THE STEREOCHEMISTRY OF DIPHENYLS AND ANALOGOUS COMPOUNDS[1]

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CONTENTS

I. INTRODUCTION

Recent advances in stereochemistry have demonstrated the occurrence of numerous molecules not containing an asymmetric carbon atom but nevertheless resolvable into optically active antipodes. For example, compounds I (130), II (106), III (137), IV (126), and many other analogous ones have been resolved into their d and l forms. In these compounds, there is present no

I
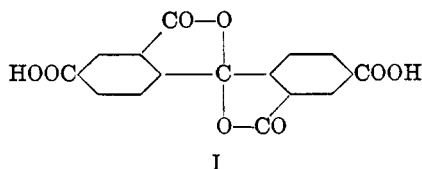
Ketodilactone of benzophenone-
2,4,2′,4′-tetracarboxylic acid

III
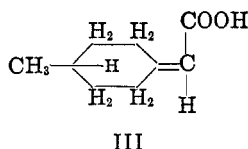
1-Methylcyclohexylidene-
4-acetic acid

II
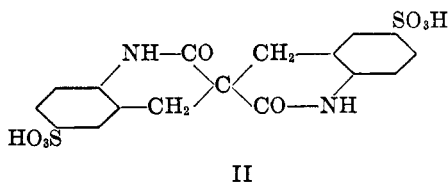
bis-Dihydrocarbostyril-3,3′-
spirane-6,6′-disulfonic acid

IV
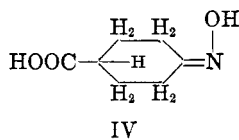
Oxime of cyclohexanone-
4-carboxylic acid

asymmetric carbon atom in the sense of the Le Bel-van't Hoff conception. However, an inspection of the space models of these molecules constructed with tetrahedral carbon atoms clearly indicates that such compounds do not possess either a center of symmetry, a plane of symmetry or an alternating axis of symmetry. Mirror images not superimposable upon the objects are, therefore, possible. Thus, in any consideration of the structural conditions necessary for the existence of optical isomers, it is the asymmetric character of the molecule as a whole

which is the determining factor.   The broader aspect of the problem covers all cases of the optical isomerism of organic compounds and shows that the asymmetric carbon atom represents only a special case of asymmetry.[2]

Among all the known types of molecules not containing asymmetric carbon atoms which may exist in optically active forms, the one which has been most extensively investigated and from which fruitful and significant results have been obtained is that of certain diphenyl derivatives.   The discovery and development of this field is curious and interesting and in the present résumé an attempt has been made to place the material in a logical order, with the historical development preserved as much as possible.

In this article the diphenyl derivatives, with the exception of those of benzidine and of diphenic acid, have been named as substitution products of diphenyl according to formula V.

V
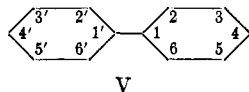
II. KAUFLER'S SPACE FORMULA

The relative position of the two benzene rings in diphenyl has been the subject of much speculative and experimental effort. Until 1907 it was usually considered that the two benzene rings in diphenyl and its derivatives were extended and coplanar.   The early literature in organic chemistry contained the description of compounds derived from benzidine in which the two amino groups apparently acted similarly to those in o-phenylenediamine. It was possible, for example, to condense benzidine with anhydrous oxalic acid (22), with carbon disulfide (167), with phosgene (124), with phthalic anhydride (79), and N, N'-diethylbenzidine with phthalic anhydride (144), to give simple derivatives.   To these compounds[3] the original discoverers assigned formulas VI,

[2] Conditions necessary for optical activity are clearly defined by Barker and Marsh (6a).

[3] There were other cyclic derivatives described in the literature such as thiocarbonyl and carbonyldianisidine (162), carbonyl-o-tolidine and oxalyl-o-tolidine (170), cycloformazyl methyl ketone (190), malonylbenzidine (140), and p-nitrobenzylidene benzidine (7).

VII, VIII, IX, and X. Another series of compounds obtained by Vaubel and Scheuer (183) were described as diazoimides with

$C_{12}H_{10}N_2C_2O_2$

VI

Oxalylbenzidine

VII

Thiocarbobenzidine

VIII

Carbonylbenzidine

IX

Monophthalylbenzidine

X

N,N'-diethylphthalylbenzidine

XI

Diazoimidobenzidine
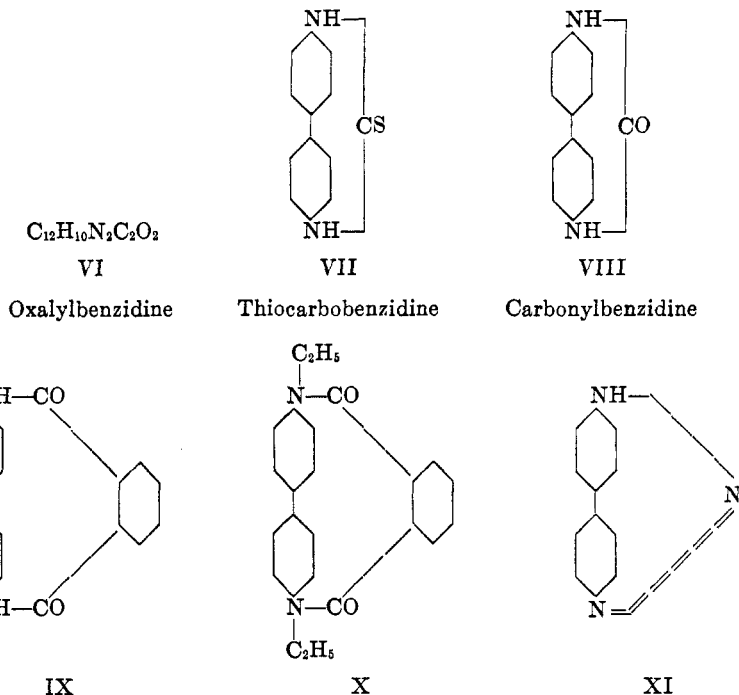
the general formula XI. Strakosch (167) recognized the possibility that thiocarbonylbenzidine might be a bimolecular compound, as shown in formula XII, but owing to the insolubility of this compound he was unable to determine its molecular weight.

XII
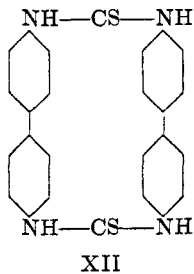
In 1907 Kaufler (65) determined the molecular weight of the monophthalylbenzidine (IX) and found it to be unimolecular. He concluded that "for the other derivatives named, an analogous constitution was made very probable." As further evidence he prepared the products from phthalic anhydride and carbon disulfide with dianisidine, and he condensed p,p'-diaminodiphenylmethane and p,p'-diaminodiphenylethane with carbon disulfide. Several of these compounds were shown to be unimolecular (66, 67).

Since the two amino groups in benzidine or analogous diphenyls reacted so readily to form ring compounds similar to those formed with o-phenylenediamine, Kaufler (65) concluded that the two amino groups must be nearer together than was indicated by the ordinary formula (XIII), and proposed a more or less rigid folded space formula (XIV) for diphenyl.[4] In this diagram (XIV) the

XIII   XIV

two rings are supposed to be lying in planes perpendicular to the plane of the paper, and the heavily printed lines indicate the sides of the hexagons which are nearer to the reader.

As further evidence for this conclusion Kaufler (65) pointed out that the diazotization of the second amino group of benzidine was more difficult than of the first amino group and also that after benzidine was tetrazotized, the second diazo group coupled with various dye intermediates with more difficulty than the first diazo group (147, 91). One group 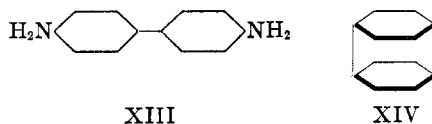produced a steric effect upon the other, such as might be expected if the substituents in benzidine and its tetrazonium salt were close together in space. Furthermore, Kaufler suggested that such a structure offered a simple explanation of the para coupling in the conversion of hydrazobenzene to benzidine. Various investigators undertook further experimental tests of the Kaufler hypothesis. These studies followed two lines: (1) further efforts to join the amino

[4] Kaufler's actual statement was that the two rings were "gegen einander geneigt." He also considered that naphthalene and other polynuclear molecules had a similar folded configuration.

groups of benzidine into a cyclic structure, and (2) the examination of the stereochemical implications of the folded structure.

(1) Many new derivatives of benzidine for which cyclic structures might be assumed, were prepared. Unfortunately, in most cases no demonstration of the suggested structures was offered. The condensation products of benzidine with glyoxal, with benzil (32), with isophthalaldehyde, and with terephthalaldehyde (1) were assigned formulas XV, XVI, XVII, and XVIII. Both oxalic acid and phosgene reacted with 4,4'-diaminodiphenylmethane but yielded products (28) too insoluble to identify.

