

magnesium in 50 cc. of ether during one hour and refluxed one-half hour more. Forty-one grams of hexyne was then dropped in at such a rate that ethane was evolved smoothly. The evolved gas was collected and its volume determined, the amount varying between 10.3 to 10.8 liters (theory 12.5). Two hours were usually sufficient for the last gas bubbles to be evolved. 0.41 to 0.43 mole of ketone (corresponding to the amount of ethane evolved) was then added and the reaction mixture was heated an additional hour. On working up in the usual manner a yield of acetylenic carbinol over 85% was obtained in every case, based on the ketone used. The results are summarized in the lower half of Table I.

**Decomposition of Acetylenic Carbinols over Alumina.**—Standard conditions were developed for studying the reactions of the carbinols over alumina as follows. Thirty grams of carbinol was allowed to drop into a Pyrex tube 2.4 × 30 cm., filled with 8–14 mesh alumina and maintained at 230° in an electric furnace. It was established that the use of temperatures below 230° did not change the course of the reaction, but only the extent. The carbinol was swept through the reaction chamber in a stream of nitrogen. Two hours were sufficient to drive all the products into the receivers, the last of which was cooled with dry-ice. Acetylene gas was absorbed in three Emmerling towers kept saturated with bromine. The acetylene tetrabromide so formed was dissolved in carbon tetrachloride, washed free of bromine with bisulfite, and purified by vacuum distillation. From the weight of acetylene tetrabromide the weight of evolved acetylene was calculated. The liquid products were collected, the water separated and weighed, and the organic layer fractionated in an efficient Widmer column. Although an absolutely quantitative recovery was not possible, Table II furnishes quite an accurate picture of the course of the reaction. In most cases the recovered ketones were further characterized by the preparation of a derivative.

The vinylacetylene derivatives which resulted in excellent yields from the hexynyl carbinols were new com-

pounds. Since the hexynyl carbinols were derived from unsymmetrical ketones, the vinylacetylene fraction may consist in each case of two isomeric hydrocarbons.<sup>11</sup> No attempt was made to separate the two isomers but the hydrocarbon mixtures were analyzed by quantitative hydrogenation, and by elementary analyses<sup>12</sup> to establish their vinylacetylene character. The data are included in Table II.

**Dehydration of Diethylethynylcarbinol with Acetic Anhydride.**—Results for dehydration of this carbinol were typical of the series: 100 g. of carbinol was slowly dropped into 100 g. of acetic anhydride containing 1 g. of sulfuric acid. The temperature and rate of addition were maintained so that the substance distilled from the fractionating column below 110°. On washing free of acid, drying, and refractionating 31 g. of 3-ethylpentyn-1-ene-3 was obtained, b. p. 93–95°; yield 38%.

### Summary

A number of acetylenic tertiary carbinols have been prepared. Ethynyl carbinols resulted in improved yields by condensation of ketones with acetylene using potassium *t*-amylate as condensing agent. Hexynyl carbinols were best prepared by use of hexynylmagnesium bromide. The decomposition of dialkylethynyl carbinols over alumina at 230° proceeded abnormally to yield acetylene and the ketone as the main products. With dialkylhexynyl carbinols, on the other hand, the normal products of dehydration resulted in excellent yields.

(11) Church, Whitmore and McGrew, *THIS JOURNAL*, **56**, 176 (1934).

(12) The authors wish to take this opportunity to thank Mr. Julius Kovitz who did the semi-micro carbon and hydrogen analyses included in this paper.

CAMBRIDGE, MASS.

RECEIVED OCTOBER 8, 1940

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

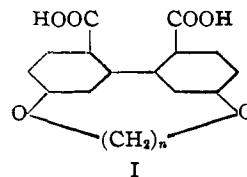
## Stereochemistry of Biphenyls. LI. Resolution of Diphenic Acids Having Many-Membered Bridges Across the 5,5'-Positions: A Novel Type of Restricted Rotation<sup>1</sup>

BY ROGER ADAMS AND NATHAN KORNBLUM

A large number of biphenyls, and related compounds, have been resolved.<sup>2</sup> In every instance, the required asymmetry has resulted from restricted rotation about a single bond produced by *ortho* substituents. The present investigation has been concerned with the production of restricted rotation by means of many-membered rings across the 5,5'-positions of diphenic acid, (I).

(1) For previous paper see Adams and Teeter, *THIS JOURNAL*, **62**, 2188 (1940).

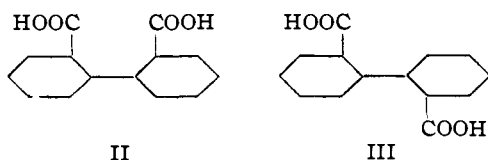
(2) H. Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 259.



Diphenic acid has been found to be incapable of resolution.<sup>3</sup> There is a large body of evi-

(3) Kamm in C. S. Palmer's Thesis on "A Study of Optical Activity," University of Illinois, 1917; Bell and Kenyon, *J. Chem. Soc.* 3044 (1926).

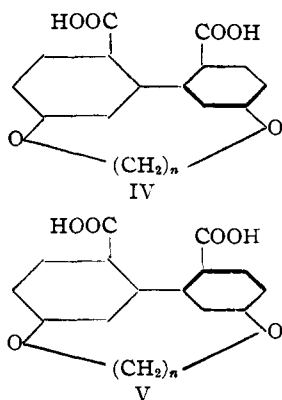
dence<sup>4</sup> to support the view that the two carboxyl groups block each other in the positions of closest proximity and thus render impossible the existence under ordinary conditions of the planar state shown in II. However, when the carboxyl groups are in the *trans*-position (III) the molecule



is able to assume a planar configuration because an *ortho* hydrogen atom is not large enough to interfere with a carboxyl. In the normal rotational oscillations of the two phenyl groups on the bond axis between them, there will be a continuous periodic formation of the symmetrical state III; consequently resolution is impossible.

The 5,5'-(polymethylenedioxy)-diphenic acids (I) are of considerable stereochemical interest. If it is assumed that the two carboxyl groups interfere, an assumption which is unquestionably sound, then these 5,5'-bridged compounds may best be discussed under three headings, depending on the number of methylene groups in the bridge.

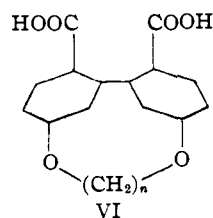
**Case 1.**—The polymethylene chain allows the "*cis*" configuration of the carboxyls to exist, but it is not long enough to permit formation of a molecule with the carboxyls "*trans*" to each other. Free rotation of the biphenyl nucleus within the polymethylene bridge is then out of the question. A pair of enantiomorphs (IV and V) will result



which, if the benzene rings maintain their coaxial relationship and if the carboxyl groups do not slip

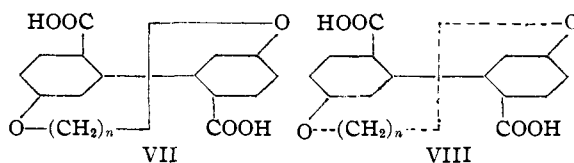
(4) Bell and Robinson, *J. Chem. Soc.*, 1695 (1927); Christie and Kenner, *ibid.*, 123, 779 (1923); Christie, Holderness and Kenner, *ibid.*, 871 (1926); Kenner and Turner, *ibid.*, 2340 (1928); Stanley, McMahon and Adams, *THIS JOURNAL*, 55, 706 (1933).

past one another, should not racemize. The right-hand rings of IV and V are perpendicular to the paper; in formula IV, the carboxyl on the right-hand ring is projecting below the plane of the paper, in formula V the carboxyl is projecting above the plane of the paper; the left-hand rings in both are in the plane of the paper. It is conceivable that a diphenic acid having a relatively small many-membered bridge across the 5,5'-positions, if such a molecule could be synthesized at all, would not be resolvable. The strain imposed by the tightly drawn polymethylene ring would cause the biphenyl nucleus to become non-coaxial, thus permitting sufficient separation of the carboxyl groups to allow them to lie in the same plane (VI) with the resulting formation of a symmetrical and therefore non-resolvable molecule.



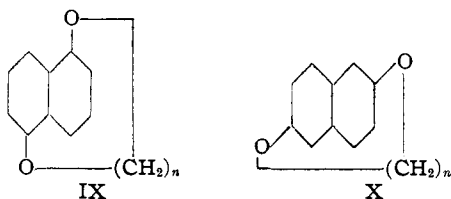
**Case 2.**—In contrast to Case 1, when the polymethylenedioxy chain is long enough the biphenyl nucleus is able to rotate freely within the many-membered ring and optical isomerism is not possible; the molecule is, in effect, an unsubstituted diphenic acid.

**Case 3.**—The polymethylene bridge is larger than in Case 1, smaller than in Case 2 and of sufficient size to permit the carboxyl groups to be "*trans*" to each other. The biphenyl nucleus in the "*trans*" form is then planar. The "*trans*" acid is capable of existing in two enantiomeric forms VII and VIII. In VII the polymethylene

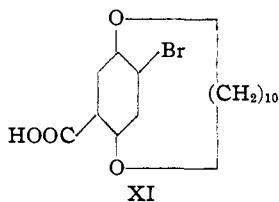


bridge is above the plane of the biphenyl nucleus; in VIII it is below this plane. This type of asymmetry bears a close resemblance to that postulated by Ziegler and Lüttringhaus<sup>5</sup> for the 1,5- and 2,6-disubstituted naphthalenes, IX and X, in which the naphthalene nucleus would have to be incapable of rotation within the many-membered ring.

