dry benzene was heated to boiling in a 1-liter, round-bottomed flask fitted with a reflux condenser. Eight cubic centimeters of pyridine was dropped in slowly with agitation. The mixture was refluxed for one hour. Pyridine hydrochloride which separated was filtered off. The benzene solution was washed successively with about 200-cc. portions of water, 1% sodium carbonate, 2% hydrochloric acid, and finally water. The benzene layer was dried with calcium chloride, the drying agent removed by filtration, and benzene distilled off on a steam cone. The product weighed 32 g. (theoretical yield) and consisted of a mixture of diastereoisomeric molecules.

Rotation. 0.3030 g. made up to 10 cc. with ethyl acetate gave α_D, $-1.65°$; $l = 1$, $[\alpha]^{27}_{D}$, $-54.4°$.

Separation of Isomers.—A solution of 10 g. of the menthoxyacetates in 100 cc. of acetone was allowed to stand in a refrigerator for twenty-four hours and 4.8 g. of material crystallized. Five crystallizations of the solid thus obtained (using about ten times its weight of acetone) yielded 1.9 g. of material having constant melting point and rotation; m. p. 155°.

Rotation. 0.1655 g. made up to 10 cc. in ethyl acetate gave α_D. -1.10; $l = 1$, $[\alpha]^{26}_{D}$, $-66.4°$.

Anal. Calcd. for $C_{48}H_{62}O_6Br_4$: Br, 30.32. Found: Br, 30.42.

The mother liquor from the solid obtained in the first crystallization of the mixture was reduced in volume by 20 cc. and allowed to stand in a refrigerator for twenty-four hours. At the end of this time 1.4 g. of crystals was removed. This process of removing 20 cc. of solvent was repeated twice, yielding crops of 0.6 g. and 0.3 g. of solid. These fractions were discarded. The remaining mother liquor was evaporated to 10 cc. and after standing in a refrigerator for twenty-four hours gave 2.5 g. of crystals. Two more crystallizations of the 2.5-g. fraction from acetone gave 1.2 g. of material having a constant melting point and rotation; m. p. 141–143°.

Rotation. 0.2028 g. made up to 15 cc. in ethyl acetate gave α_D, $-0.81°$; $l = 1$, $[\alpha]^{25}_{D}$, $-39.94°$.

Anal. Calcd. for $C_{48}H_{62}O_6Br_4$: Br. 30.32. Found: Br, 30.51.

***l*-2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone.**—A solution of 1.8 g. of the less-soluble form of the ester in 125 cc. of alcohol was placed in a 200-cc., round-bottomed, 3-necked flask fitted with a mechanical stirrer, reflux condenser, dropping funnel and tube for admitting hydrogen. The solid was dissolved by heating, the air in the apparatus replaced by hydrogen, and a solution of 5 g. of sodium hydroxide in 20 cc. of water slowly added through the dropping funnel. Stirring and refluxing were continued for about one hour. Then 50 cc. of 20% hydrochloric acid was added, the mixture transferred to a beaker and the alcohol removed by boiling. The precipitated solid was filtered off and dissolved in 50 cc. of acetone. After addition of 1 cc. of hydrochloric acid, 0.5 g. of stannous chloride and 15 cc. of water, the mixture was boiled for several minutes. The precipitate was filtered off, dried, and crystallized from 50 cc. of benzene; yield, 0.9 g. (79%); m. p. 290–291°.

Rotation. 0.2469 g. made up to 10 cc. in ethyl acetate gave α_D, -0.41; $l = 1$, $[\alpha]^{25}_{D}$, $-16.2°$.

Anal. Calcd. for $C_{24}H_{22}O_2Br_4$: Br. 48.31. Found: Br, 48.16.

***d*-Hydroquinone.**—From 2.0 g. of the more-soluble form of ester, 0.9 g. (75% of theoretical) of the corresponding hydroquinone was obtained; m. p. 289–290°.

Rotation. 0.2010 g. made up to 10 cc. in ethyl acetate gave α_D, $+0.27°$; $l = 1$, $[\alpha]^{26}_{D}$, $+13.4°$.

Anal. Calcd. for $C_{24}H_{22}O_2Br_4$: Br, 48.31. Found: Br, 48.52.

***d*-2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromoquinone.**—A solution of 1.0 g. of *l*-hydroquinone, 1.0 g. of benzoquinone and 50 cc. of ethyl alcohol was refluxed for one hour and then half of the alcohol was removed by distillation. From the solution remaining 0.9 g. of material crystallized which when purified from benzene gave 0.7 g. (70% of theoretical) of solid melting at 284–285°.

Rotation. 0.1851 g. made up to 10 cc. in chloroform gave α_D, $+0.68°$; $l = 1$, $[\alpha]^{28}_{D}$, $+36.74°$.

Anal. Calcd. for $C_{24}H_{20}O_2Br_4$: Br, 48.44. Found: Br, 48.3.

Reduction to Hydroquinone.—A solution of 0.5 g. of the *d*-quinone, 2 g. of stannous chloride and 5 cc. of pyridine was refluxed until the solution lost its yellow color. It was then poured into water and the resulting solid filtered off, washed with dilute hydrochloric acid and crystallized from acetone; yield, 0.35 g. (70%); m. p. 289–290°. Mixed melting point with the *l*-hydroquinone showed no depression.