XV	XVI	XVII	XVIII
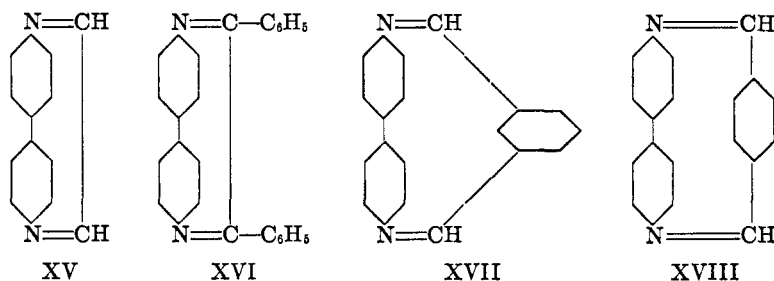
Morgan and his coworkers (131, 132) extended Vaubel and Scheuer's work on diazoimides (XII) by converting naphthalene-β-sulfonylbenzidine into a substance which was formulated as XIX.

XIX
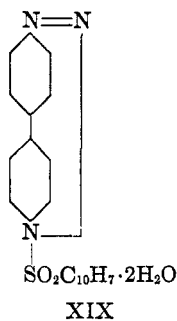
(2) From the stereochemical standpoint, the Kaufler formula made possible certain isomeric substituted diphenyls which otherwise would be non-existent. There were two dinitrobenzidines described in the literature, one prepared by Strakosch (167) and

the other by Bandrowski (5). The former was shown definitely to be the 3,3'-dinitro derivative (XX) (26, 23), and the second apparently had the nitro groups in the same positions. In 1912, Cain and his coworkers (29, 30, 31) adopted the Kaufler structure to explain the existence of these conventionally inexplicable isomers; he called the one a 3,3'-dinitro derivative (XXI), and the other a 3,5'-dinitro derivative (XXII); further support of such a viewpoint resulted from the experiments of Brady and McHugh (23). Later, Cain reported the preparation of two pairs

XX	XXI	XXII
	Bandrowski's m.p. 233°	Strakosch's m.p. 275°
3,3'-Dinitro-4,4'-diaminodiphenyl	3,3'-Dinitro-4,4'-diaminodiphenyl	3,5'-Dinitro-4,4'-diaminodiphenyl
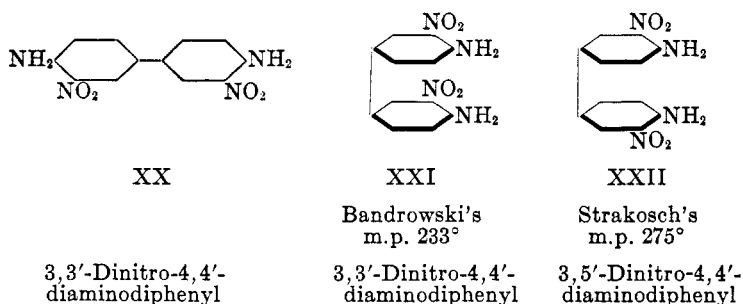
of geometric isomers of the m-dinitro-o-tolidines (169, 33)— XXIII, XXIV, XXV, and XXVI. The results of these investigations conformed so perfectly to the theory that they greatly strengthened the Kaufler hypothesis.

XXIII	XXIV	XXV	XXVI
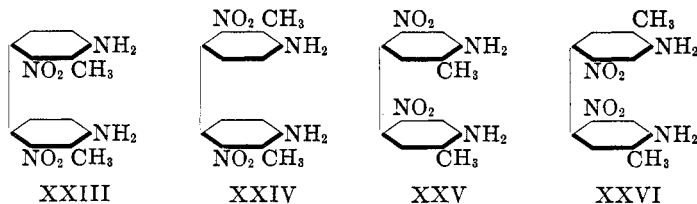
Still another pair of stereoisomers was discovered. By oxidation of the nitration products of phenanthraquinone and also by direct nitration of diphenic acid, Schultz (146) obtained a dinitrodiphenic acid, which was later (145) demonstrated to be 2,2'-dinitro-6,6'-dicarboxydiphenyl (XXVII). When Kenner and Stubbings (71) attempted to prepare this acid by coupling the ester of 2-iodo-3-nitrobenzoic acid in the presence of copper

powder and saponification, they obtained a different acid. On reduction, Schultz's acid yielded the corresponding diamino acid, whereas Kenner's acid produced an internal dilactam with extraordinary readiness. Kenner and Stubbings concluded that these acids constituted a pair of geometric isomers and assumed that Schultz's acid was the *cis* form (XXVII) and their own compound was the *trans* form (XXVIII).

XXVII

Schultz's acid

XXVIII

Kenner's acid
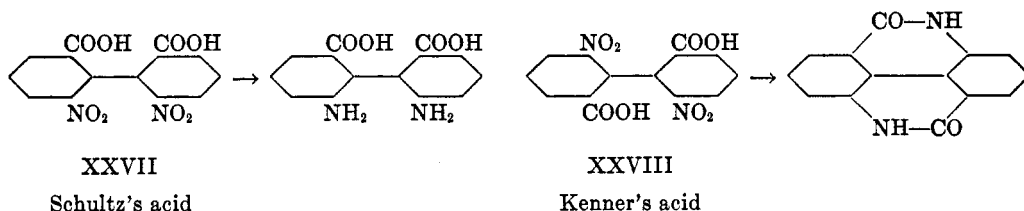
After the description of Cain's two dinitrobenzidines had been published, King (74) in an article entitled "The Possibility of a New Instance of Optical Activity without an Asymmetric Carbon Atom," pointed out that if Kaufler's formula were correct, one of Cain's dinitrobenzidines, the $3,5'$ derivative (XXII), but not the $3,3'$ (XXI) should be resolvable. Thorpe (171) also mentioned a similar possibility in one of the dinitrodiphenic acids prepared by Schultz and by Kenner and Stubbings. Kamm (63) attempted the resolution of diphenic acid, but without success.

Christie and Kenner (41) discussed further in some detail the stereochemistry of the three possible space formulas of the two dinitrodiphenic acids. On the basis of the coplanar formula for diphenyl, the *cis* form (XXVII) possessed a plane of symmetry and the *trans* form (XXVIII) had a center of symmetry, so that neither form should be resolvable into optical isomers. On the basis of the Kaufler formula, however, the *cis* form (XXIX) possessed a plane of symmetry but the *trans* form (XXX) did not, and a pair of mirror images should exist for this latter form. On the basis of formulas with a common axis for the two benzene rings but with the rings noncoplanar, both forms should be resolvable. The limiting case (XXXI) of this kind in which the planes of the two rings were at right angles was excluded, since it did not allow the existence of geometric isomers.

NO$_2$

COOH

NO$_2$

COOH

XXIX

NO$_2$

COOH

COOH

NO$_2$

XXX

NO$_2$ COOH

COOH NO$_2$
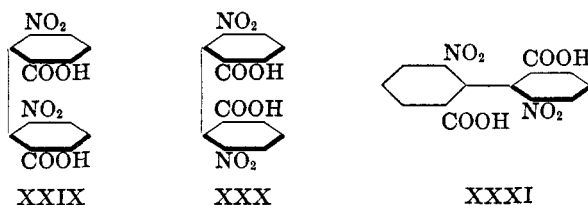
XXXI

The climax of these stereochemical considerations was reached when Christie and Kenner (41) successfully resolved their dinitrophenic acid, the supposed *trans* form (XXX), into antipodal forms.[5] Very convincing support was thus given to Kaufler's formula for the diphenyl system.

In addition to all the chemical evidence in favor of Kaufler's hypothesis, an attempt was made to attack this problem by a physical method. Mack (111) calculated the average cross-sectional area of the diphenyl molecule from the diffusion coefficient and the result was in better agreement with the folded structure than with the extended formula.

In summary: There are six types of observations which were considered to receive explanation by means of Kaufler's formula, namely:—

1. The formation of cyclic derivatives of benzidine.

2. The existence of geometrical isomers of substituted diphenyls.

3. The optical resolution of substituted diphenic acids.

4. The inactivity of the second amino group in benzidine or of the second diazo group in tetrazotized benzidine.

5. The para conversion of hydrazobenzene to benzidine.

6. Physical data.

III. THE COLLAPSE OF THE EVIDENCE FOR THE KAUFLER FORMULA

In spite of the numerous experimental facts which supported Kaufler's view, other experiments which were intended to verify the folded formula but failed to do so, could not be overlooked.