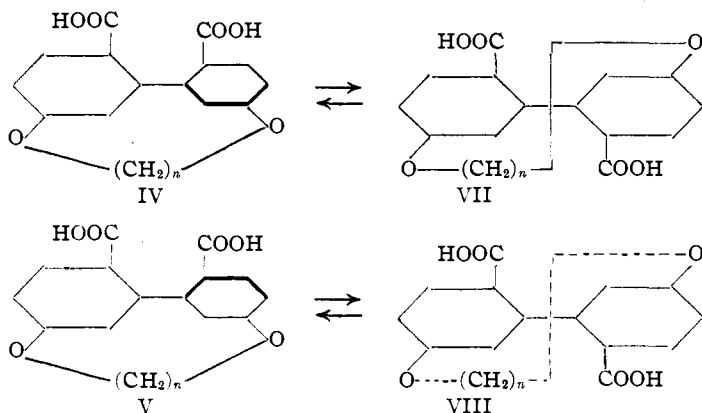
(5) Ziegler and Lüttringhaus, *Ann.*, 511, 1 (1934).



Only within the last few months, optical isomerism resulting from the presence of a many-membered ring attached to a planar structure has been demonstrated experimentally. Lüttringhaus and Gralheer<sup>6</sup> have resolved the substituted benzoic acid (XI); its optical activity undoubtedly arises from the disposition of the decamethylenedioxy bridge either above or below the plane of the benzene nucleus. It is obvious that the benzene nucleus is incapable of complete rotation within the big ring, otherwise resolution would have been impossible.



The enantiomorphous *trans* forms (VII and VIII) will probably be in equilibrium with the enantiomorphous *cis* forms (IV and V) discussed in Case 1. These equilibria are shown below in the pairs of formulas, IV, VII and V, VIII.



When the diphenic acid with a decamethylenedioxy bridge ( $I, n = 10$ ) across the 5,5'-positions is constructed using the models developed by Stuart,<sup>7</sup> it is found that both the *cis* and *trans* modifications are readily obtained and that they are easily interconverted. Complete rotation of

the biphenyl nucleus within the decamethylene bridge is, however, not possible. The substance is thus a representative of Case 3. Hence, the racemic modification will actually be composed of an equilibrium mixture of two pairs of active compounds corresponding to the general formulas IV, VII and V, VIII. Inasmuch as each of the four forms is asymmetric, and since no symmetrical intermediates are involved, the interconversion of IV and VII and of V and VIII is not to be considered a process of racemization but as the equivalent of tautomerization between active forms.

With an octamethylenedioxy bridge ( $I, n = 8$ ), the *cis* modification is easily constructed but the *trans* form can be obtained only at the expense of slight distortion from the normal coaxial biphenyl structure. Here also, the *cis* and *trans* forms are readily interconverted and again rotation of the biphenyl nucleus inside the large ring is, of course, not possible.

A heptamethylenedioxy or hexamethylenedioxy chain ( $I, n = 7, 6$ ), allows the formation of a *cis* bridge but the molecule can no longer be obtained in the *trans* modification. With a pentamethylenedioxy bridge ( $I, n = 5$ ), ring closure cannot be effected even in the *cis* configuration without distorting the co-axis of the two phenyl groups. A very large polymethylenedioxy chain of the order of fifty to one hundred methylenes is apparently necessary for a molecule falling in Case

2, in which free rotation of the biphenyl nucleus within the many-membered ring is possible.

According to the Stuart models any bridge long enough to span the molecule when it is in the *trans* configuration will permit of rotation into the *cis* form. Therefore, it will not be possible to obtain a molecule of this type which can exist solely as the *trans* isomer.

In this investigation the decamethylenedioxy and the octamethylenedioxy acids ( $I, n = 10, 8$ ) were prepared and resolved, thus demonstrating that restricted rotation is produced by a many-membered ring of suitable size. Both acids undergo racemization in dioxane solution. At 23° the half-life of the octamethylenedioxy acid is 1955 minutes, that of the decamethylenedioxy compound 1491 minutes. At 43° the half-life periods are 170 minutes and 120 minutes, respec-

(6) Lüttringhaus and Gralheer, *Naturwissenschaften*, **16**, 255 (1940).

(7) Stuart, *Z. physik. Chem.*, **B27**, 350 (1934).

TABLE I  
 RATE OF RACEMIZATION OF FREE DIPHENIC ACIDS IN DIOXANE<sup>a</sup>

Compound group at 5,5'-positions	Weight, <sup>b</sup> g.	Max. [ $\alpha$ ] <sub>D</sub> calcd.	Rotations in Degrees <sup>c</sup>		Av. $K^d$	Av. dev. $K$	Half-life, min.	Period ratio	
			Time, min.	Initial					
—O—(CH <sub>2</sub> ) <sub>10</sub> —O— <sup>e</sup>	0.0739	+114	15	+0.83	+112	0.000232	0.000024	1,491	1
—O—(CH <sub>2</sub> ) <sub>8</sub> —O— <sup>e</sup>	.0612	-216	48	-1.30	-212	.000177	.000019	1,955	1.32
—O—(CH <sub>2</sub> ) <sub>10</sub> —O— <sup>f</sup>	.0796	+101	44	+0.62	+ 77.9	.00289	.00010	120	1
—O—(CH <sub>2</sub> ) <sub>8</sub> —O— <sup>f</sup>	.0608	-209	54	-1.02	-168	.00204	.00004	170	1.42

<sup>a</sup> The dioxane was purified by refluxing with 10% of its volume of *N* hydrochloric acid for 120 hours. When cold, sodium hydroxide pellets were added, the dioxane separated, dried over anhydrous magnesium sulfate and finally distilled over sodium; b. p. 101° (760 mm.). <sup>b</sup> Made up to 10 cc.;  $l = 1$ . <sup>c</sup> The final rotations in every case were zero. <sup>d</sup>  $K$  calculated according to the equation for a reversible monomolecular reaction. (H. Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 178.) <sup>e</sup> At 23.0  $\pm$  0.2°. <sup>f</sup> At 43.0  $\pm$  0.2°.

tively. Thus the decamethylenedioxy acid racemizes 1.42 times as rapidly as its octamethylenedioxy homolog (see Table I).

The inviting suggestion that racemization takes place by rotation of the biphenyl nucleus within the polymethylenedioxy ring, and that with the larger decamethylenedioxy bridge such free rotation would occur more easily than for the octamethylenedioxy ring, must be excluded on the basis of deductions from examination of the Stuart models previously discussed. If these are even remotely accurate, such free rotation within the many-membered ring of I is impossible when  $n = 10$  or 8. In this connection it is significant that the optically active compound XI is very stable and suffers no racemization after one hour at 90°. Even though the decamethylenedioxy bridge of XI has only a single benzene nucleus to span, free rotation of the benzene ring inside the many-membered bridge is not possible under the conditions described.

It is very likely that the racemization of the polymethylenedioxy diphenic acids is achieved by slippage of the carboxyl groups past one another. On this basis, the most probable explanation for the observed differences in the rates of racemization is that the shorter the bridge across the 5,5'-positions, the less vigorous are the semicircular oscillations which the benzene nuclei may undergo about the bond joining them.

A very striking increase in the rates of racemi-

zation was obtained by dissolving these diphenic acids in dilute aqueous alkali at 34.5° (see Table II). The octamethylenedioxy acid has a half-life of 19.1 minutes, the decamethylenedioxy acid a half-life of 22 minutes. While the data for the octamethylenedioxy acid are accurate to within 5%, the values of the decamethylenedioxy acid may be in error as much as 15% because of the low rotational values involved. Consequently, it appears that within the limits of experimental error the two acids have the same half-life in dilute aqueous alkali. The increase in the rates of racemization in spite of the electrostatic repulsions of the carboxylate ions may mean that such repulsions are relatively unimportant at the distances involved and that other factors must have a greater bearing on the ease with which coplanarity in the "cis" configuration is achieved.

The energy of activation,  $E$ , for the racemization process is the same for the two diphenic acids, approximately 23,000 calories. A survey of the literature reveals that the value of  $E$  is not critical (see Table III). Undoubtedly, this is due to the large experimental error to which its determination is subject. As a consequence, its employment as a criterion of the ease of racemization, and hence of the actual magnitude of the restriction of rotation, is of dubious utility. The half-life periods appear to be much more satisfactory as a qualitative guide.