Rotation. 0.2138 g. made up to 10 cc. in ethyl acetate gave α_D, −0.35°; l = 1. $[\alpha]^{26}_D$, −16.4°.

l-Quinone.—From 1.0 g. of *d*-hydroquinone upon oxidation as just described 0.85 g. of quinone having m. p. 283–284° was obtained.

Rotation. 0.1530 g. made up to 10 cc. with chloroform gave α_D, −0.40°; l = 1. $[\alpha]^{26}_D$, −26.5°.

Anal. Calcd. for $C_{24}H_{20}O_2Br_4$: Br, 48.44. Found: Br, 48.5.

Reduction to Hydroquinone.—From 0.5 g. of the *l*-quinone 0.34 g. of active hydroquinone having m. p. 289–290° was obtained. Mixed melting point with the *d*-hydroquinone showed no depression.

Rotation. 0.1288 g. made up to 10 cc. in chloroform gave α_D, +0.17°; l = 1, $[\alpha]^{25}_D$, +13.2°.

Dimenthoxyacetate of *Trans* 2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone.—A solution of 5.0 g. of *trans* 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone, 5 cc. of *l*-menthoxyacetyl chloride, 2 cc. of pyridine and 100 cc. of dry benzene was treated in the same manner as in the preparation of the *cis* ester. The product weighed 8.5 g. This was dissolved in 200 cc. of boiling acetone. On standing there appeared snow-white clusters of microscopic crystals and also large transparent clusters. The white clumps melted at 144–146°, resolidified and melted again at 161–163°. The transparent crystals melted at 163–164°. When inserted into the hot bath the white clumps melted at 145–146°; the transparent crystals at 167–168°. Either crystalline form when crystallized again from acetone gave a mixture of forms. Crystallization from petroleum ether gave only the higher-melting form.

Anal. Calcd. for $C_{48}H_{62}O_6Br_4$: Br, 30.32. Found: Br, 30.45.

Rotation of mixture. 0.1954 g. made up to 10 cc. in ethyl acetate gave α_D, −0.98°; l = 1, $[\alpha]^{26}_D$, −50.2°.

Rotation of material melting at 145–146°. 0.1917 g. made up to 10 cc. in ethyl acetate gave α_D, −0.95°; l = 1, $[\alpha]^{26}_D$, −49.6°.

Rotation of material melting at 167–168°. 0.2020 g. made up to 10 cc. in ethyl acetate gave α_D, −1.00; l = 1, $[\alpha]^{26}_D$, −50.9°.

Fractional crystallization from ethyl alcohol, ethyl acetate and petroleum ether gave no evidence of separation into two diastereoisomers.

Portions of the ester melting at 145–146° and 167–168° and also the end fractions obtained by crystallization from the above solvents were separately hydrolyzed and the resulting hydroquinone examined for signs of optical activity. All samples were optically inactive. Melting point of all these samples was 325–326° and mixed melting point with sample of original *cis* form of the hydroquinone showed no depression.

Dimenthoxyacetate of *Cis* 3,6-Di-(2,4-dimethylphenyl)-2,5-dibromohydroquinone.—A mixture of 5 g. of *cis* 3,6-di-(2.4-dimethylphenyl)-2,5-dibromohydroquinone, 7 g. of menthoxyacetyl chloride, and 100 cc. of benzene was treated according to the method for making the previous menthoxyacetates. The product weighed 9 g. (quant. yield) and when crystallized from ethyl alcohol melted at 120–124°.

Rotation. 0.1775 g. made up to 10 cc. in ethyl acetate gave α_D, −1.28; l = 1, $[\alpha]^{27}_D$, 71.8°.

Anal. Calcd. for $C_{46}H_{58}O_6Br_2$: Br, 18.33. Found: Br, 18.2.

The end fractions obtained by fractional crystallization from acetone, ethyl alcohol, methyl alcohol and petroleum ether gave the same melting and rotation as the starting material.

Dimenthoxyacetate of *Trans* 3,6-Di-(2,4-dimethylphenyl)-2,5-dibromohydroquinone.—This was prepared in the same manner as the previous ester and was obtained in quantitative yield, m. p. 154°.

Rotation. 0.2075 g. made up to 10 cc. in ethyl acetate gave α_D, −1.50; l = 1, $[\alpha]^{28}_D$, −72.3°.

The end fractions obtained by fractional crystallization from acetone, ethyl alcohol, methyl alcohol and petroleum ether had the same melting point and rotation as the original material.

Anal. Calcd. for $C_{46}H_{58}O_6Br_2$: Br, 18.33. Found: Br, 18.45.

Summary

1. The *cis* and *trans* 3,6-di-(3-bromo-2,4,-6-trimethylphenyl)-2,5-dibromohydroquinones were converted to the corresponding dimenthoxyacetates. From the former the two diastereoisomeric forms were isolated and each on hydrolysis gave an active hydroquinone. The active hydroquinones could be oxidized to active quinones and these reduced again to the original active hydroquinones The *trans* modification of the dimenthoxyacetate existed in two crystalline modifications but no diastereoisomers could be isolated.

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