[5] Soon after Christie and Kenner's discovery, five more diphenic acids of the same type were resolved and the phenomenon was regarded as supporting Kaufler's formula before the latter was abandoned. The resolution of these acids will be fully considered in a later part of this review.

Obviously, on the Kaufler hypothesis, the 4,4' and 3,3' positions must be almost as near together in space as the 2,2' positions. But in most cases reactions take place at the 2,2', positions only. It was shown that neither 3,3'-dicarboxydiphenyl (181) nor 3,3',-5,5'-tetracarboxydiphenyl (27) formed an anhydride, that 4,4'-dibromodiphenyl did not condense with sodium (172), that 4,4'-diiododiphenyl did not form p,p'-diphenylene with copper (152),[6] and that 4,4'-dinitrodiphenyl did not give intramolecular azo or azoxy compounds (172). Benzidine did not condense with phenanthraquinone (32). When it reacted with acetylacetone or benzoylacetone (173), or anhydrides of naphthalic, camphoric, or quinolinic acid (155), two molecules of ketone or anhydride condensed with one molecule of the base or only one amino group was attacked, but no cyclic compound could be obtained. Again, if the 4,4' positions are close together, there is a reasonable probability that those types of reactions which involve the para migration of certain groups in simple benzene compounds, might also be exhibited by certain derivatives of diphenyl, the migrating group passing from the 4 to the 4' position. All attempts (139, 13, 14) along this line resulted in failure.

Bell and Kenyon (10a) have pointed out that the Kaufler formula involves some very awkward changes in configuration. For example, the following series of reactions would indicate the formation of a meso tetranitrodiphenic acid from dinitrophenanthraquinone, whereas actually a racemic, resolvable modification was obtained.
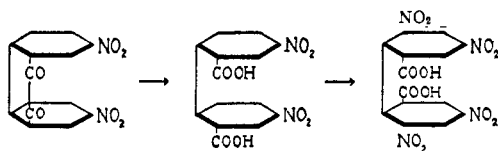

In considering these negative results, Adams (1) and also Adkins (2), as earlier investigators had intimated (69), pointed out that a fixed folded formula for all diphenyl derivatives was unten-

[6] Sircar (153) described one of the products as tetraphenylene but this was proved by Kuhn (81) to be 4,4'-diphenyldiphenyl.

able, and that whether the rings were superimposed or extended possibly depended on the nature of the substituents.

Kenner and Mathews (69) and Morgan and Mickelthwait (132) questioned the structure of the condensation products of benzidine and α-diketones (XV, XVI) reported by Cain. The products differed in properties from the similar condensations of 2,2'-diaminodiphenyl with benzil. Upon reinvestigation of the benzidine derivatives, Ferriss and Turner (52) found them to be so complicated in character that no definite conclusions about structure could be drawn.

It was shown almost simultaneously by Turner (97, 98), Kuhn (89), and Sircar (154) and their collaborators that monophthalylbenzidine (IX), the most fully investigated Kaufler compound, had the constitution (XXXII)[7] rather than that (IX) hitherto
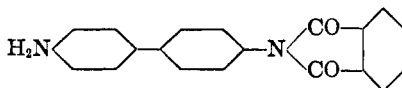
XXXII

assigned to it since it contained a free amino group, the presence of which was demonstrated by (1) condensation with various aldehydes, (2) condensation with another molecule of phthalic anhydride,[8] and (3) diazotization of the amino group and coupling with β-naphthol. Then Le Fèvre and Turner examined a number of other supposed ring compounds and found that oxalylbenzidine (VI) contained a free amino group; that the thiocarbonyl derivative (VII) was certainly XXXIII; that the carbonylbenzidine (VIII) was XXXIV (98, 99); that the N,N'-diethylphthalyl-

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[7] Recently (55, 56) other structures were proposed for the monophthalylbenzidine, but they were proved by Turner (176) to be erroneous.

[8] Shimomura (151) formulated the change as being the conversion into structure
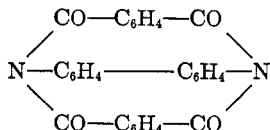
Formula XXXII explains this conversion in a normal manner.

benzidine (X) was not a chemical individual.   Moreover, Cain's
condensation product from benzidine and benzil was shown
actually to be compound XXXV (98).   A reëxamination of the
compound to which Morgan assigned the formula XIX indicated
that its properties were accounted for more adequately by formula
XXXVI (98).

$$H_2N\langle\ \rangle-\langle\ \rangle N=C=S \qquad \left[H_2N\langle\ \rangle-\langle\ \rangle NH\right]CO_2$$

XXXIII   XXXIV

$$\begin{matrix}C_6H_5-CO \\ C_6H_5-C=N\end{matrix}\langle\ \rangle-\langle\ \rangle N=C\begin{matrix}COC_6H_5 \\ -C_6H_5\end{matrix} \qquad \begin{matrix}N \\ \| \\ N\end{matrix}\langle\ \rangle=\langle\ \rangle=N-SO_2C_{10}H_7$$

XXXV   XXXVI
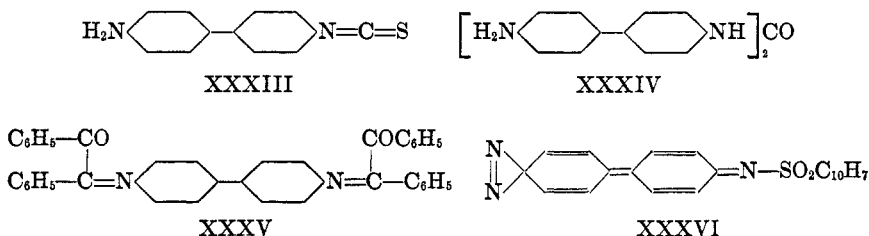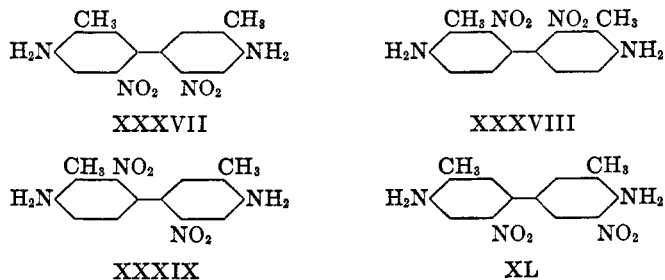
As for other products of a supposedly similar structure, they were
either ill-defined compounds of unknown molecular structure or
contained one free amino group (154, 50, 94).   In none of these
cases, as can be seen, were the two amino groups of the benzidine
molecule combined in a ring, and thus the first set of phenomena
which the Kaufler formula was intended to explain did not exist.

The question regarding the geometrical isomers next received
attention.   Le Fèvre and Turner (96, 95) proved that the most
fully investigated of Cain's pairs of isomers, namely, the two
dinitrobenzidines (XXI and XXII), were not stereoisomers but
position isomers.   Bandrowski's diamino compound was not the
3,3'-dinitro derivative but was impure 2,2'-dinitro-4,4'-diamino-
diphenyl.   And Cain's two pairs of isomers of dinitrotolidine were
not XXIII, XXIV, XXV, and XXVI, but were the position
isomers XXXVII, XXXVIII, XXXIX, and XL (100).

$$\underset{NO_2\ \ NO_2}{\overset{CH_3\qquad CH_3}{H_2N\langle\ \rangle-\langle\ \rangle NH_2}} \qquad \overset{CH_3\ NO_2\ \ NO_2\ CH_3}{H_2N\langle\ \rangle-\langle\ \rangle NH_2}$$

XXXVII   XXXVIII

$$\underset{NO_2}{\overset{CH_3\ NO_2\qquad CH_3}{H_2N\langle\ \rangle-\langle\ \rangle NH_2}} \qquad \underset{NO_2\qquad NO_2}{\overset{CH_3\qquad CH_3}{H_2N\langle\ \rangle-\langle\ \rangle NH_2}}$$

XXXIX   XL

The reinvestigation (43, 39) of Schultz's acid (XXVII) led to the conclusion that it was not 2,2'-dinitro-6,6'-dicarboxydiphenyl but was its position isomer, 2,4'-dinitro-6,6'-dicarboxydiphenyl. Thus Schultz's acid and Kenner's acid were not stereoisomers, and Schultz's acid, previously regarded as probably belonging to the *cis* form, nonresolvable class, should be resolvable, and, in fact, was later resolved. Therefore, the second important line of evidence, the existence of geometrical isomers, which was regarded as supporting the Kaufler formula, proved to be misleading on account of erroneous experimental results.