The type of procedure selected for the synthe-

 TABLE II  
 RATE OF RACEMIZATION OF DIPHENIC ACIDS IN 0.476 *N* SODIUM HYDROXIDE AT 34.5°

Compound group at 5,5'-positions	Weight, <sup>a</sup> g.	Max. [ $\alpha$ ] <sub>D</sub> calcd.	Rotations in degrees <sup>b</sup>		Av. $K^c$	Av. dev. $K$	Half-life, min.	
			Time, min.	Initial				
—O—(CH <sub>2</sub> ) <sub>10</sub> —O—	0.0300	+24.5	4	+0.13	+ 21.7	0.0157	0.0007	22
—O—(CH <sub>2</sub> ) <sub>8</sub> —O—	.0256	-145	4	-0.64	-125	.0181	.0001	19.1

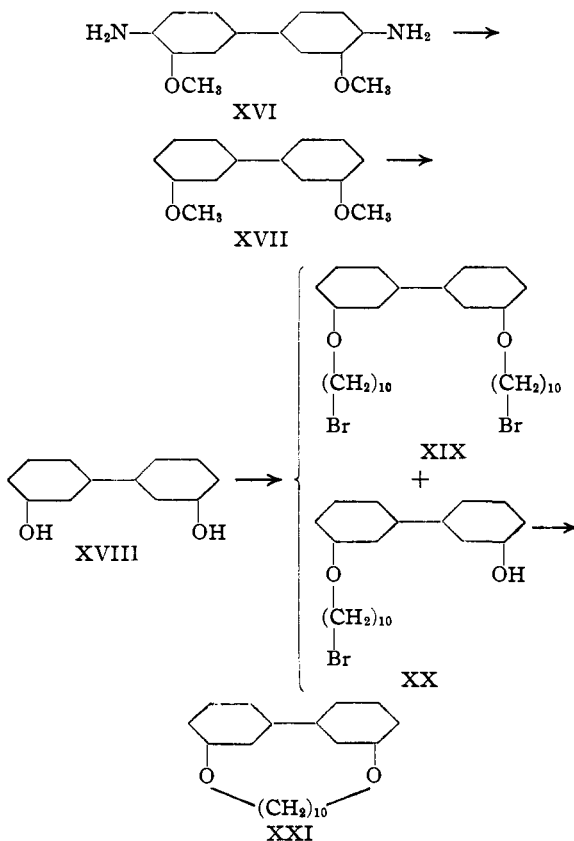
<sup>a</sup> Made up to 5 cc.;  $l = 1$ . <sup>b</sup> The final rotation in each case was zero. <sup>c</sup>  $K$  calculated for a reversible monomolecular reaction.

TABLE III  
COMPARISON OF THE HALF-LIFE AND ACTIVATION ENERGY OF SEVERAL COMPOUNDS IN WHICH RESTRICTED ROTATION EXISTS

Compound	Half-life, min.	Temp., °C.	Energy of activation, cal.	Ref.
<i>N</i> -Benzoyl-4,6,4'-tribromodiphenylamine-2-carboxylic acid	3	17.7	18,200	<sup>a</sup>
<i>N</i> -Benzenesulfonyl-8-nitro-1-naphthylglycine	17	14.9	18,500	<sup>b</sup>
2,2'-Dicarboxy-4,6'-dinitrobiphenyl	215	73.5	26,000	<sup>c</sup>
2,2'-Dicarboxy-4,6,4'-trinitrobiphenyl	407	74.6	22,400	<sup>c</sup>
2-Nitro-6-carboxy-2'-methoxybiphenyl	25	18	20,000	<sup>d</sup>
2-Nitro-6-carboxy-2'- <i>n</i> -propoxybiphenyl	220	18	20,000	<sup>d</sup>
2,2'-Dicarboxy-5,5'-(octamethylenedioxy)-biphenyl	1,955	23	23,000	

<sup>a</sup> Jamison and Turner, *J. Chem. Soc.*, 1652 (1938). <sup>b</sup> Mills and Elliot, *ibid.*, 1296 (1928). <sup>c</sup> Kuhn and Albrecht, *Ann.*, 455, 286 (1927); 458, 221 (1927). <sup>d</sup> Li and Adams, 57, 1565 (1935).

sis of the desired many-membered ring compounds is shown in formulas XVI-XXI. *o*-Dianisidine (XVI) was converted to 3,3'-dimethoxybiphenyl



(XVII) in excellent yields by tetrazotizing and treating with 30% aqueous hypophosphorous acid. This reaction for replacing aromatic amino groups by hydrogen, discovered by Mai,<sup>8</sup> is a very smooth process which apparently is far superior to the more commonly used ethanol procedure. It has been found equally satisfactory for the demination of *o*-tolidine, 2,2'-dimethyl-4,4'-di-

(8) Mai, *Ber.*, 35, 162 (1902).

amino-5,5'-dimethoxybiphenyl and 2,4-diethyl-6-bromoaniline.<sup>9</sup> The hypophosphorous acid deminations studied have been characterized by simplicity of operation and products of high purity. In view of these facts, it is surprising that it has been very infrequently used.<sup>10</sup>

The dimethoxybiphenyl (XVII) was demethylated with hydriodic acid to the 3,3'-dihydroxybiphenyl (XVIII) and the latter converted to 3-hydroxy-3'-( $\omega$ -bromo-*n*-decyloxy)-biphenyl (XX) by treatment with less than the theoretical amount of potassium hydroxide and a large excess of decamethylene bromide. As a by-product, a small amount of the *bis* ether (XIX) was isolated.

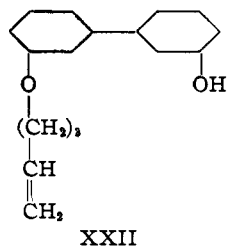
In order to obtain intramolecular cyclization of the half-ether (XX) rather than chain polymerization, it was necessary to carry out the reaction at high dilution. A satisfactory high dilution apparatus was constructed along the lines laid down by Lüttringhaus and Ziegler.<sup>11</sup> The apparatus is discussed in detail in the experimental part. The reaction consisted merely in introducing at very high dilution the half-ether into a boiling, vigorously stirred suspension of anhydrous potassium carbonate and isoamyl alcohol.

Pure 3,3'-(decamethylenedioxy)-biphenyl (XXI) was obtained in 70% yield and shown to be monomeric by molecular weight determinations. That hydrogen bromide had not been eliminated from the side chain of the half-ether with resultant formation of the isomeric olefin (XXII) was demonstrated by absence of reaction of the product with hydrogen in the presence of a platinum catalyst and failure of it to decolorize a 2% potassium permanganate solution. Furthermore, while the

(9) H. R. Snyder and Robert Adams have performed this last reaction in connection with another investigation.

(10) Raiford and Oberst, *Am. J. Pharm.*, 107, 242 (1935).

(11) Lüttringhaus and Ziegler, *Ann.*, 528, 159, 217 (1937).



half-ether (XX) is very soluble in Claisen potash<sup>12</sup> and was found to possess one active hydrogen atom by a Zerewitinoff determination, the cyclization product is insoluble in Claisen potash and gave no methane in the Grignard machine.

Having established a satisfactory synthesis of a decamethylenedioxy bridge across the 3,3'-positions of biphenyl, the next goal was the preparation and resolution of the corresponding diphenic acid (I). This was accomplished by the use of 2,2'-dimethyl-4,4'-diamino-5,5'-dimethoxybiphenyl (XXIII) prepared from 3-nitro-4-methoxytoluene through the hydrazo compound followed by a benzidine rearrangement. Deamination followed by dealkylation gave 2,2'-dimethyl-5,5'-dihydroxybiphenyl (XXIV) identical with the product of this structure synthesized by another route.<sup>13</sup> Moreover, the 2,2'-dimethyl-5,5'-dimethoxybiphenyl on oxidation gave 2,2'-dicarboxy-5,5'-dimethoxybiphenyl, which conformed in properties with the compound prepared by Fieser.<sup>14</sup>

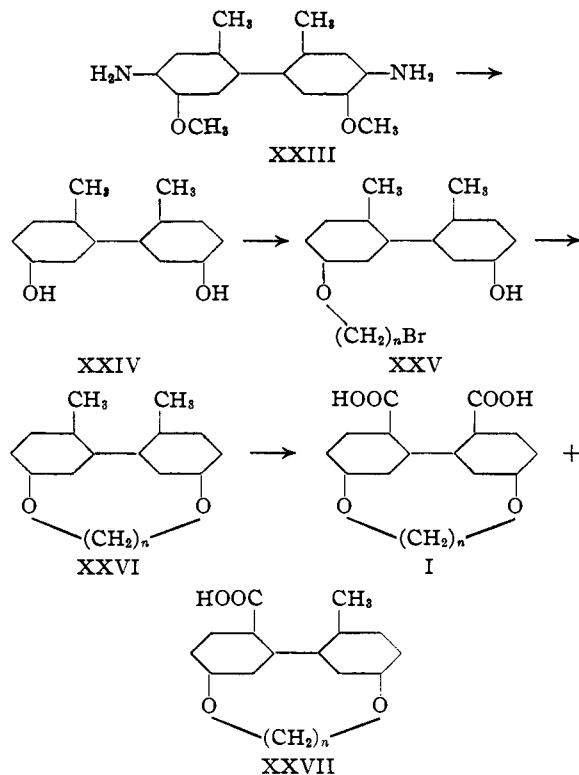
Treatment of the dicresol (XXIV) with ethanolic potassium hydroxide and excess of decamethylene bromide gave the half-ether, 2,2'-dimethyl-5-hydroxy-5'-( $\omega$ -bromo- $n$ -decyloxy)-biphenyl (XXV) which was cyclized to 2,2'-dimethyl-5,5'-(decamethylenedioxy)-biphenyl (XXVI,  $n = 10$ ). Its structure as indicated was established in a manner similar to that used for 3,3'-(decamethylenedioxy)-biphenyl.

The 2,2'-dimethyl-5,5'-(decamethylenedioxy)-biphenyl (XXVI) proved to have interesting properties. When crystallized from petroleum ether it melted at 84–85.5°. Recrystallization from methanol raised the melting point to 110–111°. When the high-melting modification was recrystallized from petroleum ether it was converted back to the low-melting form. While crystallization from methanol and petroleum ether usually gave the high- and low-melting varieties, respectively, this was by no means always the

(12) Claisen, *Ann.*, **418**, 96 (1919).

(13) Pummerer, Puttfarcken and Schopflocher, *Ber.*, **58**, 1817 (1925).

(14) Fieser, *This Journal*, **51**, 2484 (1929).



case. A mixture of the two modifications on standing at room temperature for two months was completely converted to the high-melting form. At 90° such a mixture required but a few minutes for the transformation. Heating the low-melting form very slowly above its melting point resulted in resolidification and subsequent remelting at 110–111°. An X-ray study by Dr. S. T. Gross of this Department showed that the two forms did not exhibit the properties of dimorphs. The possibility that these modifications represent two labile forms corresponding to formulas IV and VII for the diphenic acids and capable of being oriented by a given type of solvent seems unlikely.<sup>15</sup>

Although the 2,2'-dimethyl-5,5'-dimethoxybiphenyl is oxidized to the corresponding dibasic acid with ease, oxidation of 2,2'-dimethyl-5,5'-(decamethylenedioxy)-biphenyl (XXVI,  $n = 10$ ) to the diphenic acid (I,  $n = 10$ ) presented unexpected difficulties. With a large variety of reagents, it was found that when the cyclic ether was not recovered unchanged, it was completely degraded; at best, only traces of acidic materials were obtained. The procedure which finally suc-

(15) In connection with this phenomenon, the alleged *cis-trans* isomerism of  $\alpha$ - and  $\beta$ -*p*-azophenol is of interest. Lauer, Klug and Harrison, *ibid.*, **61**, 2775 (1939).

ceeded involved the use of very small amounts of solvent (aqueous pyridine) and of solid potassium permanganate at about 95°; the yields left much to be desired. Very appreciable amounts of 2-methyl-2'-carboxy-5,5'-(decamethylenedioxy)-biphenyl (XXVII,  $n = 10$ ) were formed along with the desired diphenic acid (I,  $n = 10$ ). The impurity was removed by repeated extraction of the finely powdered mixture with boiling benzene, the monobasic acid being slightly soluble in this medium, the dibasic acid insoluble. Upon recrystallization of the residual material from ethanol, analytically pure 2,2'-dicarboxy-5,5'-(decamethylenedioxy)-biphenyl (I,  $n = 10$ ) was obtained in 20% yield.

The synthesis of 2,2'-dicarboxy-5,5'-(octamethylenedioxy)-biphenyl (I,  $n = 8$ ) was effected by using octamethylene bromide in place of decamethylene bromide. The octamethylene bromide was prepared from suberic acid via the ester and glycol.

As was expected, cyclization of the octamethylene half-ether (XXV,  $n = 8$ ) took place less readily than in the case of the decamethylene compounds. Even though the reaction was run at a considerably higher dilution than that used in forming the decamethylenedioxy bridge the yield of analytically pure cyclic ether was less. Oxidation of the cyclic ether (XXVI,  $n = 8$ ) was attended with the same difficulties encountered in the preparation of the decamethylenedioxydiphenic acid. The yield of pure 2,2'-dicarboxy-5,5'-(octamethylenedioxy)-biphenyl (I,  $n = 8$ ) was 23%.

The decamethylenedioxydiphenic acid (I,  $n = 10$ ) was resolved readily through the dibrucine salt. Only a single salt, that of the *d*-acid, was obtained. On being dissolved in chloroform mutarotation occurred, about thirty hours at room temperature being required for the attainment of equilibrium.

Resolution of the octamethylenedioxydiphenic acid (I,  $n = 8$ ) was attempted via the brucine salt. Although a beautifully crystalline compound was obtained there was no evidence of resolution and the recovered acid was inactive. The use of cinchonine led to resolution. Only a single salt, that of the *l*-acid, was isolated. When dissolved in chloroform it mutarotated; in about sixty hours at room temperature equilibrium was reached.

Decomposition of the salts with cold hydrochloric acid gave the active acids.

### Experimental

**3,3'-Dimethoxybiphenyl.**—A mixture of 400 cc. of water and 31 cc. of concentrated hydrochloric acid (sp. gr. 1.19)

was heated to boiling, the flame removed, and 40 g. of technical *o*-dianisidine added. The hot mixture was stirred for about three minutes and then cooled in an ice-salt-bath, while mechanical stirring was maintained. When the temperature reached 15°, 35 cc. more of concentrated hydrochloric acid was added. After the temperature of the mixture had fallen to 10–13° a solution of 23.3 g. of 97% sodium nitrite in 50 cc. of water was added in about fifteen minutes. Stirring was maintained for about twenty minutes more at 5–10° and then the mixture was filtered rapidly with suction.

The cold, clear red filtrate was poured rapidly into a 2-l. flask which contained 325 cc. of ice cold 30% hypophosphorous acid. Immediate evolution of nitrogen occurred. The loosely stoppered flask was placed in a refrigerator for about ten hours and then allowed to stand at room temperature for another ten hours. The lower dark brown layer was separated from the aqueous phase and the aqueous layer extracted with ether. The brown oil was combined with the ether extracts and the solution washed with 20% aqueous sodium hydroxide and then dried over anhydrous potassium carbonate. After filtration, the ether solution was concentrated on the steam cone and the residue distilled under diminished pressure. After a forerun of 1–1.5 g., b. p. 155–157° (4 mm.), the main fraction, b. p. 157–159°, was obtained. By raising the bath temperature to 240° an additional 3–4 g. resulted; yield, 23–27.5 g. (66–78%). All three fractions usually crystallize spontaneously; if they do not, rubbing with a glass rod easily causes crystallization. The melting point of the main fraction was 41–43° (cor.); the other two melted a degree or two lower. This material was used without further purification. Recrystallization from 60% aqueous ethanol by volume, gave flat, colorless needles, m. p. 42–43.5° (cor.).

This procedure was repeated by Dr. W. E. Bachmann.<sup>16</sup> He found a melting point of 34–35°, in common with all others who have prepared 3,3'-dimethoxybiphenyl. On seeding a melt, or a solution of his material with crystals of the 43.5° modification, Bachmann was able to effect conversion to the high-melting form.

By use of this deamination procedure<sup>8</sup> *o*-tolidine was converted to 3,3'-dinethylbiphenyl in 76–82% yield.

**3,3'-Dihydroxybiphenyl.**—This compound was prepared by the procedure of Mascarelli and Vinsintin<sup>17</sup>; yield, 88–93%. In order to obtain a perfectly white product recrystallization from water was necessary; prismatic needles, several centimeters long, m. p. 125.5–126° (cor.). Mascarelli and Vinsintin report yellow prismatic needles, m. p. 123°; Teichmann, m. p. 124°.<sup>18</sup> 3,3'-Dihydroxybiphenyl is moderately soluble in boiling water; slightly soluble in cold water.

**3-Hydroxy-3'-( $\omega$ -bromo-*n*-decyloxy)-biphenyl and bis-3,3'-( $\omega$ -Bromo-*n*-decyloxy)-biphenyl.**—In the course of five hours 60 cc. of 1.43 *N* ethanolic potassium hydroxide (0.45 mole equiv.) was added to a boiling, well-stirred solution of 34.7 g. (1 mole equiv.) of 3,3'-dihydroxybiphenyl and 375 g. (6.8 mole equiv.) of decamethylene bromide in 250 cc. of absolute ethanol. Stirring and

(16) Private communication.

(17) Mascarelli and Vinsintin, *Gazz. chim. ital.*, **62**, 358 (1932).

(18) Teichmann, *Inaug. Dissertation*, p. 17, Stuttgart (1894).



heating were continued for twenty minutes longer, at which time the mixture was neutral to litmus. The hot mixture was filtered and the potassium bromide washed with boiling ethanol. The filtrate and washings were combined, the ethanol boiled off and the hot residue transferred to a Pyrex separatory funnel where it was extracted with six 500-cc. portions of boiling water. On standing overnight in the icebox, the aqueous extracts deposited 20 g. of pure 3,3'-dihydroxybiphenyl.

The water-insoluble material was distilled at approximately 0.01 mm. pressure. In this way 350 g. of decamethylene bromide, boiling in the neighborhood of 130°, was recovered.

The dark, sirupy residue was treated with 100 cc. of methanol. After cooling the mixture in an ice-bath, 2.2 g. of a light brown precipitate was removed by filtration. This solid was treated with Norit in boiling benzene and precipitated by the addition of 95% ethanol as a tan crystalline powder. After three more recrystallizations from benzene-ethanol mixtures and one recrystallization from methanol-benzene, a white crystalline material, m. p. 86-87° (cor.), was obtained. This compound had the composition of *bis*-3,3'-( $\omega$ -bromo-*n*-decyloxy)-biphenyl.

*Anal.* Calcd. for  $C_{32}H_{48}O_2Br_2$ : C, 61.52; H, 7.75. Found: C, 61.43; H, 7.92.

It was readily soluble in either toluene or benzene; moderately soluble in either boiling ethanol or butanol-1, but insoluble in the cold. It was insoluble in methanol, petroleum ether (b. p. 60-110°) and Claisen potash.<sup>12</sup>

The residue obtained on evaporation of the methanol mother liquor of the *bis* ether was molecularly distilled at  $10^{-4}$  mm. (bath temperature 130-150°). The distillate was twice recrystallized from petroleum ether (b. p. 60-110°); white needles, m. p. 51.5-52.5° (cor.); yield, 11.5-13.9 g. (30-40% based on the potassium hydroxide).

*Anal.* Calcd. for  $C_{22}H_{29}O_2Br$ : C, 65.17; H, 7.21; Br, 19.75. Found: C, 65.26; H, 7.35; Br, 19.91. Zerewitinoff: 0.2233 g. gave 13.4 cc. of methane (S. T. P.); calcd. for one active hydrogen atom, 12.4 cc.

This half-ether is readily soluble in methanol, glacial acetic acid, ethyl acetate and boiling petroleum ether (b. p. 60-110°). It is insoluble in saturated aqueous potassium hydroxide and in 10% aqueous sodium hydroxide, but dissolves very readily in Claisen potash.