As mentioned previously, Kaufler considered that his formula, because of the steric hindrance effect of 4,4' groups upon each other, explained (1) the difficulty of diazotizing the second amino group in benzidine, (2) the slowness of coupling of the second diazo group in benzidinetetrazonium chloride, and (3) the para-hydrazobenzene–benzidine rearrangement. There is considerable question whether the first difficulty exists (187). Le Fèvre and Turner have assumed that the second is sufficiently explained by the insolubility of the intermediate monocoupled product[9] formed as the first step in the coupling of benzidinetetrazonium chloride (98). In regard to the benzidine change there is little advantage in Kaufler's formulation, since the closeness of positions has no correlation with intramolecular rearrangement and certainly does not explain the semidine rearrangement which frequently takes place simultaneously with the benzidine rearrangement.

Mack's (112) conclusions from diffusion coefficients and collision area that diphenyl had the Kaufler formula, were based on certain assumptions which later proved to be erroneous. More recent studies of this same investigator, with improved technique, have led him, on the basis of gas kinetic evidence, to favor the extended coplanar formula.

It has been pointed out by Carothers (34) and by Mascarelli (117) that an objection to the Kaufler formula which has never

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[9] Information from an expert in benzidine dyes is that benzidinetetrazonium salts give in some instances soluble monocoupled products. As a consequence the question as to this characteristic of benzidinetetrazonium salts may be considered as still lacking satisfactory explanation.

been emphasized is the necessity of bending a bond to an angle of 90°. With a Kekulé nucleus such a formula cannot be constructed, and each time that chemists adopt assumptions that cannot be reconciled with the Kekulé nucleus they encounter difficulties.

In the meantime several investigations were published, the results of which brought forward fresh valuable evidence opposed to Kaufler's view. Barber and Smiles (6) observed that the diphenylene disulfide (XLI) was obtained by oxidizing 2,2'-dithioldiphenyl (XLII). If Kaufler's view is accurate, 4,4'-dithioldiphenyl should also give a disulfide on oxidation. In fact, however, neither the 4,4'-dithiol- nor the 3,3'-dithiol-diphenyl yielded any such result.

XLI   XLII
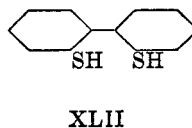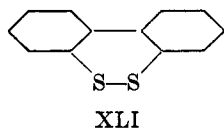
Kuhn and Zumstein (90) determined the dissociation constant of benzidine and compared it with the corresponding values for the three phenylenediamines. Their data indicated that the amino groups in benzidine were farther apart than Kaufler's formula suggested.

Williams and Weissberger (192) measured the dipole moments of several diphenyls. For a 4,4' symmetrically substituted diphenyl, any angle other than 180° between the axes of the rings should correspond to a definite dipole moment. They discovered, however, that in 4,4'-dichlorodiphenyl and 4,4'-dinitrodiphenyl, the moment was zero. Therefore, the rings were coaxial and could not be inclined toward each other.

The resolution of Kenner's dinitrodiphenic acid was followed by the resolution of several other diphenyls, but at the same time an even larger number of molecules which, according to the Kaufler formula should exist in enantiomorphic forms, resisted resolution.

A summary of this phase of the diphenyl problem shows that four of the six lines of evidence which supported the Kaufler

folded structure have been discredited and doubt has been thrown upon a fifth. Additional experimental data which are in better agreement with an extended formula have been obtained. The sole important remaining piece of evidence which is still experimentally sound, is the fact that several substituted diphenic acids do exist in optically active isomeric forms. It is, therefore, now possible to consider this phenomenon independently and seek a logical and correct explanation for it.

IV. OPTICAL ACTIVITY OF DIPHENYLS

Resolvable and nonresolvable diphenyls

The collapse of the evidence for the Kaufler formula left unchallenged Christie and Kenner's resolution of 2,2'-dinitro-6,6'-dicarboxydiphenyl into optically active forms. This opened an entirely new field of stereochemistry and experimental confirmation that certain other diphenyl derivatives could be resolved was speedily forthcoming. The optical antipodes of the following— XLIII, XLIV, Schultz's acid, and XLV—were among the first to be isolated:

NO₂ NO₂

O_2N ⟨ ⟩—⟨ ⟩ NO_2

COOH COOH
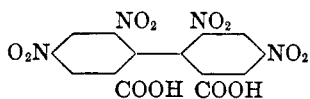
XLIII(41)

2,2',4,4'-Tetranitro-6,6'-dicarboxydiphenyl

NO₂

O_2N ⟨ ⟩—⟨ ⟩ NO_2

COOH COOH
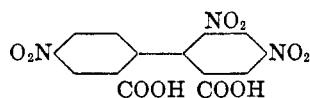
XLIV(42)

2,4,4'-Trinitro-6,6'-dicarboxydiphenyl

NO₂

⟨ ⟩—⟨ ⟩ NO_2

COOH COOH
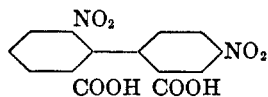
Schultz's acid(39)

2,4'-Dinitro-6,6'-dicarboxydiphenyl

NO₂

⟨ ⟩—⟨ ⟩

COOH COOH
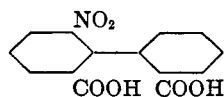
XLV(14)

2-Nitro-6,6'-dicarboxy-diphenyl

At the same time, however, many compounds chemically and structurally closely related to the above diphenyls were found to be nonresolvable. Kamm (63) was unable to resolve diphenic acid (XLVI).

Bell and Kenyon (11) studied 2-carboxydiphenyl (XLVII), which formed well-defined brucine and morphine salts, without

any indication of resolution being obtained. These authors (12) again attempted the resolution of diphenic acid, but unsuccessfully. The dimenthyl diphenate and the d-β-octyl hydrogen diphenate (14) were nonresolvable.

2,2'-Dinitro-4,4'-dicarboxydiphenyl (XLVIII) was prepared by Bell and Robinson (15). Its excessive insolubility militated against the production of uniform normal alkaloidal salts. The acid liberated from the brucine salt was found inactive. 4-Nitro-2,2'-dicarboxydiphenyl (XLIX) (15) and 2-carboxy-2'-carbomethoxydiphenyl (L) were also found to be nonresolvable.

No active forms of 4,4'-dinitro-2,2'-dicarboxydiphenyl (LI) could be obtained, although its quinine salt had abnormal positive rotation which was considered by some chemists as evidence of the existence of the labile d form (83).

XLVI XLVII XLVIII XLIX L LI
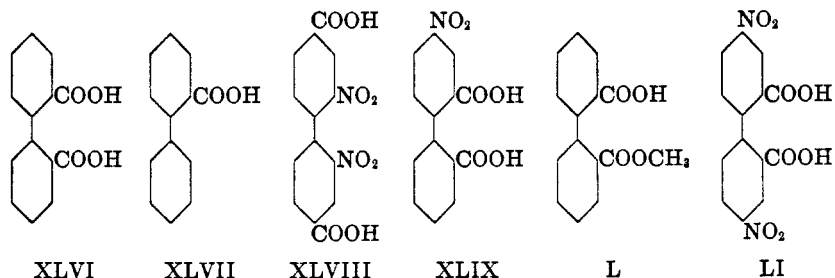
The compounds previously resolved were limited to those containing nitro and carboxyl groups. Christie, James, and Kenner (40), by resolving 2,2'-dichloro-6,6'-dicarboxydiphenyl (LII), showed that no specific effect of the nitro group was involved and somewhat later Kenner and H. A. Turner (72) obtained active forms of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl (LIII).
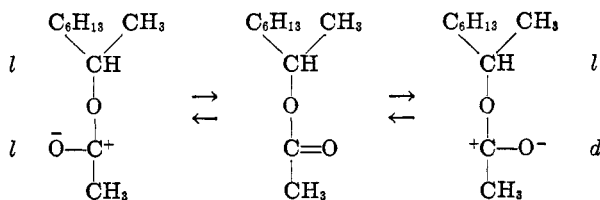
LII LIII LIV
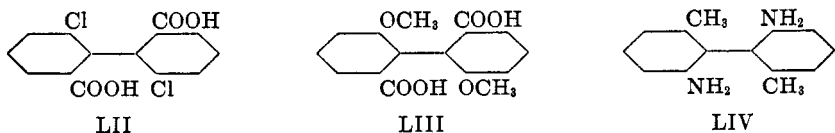
Possible sources of optical activity

At this stage of the development, several hypotheses concerning the cause of the peculiar optical isomerism were made possible.
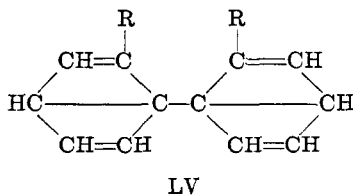
Because all the resolvable compounds contained carboxyl groups, Phillips' views on active esters were considered. To account for the abnormal rotatory dispersion exhibited by some active esters, he (136a) postulated that the carbon atom in the carboxyl group might be an asymmetric center. For example, l-β-octylacetate could be written:

$$
\begin{array}{ccccc}
& C_6H_{13}\ CH_3 & & C_6H_{13}\ CH_3 & & C_6H_{13}\ CH_3 \\
& \diagdown\diagup & & \diagdown\diagup & & \diagdown\diagup \\
l & CH & & CH & & CH & l \\
& | & & | & & | \\
& O & \underset{\longleftarrow}{\longrightarrow} & O & \underset{\longleftarrow}{\longrightarrow} & O \\
& | & & | & & | \\
l\ \ \bar{O}-C^+ & & C{=}O & & ^+C{-}O^- & d \\
& | & & | & & | \\
& CH_3 & & CH_3 & & CH_3
\end{array}
$$

But the possibility of applying this theory to the stereoisomerism of diphenyls was entirely eliminated when Meisenheimer and Höring (121) were able to resolve 2,2'-dimethyl-6,6'-diaminodiphenyl (LIV). This resolution was confirmed by Mascarelli (114). It became apparent, then, that the optical activity of diphenyls was not associated with the presence of the nitro or the carboxyl group and the isomerism was probably not due to the specific effect of any individual group in the ring.