**High-dilution Apparatus for Cyclizations.**—Lüttringhaus and Ziegler<sup>11</sup> have given a brief description of their high-dilution apparatus. A more detailed report is desirable since it has been our experience that the proper design and dimensions of the high-dilution equipment are important for its successful operation. The solvent (isoamyl alcohol) is distilled up through tube C, which is insulated with "85% magnesia lagging," and the condensed vapor returned to the reaction flask by way of the tube containing the U bend. The U portion of the return tube is immersed in a bath of water. Since a constant flow of cold water through this bath impedes the circulation of the alcohol by causing excessive cooling, it is best to replace the water with cold only after it has become quite hot. The solution containing the compound to be cyclized is introduced into the system at a point about 70 cm. from the reaction flask; it is displaced from the reservoir flask

with mercury, the rate of inflow being regulated by the height of the mercury column and a fine capillary A.

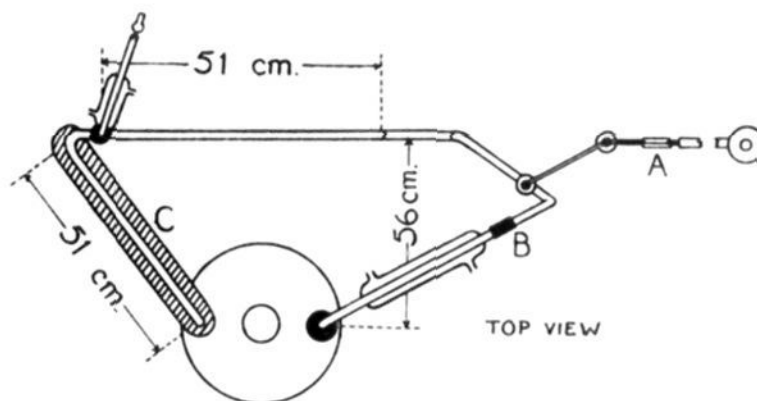


Fig. 1.

Not only does dilution occur because of the circulation of solvent, but also by virtue of a substantial amount of distillation into the return tube. In fact, it is necessary to place a short, water-cooled condenser around this tube in order to control the extent of "boiling up" into this arm of the apparatus. Generally the vapors are condensed at a point just short of the rubber connection B.

The cyclic system was constructed of Pyrex tubing having an internal diameter of 13 mm. The arm joining the reservoir to the cyclic system had an internal diameter of 6 mm., and the tube leading into the reservoir was of 3-mm. internal bore. Rubber stoppers were satisfactory.

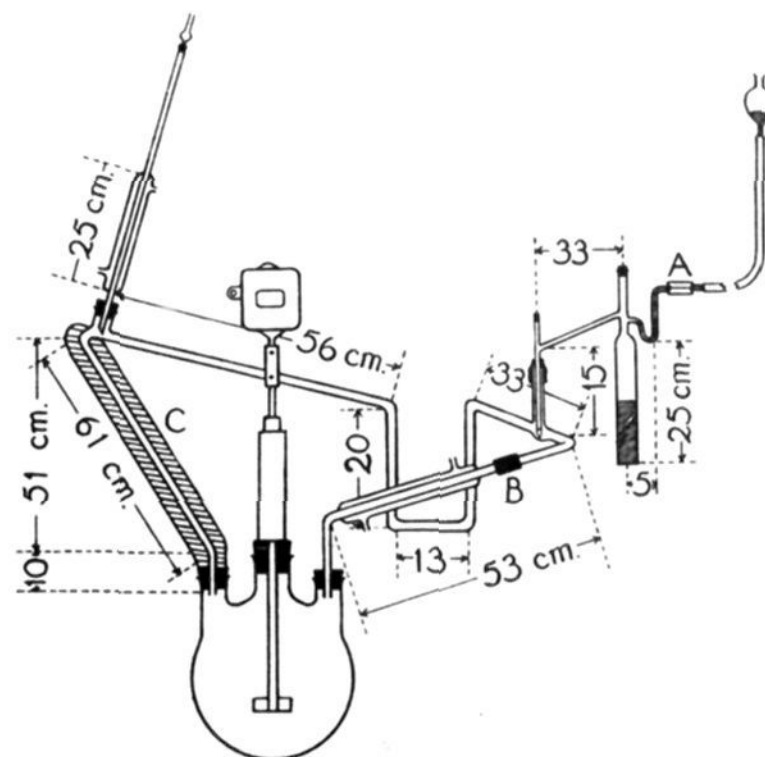


Fig. 2.

A stainless steel, mercury-sealed stirrer powered by a heavy duty, direct-drive motor was used. The introduction of a stream of nitrogen underneath the mantle of the stirrer in order to prevent the solvent from distilling up through the stirrer shaft was recommended by Lüttringhaus and Ziegler; this precaution was found to be unnecessary. The reaction flask was immersed in a deep oil-bath heated to 200-225°. At this temperature excellent circulation of the isoamyl alcohol resulted.

The system was protected from atmospheric moisture by a calcium chloride tube at the top of the condenser.



Lüttringhaus<sup>19</sup> has recently reported a simplification of the dilution apparatus but no details are given. Here again, it would undoubtedly be desirable to have a complete description of the machine.

**3,3'-(Decamethylenedioxy)-biphenyl.**—Into the 2-l. three-necked reaction flask of the high-dilution apparatus were placed 650 cc. of dry isoamyl alcohol and 4.5 g. of finely powdered, anhydrous potassium carbonate which had been heated in an open dish over a free flame for thirty minutes. A solution of 5.4 g. of 3-hydroxy-3'-( $\omega$ -bromo-*n*-decyloxy)-biphenyl in 850 cc. of dry isoamyl alcohol was added to the boiling alcohol-potassium carbonate mixture over a period of twenty-five (not consecutive) hours. After stirring and heating for an additional hour the mixture was allowed to cool, filtered and half of the solvent removed by distillation. White needles were obtained on cooling. Further concentration of the solution produced light tan needles. Recrystallization from methanol gave 3.1 g. (70%) of long white needles; m. p. 116.5–117.5° (cor.). The cyclic ether is readily soluble in petroleum ether (b. p. 30–60°), benzene, and chloroform; moderately soluble in boiling methanol, insoluble in cold methanol.

*Anal.* Calcd. for C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>: C, 81.48; H, 8.64; mol. wt., 324. Found: C, 81.55; H, 8.60; mol. wt. (b. p. chloroform) 285; (m. p. benzophenone) 330.

In order to eliminate the possibility that hydrogen bromide had been eliminated from the decamethylene chain to give the isomeric compound with a terminal double bond, a quantitative hydrogenation study in dioxane solution, using platinum oxide as catalyst, was made. No hydrogen was absorbed and the starting material was recovered unchanged. The absence of a double bond was further demonstrated by the failure of this substance to decolorize a 2% potassium permanganate solution.

A Zerewitinoff determination showed the absence of any active hydrogen atoms, and the compound was insoluble in Claisen potash, thus proving that a phenolic hydroxyl group was not present.

**3-Nitro-4-hydroxytoluene.**—As the yields obtained by previous investigators<sup>20</sup> could not be duplicated, changes were made which resulted in good yields.

A mixture of 225 g. of *p*-cresol, 700 cc. of benzene and 500 cc. of glacial acetic acid was placed in a reaction flask, cooled to 0–5° and kept at this temperature during the nitration. With mechanical stirring, 225 cc. of concentrated nitric acid (sp. gr. 1.42) was allowed to drop in during nine and one-half hours. If at any time the temperature of the mixture tended to rise above 0–5°, crushed ice was added directly.

Water was now added and the benzene layer separated and washed. The benzene layer was steam distilled; after the benzene was removed, which always contained some nitroresol, the nitroresol was steam distilled and formed yellow needles. The nitroresol in the benzene distillate was then extracted with 10% aqueous sodium hydroxide, the alkaline extract acidified and cooled.

In all, 232–245 g. (73–77%) of 3-nitro-4-hydroxytoluene

was obtained, m. p. 32–33° (cor.). Schultz reports m. p. 33°; Baranger m. p. 32°.

**3-Nitro-4-methoxytoluene.**—This was prepared by the method of De Vries<sup>21</sup>; yellow oil, b. p. 148–150° (3 mm.); yield 73–78%.

**2,2'-Dimethyl-4,4'-diamino-5,5'-dimethoxybiphenyl.**—In a 2-l. three-necked flask fitted with an efficient stirrer and reflux condenser was placed a mixture of 40 g. of 3-nitro-4-methoxytoluene, a solution of 44 g. of sodium hydroxide in 250 cc. of water and 250 cc. of 95% ethanol. A bath temperature of 80–85° and vigorous stirring was maintained throughout the reduction. The third opening in the flask was stoppered and from time to time the stopper removed for the addition of 62 g. of zinc dust (at least 90% zinc) portionwise in seventeen to twenty minutes. After three to five minutes, 625 cc. of 95% ethanol, preheated to 70°, was added. Within five to ten minutes after addition of the ethanol, the bright orange-red color faded to a pale yellow. The hot mixture was then filtered by suction, the solids washed with about 100 cc. of boiling ethanol and the combined filtrates cooled rapidly to 10°. With stirring, a solution cooled to 0° of 625 cc. of concentrated hydrochloric acid in 250 cc. of water was introduced. A deep cherry-red color appeared and a heavy precipitate formed.

After standing overnight at room temperature, the mixture was filtered. The moist hydrochloride was added to 650 cc. of boiling water, stirred for a few minutes and the solution filtered from any insoluble orange-red material. The hot filtrate was made strongly alkaline, cooled rapidly to about 5° and held at this temperature for about an hour. The free base was filtered and washed with water. It was a white powder which, on a few hours exposure to the air, took on a light lavender color; yield 10.8–12.7 g. (33–39%).

For analysis, the amine was recrystallized from 80% ethanol by volume; thin white plates, m. p. 155–156° (cor.).

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>N<sub>2</sub>: C, 70.59; H, 7.36; N, 10.29. Found: C, 70.60; H, 7.17; N, 10.50.

**2,2'-Dimethoxy-5,5'-dimethylazobenzene.**—The water-insoluble orange-red material from the previous preparation, of which there was several grams, was purified by recrystallization from petroleum ether (b. p. 60–110°) followed by several crystallizations from methanol; orange-red prisms which soften at about 160° and melt at 174–175° (cor.).

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub>: C, 71.11; H, 6.66; N, 10.37. Found: C, 71.00; H, 6.99; N, 10.20.

This azo compound could be converted to the 2,2'-dimethyl-4,4'-diamino-5,5'-dimethoxybiphenyl by essentially the same procedure used for direct conversion of the nitro compound. From 42 g. of crude azo compound (m. p. 140–160°), using as reagents 105 g. of sodium hydroxide in 450 cc. of water and 1 l. of 95% ethanol, 150 g. of zinc dust and 400 cc. of 95% ethanol, 1400 cc. of concentrated hydrochloric acid in 650 cc. of water, 21 g. of the diamino compound was obtained.

**2,2'-Dimethyl-5,5'-dimethoxybiphenyl.**—In a 2-liter beaker containing 800 cc. of water and 33 cc. of concentrated hydrochloric acid heated to boiling, was added with mechanical stirring 33 g. of 2,2'-dimethyl-4,4'-diamino-

(19) Lüttringhaus, *Ber.*, **72**, 894 (1939).

(20) Schultz, *ibid.*, **40**, 4324 (1907); Baranger, *Bull. soc. chim.*, [4] **49**, 1213 (1931).

(21) De Vries, *Rec. trav. chim.*, **28**, 287 (1909).

5,5'-dimethoxybiphenyl. After two minutes, the hot mixture was cooled rapidly to 10° and 40 cc. more of concentrated hydrochloric acid added. The mixture was then cooled to 0–5° and a solution of 17.5 g. of sodium nitrite (97%) in 60 cc. of water was added in the course of fifteen minutes. After thirty minutes at 0–5° a small amount of dark material was filtered off and the filtrate treated with 1200 cc. of ice cold 30% aqueous hypophosphorous acid. Immediate evolution of nitrogen occurred. The reaction flask was stoppered loosely and placed in a refrigerator for fourteen hours. It was then allowed to stand at room temperature for an additional twenty-four hours. The tan colored solid, which separated, was filtered, dried and distilled, b. p. 147–148° (3 mm.) (bath temperature raised to 250°). No fractionation was attempted. The distillate crystallized on cooling. It was dissolved in 200 cc. of petroleum ether (b. p. 30–60°) and the solution washed twice with 10% aqueous sodium hydroxide and then with water. After removal of the solvent, a white crystalline mass resulted; yield 24.5–25 g. (83–85%). For analysis the compound was recrystallized from dilute acetic acid; small, white crystals, m. p. 56.5–57.5° (cor.).

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>: C, 79.76; H, 7.50. Found: C, 79.56; H, 7.61.

**2,2'-Dimethyl-5,5'-dihydroxybiphenyl.**—A mixture of 25 g. of 2,2'-dimethyl-5,5'-dimethoxybiphenyl and 500 cc. of 57% aqueous hydriodic acid was refluxed vigorously for five hours. The water in the condenser was maintained at 80–95° so that the methyl iodide which formed would escape and thus not cause bumping. After two to three hours of refluxing, the dihydroxy compound usually crystallized spontaneously. After cooling in an ice-bath, the solid was filtered through a sintered-glass funnel and washed with water. The crystals were dissolved in 125 cc. of 10% aqueous sodium hydroxide and any turbidity removed by filtration. It was then acidified and cooled, the solid collected; yield, 21.7 g. (98%). Recrystallization from aqueous ethanol gave large prismatic needles which softened at 228°, m. p. 235–236° (cor.) to a dark melt. Pummerer, Puttfarcken and Schopfloch<sup>13</sup> prepared this compound in another way and reported m. p. 229°.

**2,2'-Dicarboxy-5,5'-dimethoxybiphenyl.**—To a mixture of 0.2 g. of 2,2'-dimethyl-5,5'-dimethoxybiphenyl and 50 cc. of water heated on a steam cone was added with vigorous stirring in 10-cc. portions over the course of an hour 60 cc. of 2% aqueous potassium permanganate. After heating an additional hour, the mixture was cooled in an ice-bath and sulfur dioxide passed in to dissolve the manganese dioxide and destroy any unreacted potassium permanganate. The white solid was filtered and treated with dilute aqueous sodium hydroxide. A small amount of unoxidized starting material was thus recovered. Upon acidification of the alkaline solution, dimethoxydiphenic acid was obtained. It was again dissolved in alkali and precipitated with acid. The product weighed 0.085 g. (34%) and formed a crystalline powder which began to soften at 213°, m. p. 231–233° (cor.).

*Anal.* Calcd. for C<sub>18</sub>H<sub>14</sub>O<sub>6</sub>: C, 63.58; H, 4.63. Found: C, 63.69; H, 4.87.

Fieser,<sup>14</sup> who prepared this compound by another method, reported m. p. 234° (cor.).

This diphenic acid was converted into the corresponding 1,6-dimethoxyfluorenone-4-carboxylic acid at a somewhat lower temperature than that described by Fieser. It melted at 297–298°; Fieser reported 303° (cor.).

**2,2' - Dimethyl - 5 - hydroxy - 5' - (ω - bromo - *n*-decyloxy)-biphenyl.**—In the course of seventy minutes, 31.1 cc. of 1.43 *N* ethanolic potassium hydroxide (0.44 mole equiv.) was added to a boiling, well-stirred solution of 22.6 g. (1 mole equiv.) of 2,2'-dimethyl-5,5'-dihydroxybiphenyl and 250 g. of decamethylene bromide (8 mole equiv.) in 150 cc. of absolute ethanol. Stirring and heating were continued for seventy minutes and the hot mixture was extracted with 600 cc. of boiling water. The lower layer of decamethylene bromide on cooling deposited crystals of the unchanged dicresol; the mixture was diluted with 200 cc. of petroleum ether (b. p. 30–60°) and the insoluble dicresol filtered. The upper aqueous layer after standing overnight in an icebox deposited crystals of the unchanged dicresol. In all, 13.5 g. of the 2,2'-dimethyl-5,5'-dihydroxybiphenyl was recovered.

After removal of the petroleum ether from the decamethylene bromide layer, the bromide was distilled at 2 mm. (bath temperature 180–190°) and 230 g. recovered. The solution of the residue in 75 cc. of methanol was cooled in an ice-bath for several hours and then decanted from a small amount of brown oily material which had separated. The methanol was then removed and the product molecularly distilled at 10<sup>-4</sup> mm. At a bath temperature of 110–120°, a small amount of distillate chiefly decamethylene bromide and dicresol was obtained. The bath temperature was then maintained at 180–190° and a very pale yellow oily distillate resulted which turned to a white, creamy crystalline mass on standing overnight. This material melted at 42–44° (cor.). Attempts at recrystallization from methanol or petroleum ether (b. p. 30–60°) were unsuccessful, oils resulting; yield, 11.5–13.1 g. (60–68%). The refractive index of supercooled product was *n*<sup>20</sup><sub>D</sub>, 1.5559.

The half-ether could also be purified without recourse to molecular distillation by subjecting the residue from methanol to a series of fractional extractions with boiling petroleum ether (b. p. 30–60°) in which the half-ether is quite soluble. The dicresol is completely insoluble and the decamethylene bromide much more soluble than the half-ether. The yield is about the same.

The product is very soluble in methanol and ethyl acetate, quite soluble in boiling petroleum ether (b. p. 30–60°) and moderately soluble in the cold. It is soluble in Claisen potash.

*Anal.* Calcd. for C<sub>24</sub>H<sub>38</sub>O<sub>2</sub>Br: C, 66.51; H, 7.62; Br, 18.48. Found: C, 66.34; H, 7.92; Br, 18.34.

**2,2' - Dimethyl - 5,5' - (decamethylenedioxy) - biphenyl.**—Into the 2-liter three-necked reaction flask of the high dilution apparatus were placed 650 cc. of dry isoamyl alcohol and 7 g. of finely powdered, freshly dried anhydrous potassium carbonate. The mixture was stirred vigorously while boiling and a solution of 7.5 g. of 2,2'-dimethyl-5-hydroxy-5'-(ω-bromo-*n*-decyloxy)-biphenyl in 850 cc. of dry isoamyl alcohol was added to the reaction flask in thirty-five hours (not consecutive). After stirring and heating for an additional hour, the mixture was cooled. It was filtered and the amyl alcohol removed by distilla-

tion under diminished pressure. The residue was treated with 150 cc. of boiling petroleum ether (b. p. 30–60°) and the solution filtered to remove a small amount of brown, amorphous material. The petroleum ether was evaporated at room temperature and the fine tan crystals which formed were filtered, m. p. 84–84.5° (cor.); yield, 4.65 g. (76%). The product was purified by recrystallization from methanol; white crystals, m. p. 110–111° (cor.). When this material was again crystallized from petroleum ether (b. p. 30–60°), it was converted back to the low-melting form; white crystals, m. p. 85–85.5° (cor.). In some cases the reversion of the forms by change of solvent did not take place. Seeding with high- or low-melting forms in either solvent, however, usually gave the same product as the seed. The transformation of the low-melting into the high-melting form proceeded rapidly at temperatures above 85.5°.