The possibility that a substituted benzene molecule is not necessarily a plane arrangement, led to the hypothesis that the optical activity might have its origin in the asymmetry of a single benzene nucleus. This viewpoint can hardly be maintained in the face of the absolute failure of numerous attempts to resolve substituted benzenes into optically active components (107).

A third theory was proposed by Turner (174), who attributed the phenomenon to the existence of para bonds; thus a substituted diphenyl would have the following formula (LV).

$$
\begin{array}{c}
R \qquad\qquad R \\
| \qquad\qquad\quad | \\
CH{=}C \qquad\quad C{=}\!{=}CH \\
\diagup\qquad\qquad\qquad\diagdown \\
HC\!-\!\!-\!\!-\!\!-\!C\!-\!C\!-\!\!-\!\!-\!\!-\!CH \\
\diagdown\qquad\qquad\qquad\diagup \\
CH{=}CH \qquad\quad CH{=}CH
\end{array}
$$

LV

Turner pointed out that the molecule contained four asymmetric carbon atoms[10] and thus made optical isomerism possible. The formation of a tetraozonide of diphenyl was considered as a support of this hypothesis. According to this theory, however, more than one racemic form should exist and many of the nonresolvable compounds previously studied should be resolvable (110). This formula was criticized by Lowry (109a), and Turner later recognized this suggestion as untenable (179).

The coaxial-noncoplanar configuration

The fourth theory, that of coaxial but noncoplanar rings, was put forward by Christie and Kenner (41) and has now been generally accepted. It was assumed that the planes of the two benzene rings were at right angles to each other; under these conditions the following diagrams (LVI, LVII) represent the two active forms of a substituted diphenyl.
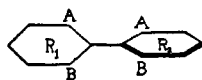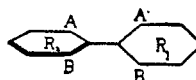

LVI   LVII

In each diagram, the R_1 ring is assumed to lie in the plane of the paper with the R_2 ring in a plane perpendicular to the paper. The two models are mirror images not superimposable. The case is comparable to that of allenic derivatives (LVIII and LIX) and to the spiranes. Thus, the optically active diphenyls represent one type of molecular asymmetry in which no asymmetric carbon atoms are present.
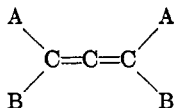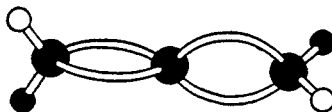
LVIII   LIX

[10] If the normal assumption is made that each of the two rings has its six carbon atoms in a plane, the para-bonded carbon atoms (so-called asymmetric by Turner) actually correspond to triple-bonded carbon atoms and no stereoisomerism in such molecules is structurally possible.—R. A.

But the coaxial-noncoplanar model alone is not sufficient, for if free rotation takes place about the bond joining the two nuclei, then the two rings could swing into a coplanar configuration and symmetry would be established and thus extinguish the optical activity of the compounds. To overcome this objection, one more postulate must be made, that of restricted rotation, a condition which was implied by Kenner.
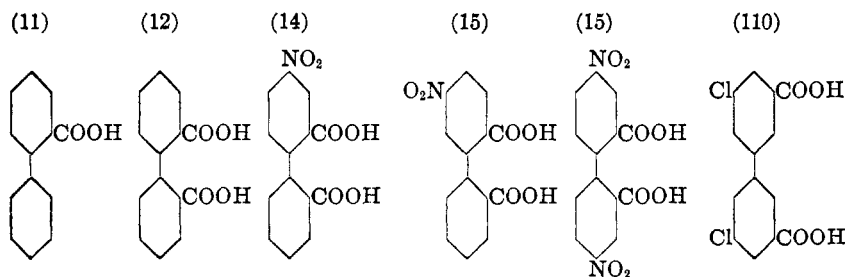
V. THE THEORY OF RESTRICTED ROTATION
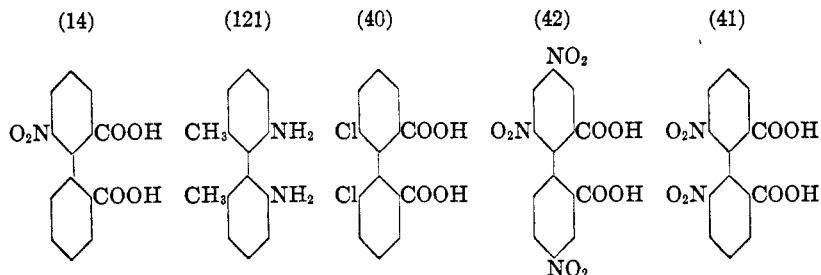
Fundamental assumptions

It is one of the fundamental assumptions in organic chemistry that two atoms joined by a single bond can have complete free rotation about the bond as an axis. Although Bischoff (18) suggested that complete rotation of carbon atoms could be hindered by substituents on them, no experimental evidence was offered for this view. But, without restricted rotation, Kenner's view of a coaxial-noncoplanar model for substituted diphenyls is impossible and, with restricted rotation, one of the commonly accepted principles of organic chemistry is violated.

Fortunately, the experimental material at this stage of the development is sufficient to give a clue to the essential feature of the problem. The formulas of several compounds, taken at random, are shown below. Those in the top line represent acids which have shown no capacity for resolution into enantiomorphs, while the formulas in the lower line represent compounds which have been obtained in optically active forms.

No resolution was attained with these acids.

Compounds which were easily resolvable:

| (14) | (121) | (40) | (42) | (41) |

O_2N_/COOH CH_3_/NH_2 Cl_/COOH O_2N_/COOH O_2N_/COOH

(with NO₂ above (42) and NO₂ below; structures shown)

Inspection of these two sets of formulas reveals the difference between them. Each of those which have been resolved into active forms has three[11] or four substituents in the 2,2′,6,6′ positions, while those not resolvable do not fulfil this condition. It becomes evident that only properly substituted diphenyls can have coaxial-noncoplanar configurations. In other words, the two rings in diphenyl rotate about the common axis and result in a coplanar structure unless there are proper substituents in the 2,2′,6,6′ positions. This led to the theory of restricted rotation which was advanced almost simultaneously in slightly different forms by Turner and Le Fèvre (179), Bell and Kenyon (10), and Mills (125).

Essentially, the theory states that substituents in 2,2′,6,6′ positions in a diphenyl molecule can, by their interference, restrict the free rotation of the two nuclei around the common axis, thus preventing the rings from becoming coplanar and thereby producing in the molecule an asymmetric configuration.[12]

Various explanations

One immediately obvious merit of the theory is that it explains why all the optically active diphenyls mentioned above possess at least three ortho substituents in the 2,2′,6,6′ positions; for only

[11] Now it is known that it is not the number but the size of ortho substituents which is of primary importance. Recently several 2,2′ disubstituted diphenyls have been resolved. This will be considered fully later.

[12] The model is by no means static, as pointed out by Mascarelli (115), since the semicircular oscillation of the two rings with respect to each other still may exist.

ortho substituents would be expected to be close enough to one another to give rise to the postulated restrictive influence. It is clear that two ortho substituents in one ring would hinder the ortho group or groups in the second ring from passing, and hence prevent the two rings from becoming coplanar. The ortho substituents, therefore, play an inhibiting rôle, just as two ortho substituents about a group in benzene exert "steric hindrance" effects in slowing down or stopping the normal reactions of that group (123).