*Anal.* Calcd. for  $C_{24}H_{32}O_2$ : C, 81.82; H, 9.09; mol. wt., 352. Found: C, 81.66; H, 8.85; mol. wt. (b. p.  $CHCl_3$ ), 355.

**2,2' - Dicarboxy - 5,5' - (decamethylenedioxy) - biphenyl and 2 - Carboxy - 2' - methyl - 5,5' - (decamethylenedioxy) - biphenyl.**—A number of unsuccessful attempts were made to oxidize the cyclic ether. After being refluxed with aqueous potassium permanganate for eight hours it was quantitatively recovered. In aqueous acetone, acetone, aqueous pyridine and benzene–water the potassium permanganate was either without effect or it caused complete destruction of the cyclic ether. An attempted oxidation with potassium ferricyanide<sup>22</sup> gave no acidic products and only a 25% recovery of starting material.

The following procedure was found to be reliable. A solution of 0.7 g. of 2,2'-dimethyl-5,5'-(decamethylenedioxy)-biphenyl in 13 cc. of reagent pyridine and 5 cc. of water was heated on a steam cone. Gradually, 4.6 g. of finely powdered potassium permanganate was added in the course of five hours. During the addition, more solvent was introduced as follows; after one hour 7.6 cc. of pyridine and 2.4 cc. of water, after two hours 14 cc. of pyridine and 4.4 cc. of water, after three hours 7.6 cc. of pyridine and 2.4 cc. of water. The reaction mixture was swirled vigorously from time to time. When all the permanganate had been reduced, 40 cc. of water and 1.0 g. of permanganate were added and the heating continued until the purple color had gone. Another 0.5 g. of permanganate was then introduced and allowed to react. Most of the pyridine and water was now removed by means of an air blast, finely powdered ice was added and the manganese dioxide destroyed with a stream of sulfur dioxide. After several hours in an ice-bath, the solid was filtered.

The dry crude finely powdered material thus obtained from 2.83 g. of cyclic ether was treated with 15 cc. of refluxing benzene for three hours and the mixture filtered hot. The extraction was repeated with another 15 cc. of benzene. The white powder was then treated with 100 cc. of hot 5% aqueous sodium hydroxide and the brown solids removed by filtration. Upon acidification of the filtrate and cooling, the product was obtained. This was not entirely free from monobasic acid and all the operations just mentioned were repeated. There was

(22) Ruzicka, de Graaff and Hosking, *Helv. Chim. Acta*, **14**, 238 (1931).

finally obtained 0.66 g. (20%) of pure product. It had a m. p. 285–290° (cor.) with decomposition when plunged into a bath preheated to 250°.

The acid is insoluble in di-*n*-butyl ether, chloroform and benzene, soluble in dioxane, glacial acetic acid, cold 2% aqueous sodium hydroxide and hot 5% aqueous sodium hydroxide. In cold 5% aqueous sodium hydroxide it is only moderately soluble. It dissolves readily in 10% aqueous sodium hydroxide at 90° but on cooling to room temperature the sodium salt is precipitated.

*Anal.* Calcd. for  $C_{24}H_{28}O_6$ : C, 69.90; H, 6.80. Found: C, 70.03, 69.81; H, 6.71, 6.92.

Upon evaporation of the benzene extracts, a mixture of mono- and dibasic acids was obtained. By dissolving 0.8 g. of this material in 85 cc. of hot 5% aqueous sodium hydroxide and cooling the solution to room temperature, a mass of white crystals was obtained. These were dissolved in boiling water and the solution acidified with hydrochloric acid. The crude monobasic acid thus obtained was leached with cold 5% aqueous sodium hydroxide to remove traces of dibasic acid. The residue was dissolved in hot 1% aqueous sodium hydroxide, extracted with boiling petroleum ether (b. p. 60–110°) and then treated with Norit and filtered. Upon acidification of the clear hot filtrate and cooling in an ice-bath for several hours, the product separated. After two recrystallizations from petroleum ether (b. p. 60–110°) and one from aqueous ethanol it was obtained pure; white crystals, softening at 155°, m. p. 163–165° (cor.).

The acid is soluble in ethanol, carbon tetrachloride and ethyl acetate, insoluble in cold 10%, 5% or 2.5% aqueous sodium hydroxide. It is slightly soluble in cold 1% aqueous sodium hydroxide. At 95° it is only slightly soluble in 10% aqueous sodium hydroxide, moderately soluble in 5% and readily soluble in 1%.

*Anal.* Calcd. for  $C_{24}H_{30}O_4$ : C, 75.38; H, 7.85. Found: C, 75.18; H, 8.15.

**Resolution of 2,2'-Dicarboxy-5,5'-(decamethylenedioxy)-biphenyl.**—To 0.629 g. of 2,2'-dicarboxy-5,5'-(decamethylenedioxy)-biphenyl in 250 cc. of hot methanol was added a solution of 1.21 g. of anhydrous brucine in 15 cc. of methanol. After removing 160 cc. of methanol, the solution was allowed to stand at room temperature for twenty-four hours. Large mushroom-like clusters of crystals separated which were freed from mother liquor by decantation; yield, 1.415 g. (77.2%). Further crops were obtained by concentration of the mother liquor. These were identical with the first crop. Furthermore, when the salt was allowed to crystallize in the course of a week it had the same rotation as the crystals obtained by more rapid precipitation; m. p. 155–163° (cor.).

*Anal.* Calcd. for  $C_{24}H_{28}O_6 \cdot 2C_{23}H_{26}O_4N_2 \cdot 4CH_3OH$ : C, 66.86; H, 7.22; N, 4.22. Found: C, 66.99; H, 6.97; N, 4.49.

*Rotation.* 0.052 g. made up to 5 cc. with chloroform at 20° gave  $\alpha_D -0.58^\circ$ ; *l*, 1;  $[\alpha]^{20}_D -55.8^\circ$ . In about thirty hours the salt had mutarotated to a constant value of  $-33^\circ$ .

**d - 2,2' - Dicarboxy - 5,5' - (decamethylenedioxy) - biphenyl.**—A mixture of 1.27 g. of finely ground dibrucine salt and 100 cc. of 20% ice cold hydrochloric acid was

allowed to stand for several hours in an ice-bath. The solids were collected on a sintered glass crucible and dried overnight in a vacuum desiccator. The cold hydrochloric acid filtrate was then added to the finely powdered mixture of acid and unreacted salt. After standing in an ice-bath for three hours the mixture was filtered, the active acid washed with several hundred cubic centimeters of ice cold 20% hydrochloric acid, then with increasingly dilute acid and finally with water. After drying *in vacuo* over potassium hydroxide the product weighed 0.355 g. (90%). The active acid when plunged into a bath preheated to 250° has a m. p. 280–290° (cor.) with decomposition (see Table I for rotation and racemization constants).

*Anal.* Calcd. for  $C_{24}H_{28}O_6$ : C, 69.90; H, 6.80. Found: C, 69.91; H, 6.88.

**Diethyl Suberate.**—This was prepared from suberic acid by the procedure of Micovic<sup>23</sup>; b. p. 140–141° (8 mm.); yield, 90%.

**Octamethylene Glycol.**—A mixture of 410 g. of ethyl suberate was reduced<sup>24</sup> over 40 g. of copper chromite catalyst at 250° and 6000 pounds pressure. The reaction mixture was diluted with ethanol, the catalyst removed by filtration and the ethanol distilled off. The residue was distilled *in vacuo*; yield, 236 g. (90%); b. p. 154–156° (12 mm.).

**Octamethylene Bromide.**—Dry hydrogen bromide was passed into a well-stirred melt of 236 g. of octamethylene glycol maintained at a bath temperature of 90–95°, until the mass was saturated. After saturation, the temperature of the bath was raised to 140°, and a rapid stream of hydrogen bromide was passed in for eight hours longer. The product was cooled, diluted with benzene and decanted from the small amount of water remaining in the flask. The benzene was then removed by distillation and the product distilled under diminished pressure, b. p. 118–120° (2 mm.); yield, 330 g. (75%).

**2,2' - Dimethyl - 5 - hydroxy - 5' - ( $\omega$  - bromo - *n* - octyloxy) - biphenyl.**—In seventy minutes 18 cc. of ethanolic potassium hydroxide (1.43 *N*) (0.37 mole equiv.) was run into a refluxing, vigorously stirred solution of 15 g. (1 mole equiv.) of 2,2'-dimethyl-5,5'-dihydroxybiphenyl and 150 g. (7.9 mole equiv.) of octamethylene bromide in 90 cc. of absolute ethanol. Stirring and heating were continued for another thirty-five minutes and then the hot mixture was extracted with 350 cc. of boiling water. The octamethylene bromide phase was cooled to room temperature, diluted with petroleum ether (b. p. 30–60°) and the crystals of dicresol isolated by filtration. The aqueous layer also deposited 2,2'-dimethyl-5,5'-dihydroxybiphenyl; the total recovery was 9.5 g. After removal of the petroleum ether the excess octamethylene bromide was recovered by distillation at 2 mm. (bath temperature, 185°). The residue was molecularly distilled at 10<sup>-4</sup> mm. The first fraction, which was collected at a bath temperature of 95–115°, consisted of residual octamethylene bromide and dicresol. The main fraction, obtained at a bath temperature of 140–160°, was a white solid which melted on reaching room temperature. By raising the bath temperature to 190–200° a third fraction was ob-

tained. It remained crystalline at room temperature and doubtless was the *bis* ether. In other runs none of the *bis* compound was isolated.

The 140–160° fraction was further purified by extraction with boiling petroleum ether (b. p. 30–60°). In this way a more soluble material, probably octamethylene bromide, was removed. After a series of extractions 6.0–6.9 g. (58–66%) of a light yellow, viscous oil,  $n_D^{20}$  1.5672, was obtained. It is soluble in Claisen potash, acetone, ether and ethanol. In boiling petroleum ether (b. p. 30–60°) it is moderately soluble.

*Anal.* Calcd. for  $C_{22}H_{28}O_2Br$ : C, 65.19; H, 7.16; Br, 19.75. Found: C, 65.21; H, 7.31; Br, 19.88.

The half-ether could be purified without recourse to molecular distillation. The thick dark residue left after distillation of the octamethylene bromide was treated directly with boiling petroleum ether (b. p. 30–60°). By a series of extractions with this solvent it was possible to effect a separation from the easily soluble octamethylene bromide and from the completely insoluble dicresol and dark colored materials. Removal of the petroleum ether gave a light honey colored oil with  $n_D^{20}$  ranging from 1.5659 to 1.5669. This material was suitable for use in the cyclization reaction. The yield by this method was essentially the same as that obtained when molecular distillation was employed.

**2,2' - Dimethyl - 5,5' - (octamethylenedioxy) - biphenyl.**—A mixture of 5.5 g. of anhydrous potassium carbonate and 1500 cc. of dry isoamyl alcohol was placed in the 3-liter reaction flask of the high dilution apparatus. A solution of 6.49 g. of 2,2'-dimethyl-5-hydroxy-5'-( $\omega$ -bromo-*n*-octyloxy)-biphenyl in 850 cc. of dry isoamyl alcohol was added in the course of ninety (not consecutive) hours. After stirring and heating for an additional two hours the product was cooled, filtered and the alcohol removed by distillation under reduced pressure. The brown residue was "short-path" distilled at 2 mm. and a bath temperature of 140–180°. The distillate was a light yellow oil which turned to a light tan, crystalline mass when rubbed with methanol. It was recrystallized from methanol. In addition to the hard dense, white hexagonal plates of the monomer a soft, white flocculent material, probably polymeric, was precipitated. Separation was effected by decantation and repeated washing of the heavy plates with ice-cold methanol. Another recrystallization from methanol gave 2.5 g. (48%) of white hexagonal plates; m. p. 76–77.5° (cor.). Further recrystallization did not raise the melting point. It is best to seed the hot methanol solutions with a few crystals of the monomer; large heavy plates, which were readily separated from the flocculent impurities, are thus obtained. The white flocculent material was a waxy substance which melted around 52°, gave a negative Beilstein test and was insoluble in Claisen potash. It was not investigated further.

The cyclic ether was readily soluble in cyclohexane, pyridine, ether, chloroform, and petroleum ether. It was moderately soluble in boiling methanol and insoluble in Claisen potash.

*Anal.* Calcd. for  $C_{22}H_{28}O_2$ : C, 81.48; H, 8.64; mol. wt., 324. Found: C, 81.59; H, 8.68; mol. wt. (b. p. chloroform), 318.

(23) Micovic, *Bull. soc. chim.*, [5] 4, 1661 (1937).

(24) Lazier and Arnold, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1930, p. 31.

**2,2' - Dicarboxy - 5,5' - (octamethylenedioxy) - biphenyl.**—A solution of 0.7 g. of 2,2'-dimethyl-5,5'-(octamethylenedioxy)-biphenyl in 13 cc. of reagent pyridine and 5 cc. of water was heated on the steam cone. Gradually, 4.6 g. of finely powdered potassium permanganate was added in the course of five hours. Further additions of water, pyridine and potassium permanganate were made in exactly the same amounts and fashion as prescribed for the oxidation of 0.7 g. of 2,2'-dimethyl-5,5'-(decamethylenedioxy)-biphenyl. Purification of the acid was effected in the usual way. The following treatments were necessary before the product obtained from the oxidation of 3.65 g. of octamethylene ether was completely freed of the monobasic acid: (1) Fifteen cc. benzene, three-hour reflux. (2) Fifteen cc. benzene, three-hour reflux. (3) Dissolved in 125 cc. of hot 5% sodium hydroxide, filtered and acidified with concentrated hydrochloric acid. (4) Fifteen cc. benzene, three-hour reflux. (5) Fifteen cc. benzene, three-hour reflux. (6) Dissolved in 50 cc. of hot 10% aqueous sodium hydroxide and precipitated with concentrated hydrochloric acid. (7) Fifteen cc. benzene, two-hour reflux. (8) Dissolved in 50 cc. of 10% aqueous sodium hydroxide solution and acidified with concentrated hydrochloric acid. (9) Twenty cc. benzene, two-hour reflux. (10) Twenty-five cc. benzene, two-hour reflux. (11) Dissolved in 50 cc. of 10% aqueous sodium hydroxide solution and precipitated by means of hydrochloric acid. (12) Twenty-five cc. benzene, three-hour reflux. (13) Twelve cc. benzene, three-hour reflux. (14) Recrystallization from ethanol. Only after this procedure was analytically pure 2,2'-dicarboxy-5,5'-(octamethylenedioxy)-biphenyl obtained; yield, 1 g. (23%).

The octamethylene acid is easily soluble in cold 5 or 10% aqueous sodium hydroxide solutions. It melts at 344° with decomposition (bloc Maquenne).

*Anal.* Calcd. for  $C_{22}H_{24}O_8$ : C, 68.75; H, 6.25. Found: C, 68.96, 68.83; H, 6.39, 6.47.

**Resolution of 2,2'-Dicarboxy-5,5'-(octamethylenedioxy)-biphenyl.**—While a beautifully crystalline monobrucine salt was obtained from absolute ethanol, careful fractionation gave only one compound which did not mutarotate in chloroform solution; white needles, softening at 175°, m. p. 187° (cor.) with evolution of gas.

*Anal.* Calcd. for  $C_{22}H_{24}O_8 \cdot C_{23}H_{28}O_4N_2$ : C, 69.41; H, 6.42; N, 3.59. Found: C, 68.95; H, 6.86; N, 3.32.

*Rotation.* 0.0433 g. made up to 5 cc. with chloroform at 20° gave  $\alpha_D +0.01^\circ$ ; *l*, 1;  $[\alpha]^{20}_D +1.16^\circ$ .

The acid obtained by decomposing this salt was inactive. Resolution was achieved via the dicinchonine salt.

A mixture of 0.733 g. of 2,2'-dicarboxy-5,5'-(octamethylenedioxy)-biphenyl and 1.120 g. of cinchonine was dissolved in 44 cc. of boiling absolute ethanol. The solution was allowed to stand at room temperature for twenty-four hours. Prisms separated which were freed from

mother liquor by decantation; yield, 1.20 g. Occasionally seeding was necessary to induce crystallization. A second fraction, after concentration of the mother liquor to 20 cc., weighed 0.37 g. Further concentration to 5 cc. gave a third crop, 0.12 g. All three fractions had identical specific rotations. Recrystallization of the first crop did not change its rotation; m. p. 155–170° (cor.) depending on the rate of heating.

*Anal.* Calcd. for  $C_{22}H_{24}O_8 \cdot 2C_{19}H_{22}ON_2$ : N, 5.76. Found: N, 5.72.

*Rotation.* 0.0852 g. made up to 5 cc. with chloroform at 27° gave  $\alpha_D -2.92^\circ$ ; *l*, 1;  $[\alpha]^{27}_D -171^\circ$ . In about sixty hours the salt had mutarotated to a constant value of  $-155^\circ$ .

***l* - 2,2' - Dicarboxy - 5,5' - (octamethylenedioxy) - biphenyl.**—Decomposition of 1 g. of the cinchonine salt with 100 cc. of ice cold 20% hydrochloric acid by the procedure prescribed for *d*-2,2'-dicarboxy-5,5'-(decamethylenedioxy)-biphenyl gave the active acid; m. p. 344° (bloc Maquenne); yield, 0.396 g. (92%) (see Table I for rotation and racemization constants).

*Anal.* Calcd. for  $C_{22}H_{24}O_8$ : C, 68.75; H, 6.25. Found: C, 68.55; H, 6.29.

### Summary

1. A discussion is given of the possible stereoisomeric forms of 2,2'-dicarboxy-5,5'-(polymethylenedioxy)-biphenyls dependent on the number of methylene groups present.

2. The preparation and resolution of 2,2'-dicarboxy-5,5'-(decamethylenedioxy)-biphenyl and 2,2' - dicarboxy - 5,5' - (octamethylenedioxy) - biphenyl are described.

3. The conclusion is drawn that the more rapid rate of racemization of the active decamethylene acid over the octamethylene acid is due in all probability to the increased slippage of the carboxyls past each other dependent in turn on the more vigorous semicircular oscillations which the benzene nuclei may undergo about the bond joining them.

4. In aqueous alkali, the octamethylene and decamethylene compounds have within experimental error the same rate of racemization. A striking increase in racemization rate in alkali is noted over the rate in dioxane.

5. A detailed description of a successful high-dilution reaction equipment is given.

URBANA, ILLINOIS

RECEIVED AUGUST 21, 1940