With regard to the nature of the influence which inhibits free rotation of the two nuclei, opinions differed. Turner and Le Fèvre (179, 180) attributed the cause to the electrical nature of the substituted groups, the residual affinity on each ring, and the internuclear forces. According to their view, each carbon atom in the diphenyl molecule possessed a certain amount of free affinity. Carbon atoms 3,4,5 and 3',4',5', and 6' would be mutually saturated in the Thiele sense, giving formula LX.

LX   LXI

LXII
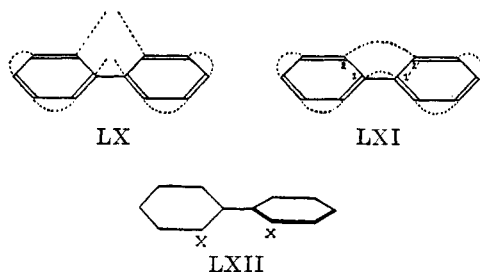
Since there was no reason to assume that the distance between carbon atoms 1 and 1' was greater than that between carbon atoms 1 and 2, some mutual saturation may occur between 1 and 1'. In this way the bond 1—1' became of the type existing in an ordinary benzene ring, and a tendency for rotation would appear to be to some extent diminished. Carbon atoms 2 and 2' would possess some free affinity, and this would tend as the major influence to stabilize the plane configuration as indicated in formula LXI. With a compound having two mutually repelling groups in positions 2 and 2', this mutual repulsion may be (1) equal to, (2) greater than, or (3) less than the original attractive

force between 2 and 2'. In case 1 there would be a tendency for free rotation; in case 3 the effect would be as in diphenyl itself, though less marked. In case 2, since there is now a repulsion and not an attraction between the 2 and 2' positions, distortion of the coplanar configuration may occur. One benzene ring would rotate about the common axis through an angle, the magnitude of which would be a function of the repulsive force. Thus results a coaxial-noncoplanar configuration (LXII).

Bell and Kenyon (10) suggested that, owing to their electrical characteristics or to their size, or to both, two ortho groups, A and B, acted as "obstacles" to the passage of an ortho group, C, on the other nucleus, thus preventing interconversion of the optical antipodes.
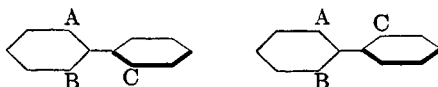
Mills (125), on the other hand, accepted the purely mechanical idea of steric hindrance and considered merely the bulk of the substituents. A model built up from the usual tetrahedra and drawn to scale, indicated that two bulky ortho substituents in the one ring would interfere with the free rotation of the second ring, owing to collisions between them and the third ortho substituent. Thus, in 2-chloro-6,6'-dicarboxydiphenyl (figure 1) the carboxyl group attached to the lower nucleus could pass neither the chlorine atom (large shaded circle) nor the other carboxyl group, and hence was confined to a limited region in front of the plane of the upper ring. On the other hand, if two of the groups were small, then free rotation was possible. This complied with the facts in the case of the diphenic acids, for in these compounds the two ortho hydrogen atoms were not bulky enough to prevent the free rotation of the two rings about their common axis.

The obstacle or mechanical theory received support from Meisenheimer, Kuhn, Mascarelli, Adams, and others, and is now the more or less generally accepted viewpoint. This theory has in recent years been put to rigid test, especially by Adams and his students, and an attempt has been made to put it on a semi-

quantitative basis from which predictions about resolvability, nonresolvability, and even optical stability of diphenyl derivatives might be made with a fair degree of accuracy.

Application of x-ray data

The application of values of atomic size obtained by physical measurements to the diphenyl problem was a natural development. Meisenheimer (121) first used atomic dimensions inferred from x-ray data to demonstrate the probability of collision between the amino and methyl groups in 2,2'-dimethyl-6,6'-diaminodiphenyl.
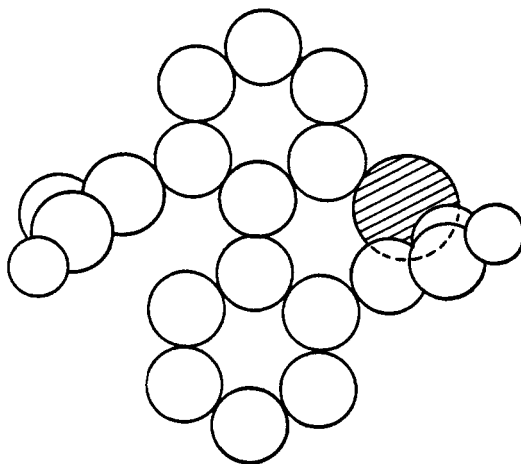
Fig. 1

Data intended to permit definite predictions concerning the resolvability of any given diphenyl were first presented by Stanley and Adams (158). On the obstacle theory the amount of interference will be determined by the size of the substituent atoms or groups. This magnitude, for the purposes in view, is not capable of being directly measured. It is possible, however, with the aid of certain assumptions to derive values which may reasonably be supposed to furnish a relative measure of the degree of interference. Distances between the centers of mutually combined atoms in the aliphatic series are known from x-ray data. These

values, slightly adjusted to bring them into line with aromatic
compounds, are the "internuclear distances" for atoms shown in
table 1. Similar "internuclear distances" for the groups CH_3,
NO_2, etc., were obtained by adding to the value for the central

TABLE 1

*Distance in Å. from the nucleus of the carbon atom of the benzene to center of
group atom or*

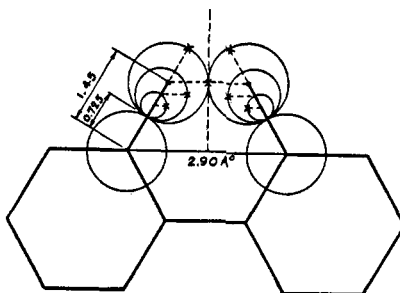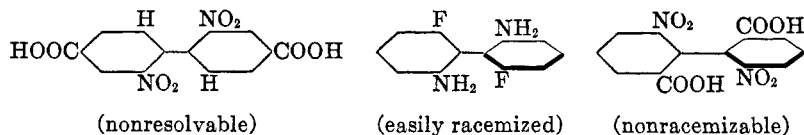|			
C—H	0.94	C—CH₃	1.73
C—F	1.39	C—Cl	1.89
C—OH	1.45	C—NO₂	1.92
C—COOH	1.56	C—Br	2.11
C—NH₂	1.56	C—I	2.20

FIG. 2

TABLE 2

"Interference values" of certain pairs of atoms or groups

| GROUPS AT 2,2′ POSITION	INTERFERENCE OVER 2.90 Å.	GROUPS AT 2,2′ POSITION	INTERFERENCE OVER 2.90 Å.
H, H	−1.02	F, NH₂	+0.05
COOH, H	−0.40	F, COOH	+0.05
Cl, H	−0.07	Cl, COOH	+0.55
NO₂, H	−0.04	NO₂, COOH	+0.58

atom an estimated quantity for the atoms attached to it. These
values are used in the following manner. The vertical distance
between the 2,2′ ring carbon atoms when coplanar has been
measured accurately and found to be 2.90Å. (51) (figure 2). The
difference between this value and the sum of the "internuclear

distances" of the atoms or groups attached to the 2,2' carbon atoms was called the "interference value" and adopted as a measure of the relative degree of interference that might be expected. Interference values for various atoms and groups are shown in table 2. These values in table 2 indicate absence of interference in the first four pairs, slight interference in the next two pairs, and relatively large interference in the last two pairs. In other words, compounds containing the first four pairs should not be resolvable, those containing the next two pairs should be capable of resolution but easily racemized, and those containing the last two pairs should be easy to resolve and difficult to racemize. Examples are given below.

HOOC —⟨ H / NO₂ ⟩— COOH   ⟨ F / NH₂ ⟩   ⟨ NO₂ / COOH ⟩
      NO₂ H   NH₂ F   COOH NO₂
(nonresolvable)   (easily racemized)   (nonracemizable)

Naturally, interferences on each side of the diphenyl molecule are necessary to prevent rotation, and the above values indicate the expected interference only in molecules which are symmetrically substituted in the 2,2',6,6' positions. In those cases where the calculated interferences are different on each side of the molecule (LXIII), the rate of racemization could be indicated in one of two ways—either by selecting the smallest of the values which show interference, or by selecting the average interference value of the two sides of the molecule. By way of illustration, formulas LXIV and LXV may be compared.

A   D   NO₂   H   NO₂   COOH
B   E   COOH NO₂   COOH NO₂
LXIII   LXIV   LXV
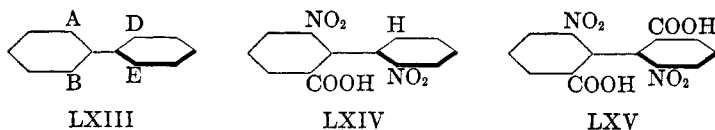
In LXIV the two interferences are NO_2—COOH, 0.58Å. (1.92Å. + 1.56Å. = 3.48Å. − 2.90Å. → +0.58Å.), or NO_2—NO_2, 0.84Å. (1.92Å. + 1.92Å. = 3.84Å. − 2.90Å. → +0.84Å.). The relative interference value for this molecule by the first method would be +0.58Å. Where the second procedure is followed,

interference in the molecule would be $+ 0.27$Å., the average of the interferences of NO_2—COOH and NO_2—H (on one side NO_2—COOH, $+0.58$Å. and on the other NO_2—H, 1.92Å. $+ 0.94$Å. $= 2.86$Å. $- 2.90$Å. $\rightarrow -0.04$Å.).[13] In the compound LXV either method gives the same value, 0.58Å. Experimentally LXV was stable to racemization, whereas LXIV racemized in boiling solution, thus indicating that the interference was not the same in both molecules and that the average interference probably represented a more appropriate value. A similar method of calculation would be equally suitable for $2,2',6,6'$-tetrasubstituted compounds where the two sides of the molecule were not symmetrical.

The estimated interferences paralleled, to a surprising degree, the relative racemization rates as found experimentally and, therefore, served admirably for the intended purpose. Thus, when the calculated interference was a minus quantity, in no instance was it possible to resolve the molecule; when the value was slightly above zero the compounds were resolvable but very readily racemized, or in some instances merely mutarotating salts were obtainable; when the value was considerably above zero, the compounds were resolvable. The rates of racemization of the active isomers of this last type varied widely but paralleled the relative interference value.

In the case of the tri- and di-substituted compounds, where one or two hydrogens were present in the $2,2',6,6'$ positions, the rate of racemization appeared to be greater than that expected from a study of the tetrasubstituted compounds. Greater mobility and possibility for distortion of the molecule during oscillation so as to let the groups slip by each other may be the explanation of this discrepancy.

The arbitrary selection of the distance from the carbon atom of the ring to the center of the atom or group attached, as an expression of the relative interference effect of an atom or group,

---

[13] For estimating the average interference value in a compound like LXIV, it is convenient merely to compare half the sum of the distances C—A, C—B, C—D, C—E with 2.90. If such a sum is larger than 2.90Å, the compound will, most probably, be resolvable.

and a comparison of the sum of the values of the 2,2′ groups with 2.90 to obtain interference values were made after a consideration of the geometry of a diphenyl molecule.

Figure 2 represents a diphenyl molecule with 2,2′ substituents in which the dots indicate the centers of substituted atoms or groups. It is obvious that with atoms or groups the radii of which are 0.725Å., a collision might be expected. With atoms or groups of larger radii interference of varying degree should result. With atoms or groups of smaller radii no interference should occur. Since the sum of the internuclear distances of the 2,2′ atoms or groups is equal to, is a little more than, or is a little less than 2.90, these differences were chosen as probably representing interference values which might approximate the actual interference of the substituents.

The method of calculating interference values described above involves assumptions to which theoretical objections can be raised. Various other methods of calculation might be used. Lesslie and Turner, for example, have recently presented for certain diphenyls models similar to those of Mills in which the atoms are drawn as spheres and to scale. Lesslie and Turner have criticized the method of calculation described above. Their method is, however, also open to criticism since it involves arbitrary assumptions as to the effective diameter of certain atoms (i.e., as to how close atoms can approach without interfering). The method of Stanley and Adams has the advantage of being simple to apply and, as has already been pointed out, of leading to conclusions in accordance with the observed facts.
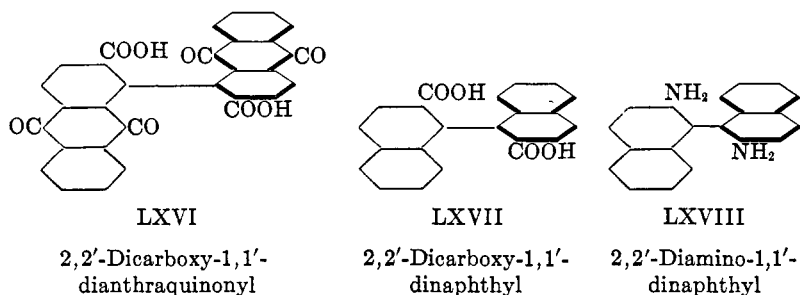
VI. EXPERIMENTAL EVIDENCE FOR THE COAXIAL-NONCOPLANAR MODEL

The conception of the coaxial-noncoplanar configuration and the theory of restricted rotation are more or less inseparable. Actually the former is much more fundamental and the latter supplementary. Experiments which may verify the restricted rotation theory incidentally will prove the noncoplanar configuration. On the other hand, those investigations which offer merely additional evidence in favor of the noncoplanar model may

advantageously be considered separately for the clarity of presentation.

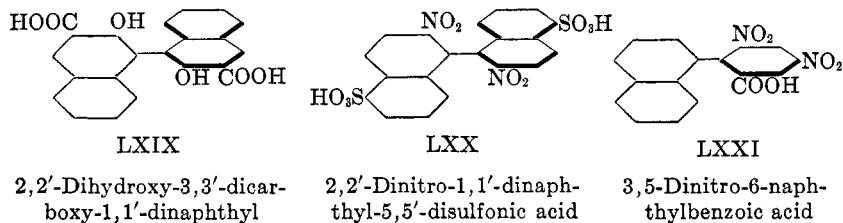*Resolution of compounds containing fused carbocyclic nuclei*

The first extension of the stereoisomerism of diphenyl was into fused ring systems; if the coaxial-noncoplanar view be correct, properly substituted dinaphthyls, dianthranyls, and other molecules of a similar character should show optical isomerism. Kuhn and his students (85, 86, 87) resolved LXVI, LXVII, and LXVIII.

LXVI

2,2′-Dicarboxy-1,1′-
dianthraquinonyl

LXVII

2,2′-Dicarboxy-1,1′-
dinaphthyl

LXVIII

2,2′-Diamino-1,1′-
dinaphthyl

Mascarelli (115) discussed the theoretical possibilities among dinaphthyl and phenylnaphthyl derivatives.

Stanley and Adams (157) separated LXIX into optical antipodes.

Murahashi (134) obtained the active forms of LXX, and Lesslie and Turner (103) prepared and resolved a substituted phenyl-α-naphthyl (LXXI).

LXIX

2,2′-Dihydroxy-3,3′-dicar-
boxy-1,1′-dinaphthyl

LXX

2,2′-Dinitro-1,1′-dinaph-
thyl-5,5′-disulfonic acid

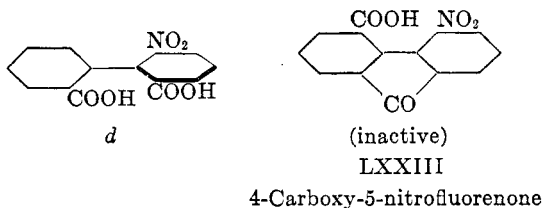LXXI

3,5-Dinitro-6-naph-
thylbenzoic acid

All these results show that optical activity persists in properly substituted fused carbocyclic systems. The active forms of all of these compounds exhibited relatively high rotation and were stable to any ordinary methods of racemization.

*Elimination of optical activity through 2,2′ ring closure*

One of the most interesting and convincing pieces of evidence demonstrating the noncoplanar structure for substituted diphenyls was accomplished through a study of certain 2,2′,6,6′-substituted diphenyls which contained groupings capable of producing rings through the 2,2′ positions. When 2,2′-dimethyl-6,6′-diaminodiphenyl (LIV) was acetylated, the introduction of acetyl groups did not effect any noticeable racemization. The diacetyl compound, in turn, was oxidized to the dicarboxylic acid which still possessed optical activity. But when the latter was hydrolyzed by cold acid, an inactive dilactam (LXXII) was obtained (121).

d

LIV
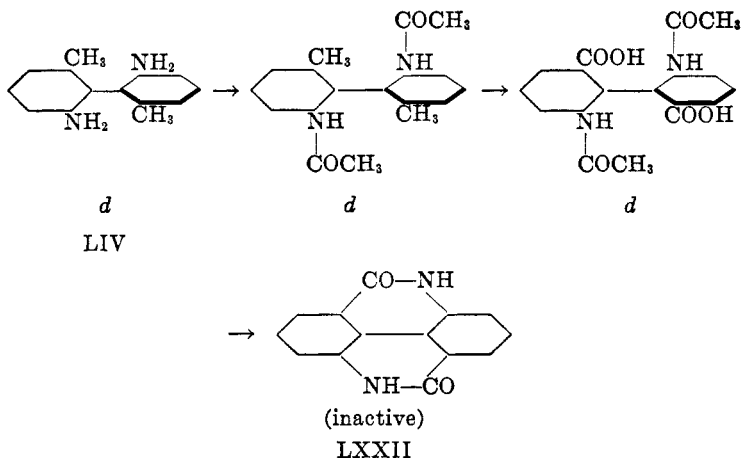
(inactive)

LXXII

The same phenomenon was noticed in 2-nitro-6,6′-dicarboxy-diphenyl, the *d* form of which produced the corresponding optically inactive fluorenone (LXXIII) when it was warmed with sulfuric acid. The fluorenone could not be resolved (15, 88, 182).

d
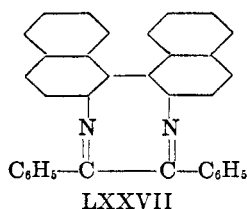
(inactive)

LXXIII

4-Carboxy-5-nitrofluorenone

Kuhn and his students (86, 87) made a similar observation in the case of the dinaphthyl (LXXIV) which, upon heating with sulfuric acid, yielded inactive anthanthrone (LXXV). Inactive naphthocarbazol (LXXVI) resulted when either the *d* or *l* form of 2,2'-diamino-1,1'-dinaphthyl (LXVIII) was heated with hydrochloric acid.
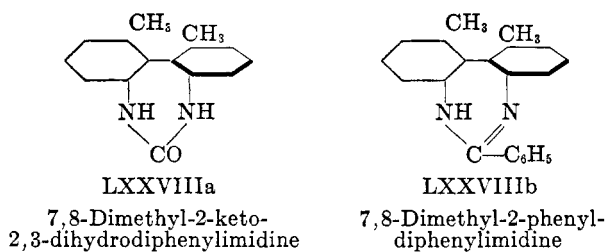

LXXIV
2,2'-Dicarboxy-1,1'-
dinaphthyl
(active)

LXXV
(inactive)

LXVIII
(active)

LXXVI
(inactive)
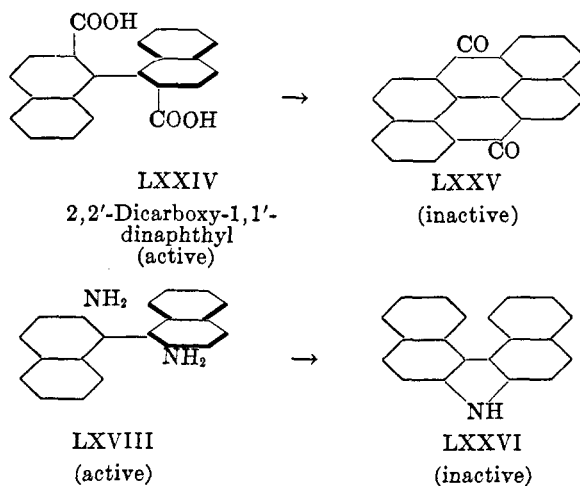
In all these cases five- or six-membered rings were formed linking the 2 and 2' positions. The disappearance of optical activity cannot be attributed to racemization, since most of these optical isomers are stable toward heat or toward many chemical reagents. It is due most probably to the change from a spatial arrangement to a coplanar structure. Before the 2 and 2' positions are linked in a ring the molecule has the coaxial-noncoplanar configuration. On the basis of the present knowledge of the stereochemistry of ring compounds, five- or six-membered rings[14] have the atoms in a single plane. As soon as the 2 and 2' carbons are linked by such a ring system, the two halves of the molecule are forced into a coplanar configuration. Thus a plane of symmetry is introduced into the molecule and optical activity disappears.

[14] This would, of course, not apply to saturated six-membered rings. All six-membered rings referred to in the diphenyls, however, would contain two C=C linkages, one from each of the benzene rings.

It is accepted that rings larger than six-membered are ordinarily strainless and the atoms do not lie in a single plane. If the 2 and 2′ positions in a resolvable diphenyl derivative are linked, therefore, in a strainless ring, the two nuclei of the molecule can still be noncoplanar and the potential optical activity can remain. This was demonstrated by the condensation of d-2,2′-diamino-1,1′-dinaphthyl with benzil with the formation of a highly active product (LXXVII) (87, 168). In this case the 2,2′ carbons are in an eight-membered ring.

$$C_6H_5-C-----C-C_6H_5$$

LXXVII

Sako (141a) has reported the preparation from active 2,2′-dimethyl-6,6′-diaminodiphenyl (LIV) of two derivatives (LXXVIIIa and LXXVIIIb) in which seven-membered rings are formed through the two amino groups. Both these compounds were optically active.

LXXVIIIa
7,8-Dimethyl-2-keto-
2,3-dihydrodiphenylimidine

LXXVIIIb
7,8-Dimethyl-2-phenyl-
diphenylimidine

*Unsymmetrical substitution in each ring*

It is implied in the coaxial-noncoplanar model that each ring in a diphenyl must be unsymmetrically substituted in itself in order that the mirror images may not be superimposable and the compound may, therefore, be capable of resolution. When the coaxial-noncoplanar theory was first suggested, the active compounds known at that time, and even those prepared directly

afterward, contained different groups in the $2,2'$ or $6,6'$ positions and are represented by Series 1 of the general formulas listed below.

Series 1.
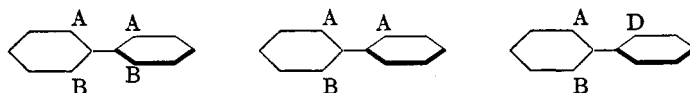
Series 2.
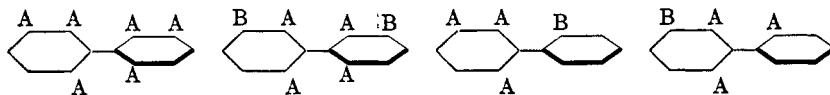
It was pointed out more specifically by Mascarelli (116) and by Hyde and Adams (62) that a benzene nucleus could be unsymmetrically substituted in several ways. All of the $2,2',6,6'$ positions could be occupied by identical atoms or groups, provided other substituents were present in the proper positions to render each ring unsymmetrically substituted. Formulas of Series 2 represent a few of the possibilities in molecules containing identical ortho substituents.

Adams and his students (133, 191, 19, 163) resolved a number of these—LXXVIII, LXXIX, LXXX, and LXXXI.
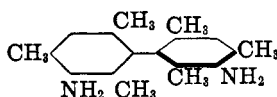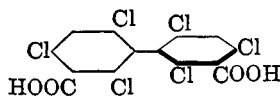

LXXVIII

3,3'-Diamino-2,4,6,2',4',6'-hexamethyldiphenyl
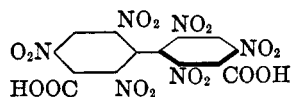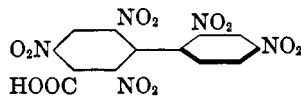

LXXIX

3,3'-Dicarboxy-2,4,6,2',4',6'-hexanitrodiphenyl

LXXX

3,3'-Dicarboxy-2,4,6,2',4',6'-hexachlorodiphenyl

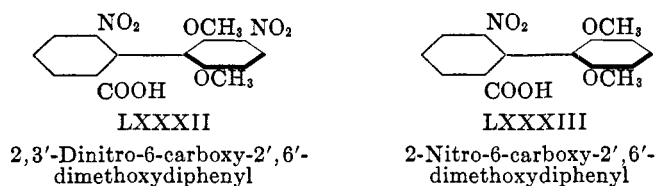

LXXXI

3-Carboxy-2,4,6,2',4'-pentanitrodiphenyl

The active forms all proved to be exceedingly stable.

The general viewpoint of a coaxial-noncoplanar structure for these diphenyls, with the supplementary assumption of unsym-

metrical substitution in each ring, was so quickly and generally adopted that, until recently, no experiments had been performed to show that a properly but symmetrically substituted diphenyl would not be capable of resolution. The resolution of a diphenyl with symmetrical substitution would render the coaxial-non-coplanar theory impossible.

Experiments of Adams and his students in the course of their researches resulted in the preparation of several tri- and tetra-substituted compounds in which one ring was symmetrically substituted, and in no instance was resolution accomplished. Van Arendonk and Adams (185) were able to resolve LXXXII into active components but not LXXXIII, and additional examples are cited in the later sections on diphenylbenzenes and phenylpyrroles that symmetrical substitution in the rings destroys the optical isomerism.


LXXXII
2,3'-Dinitro-6-carboxy-2',6'-dimethoxydiphenyl

LXXXIII
2-Nitro-6-carboxy-2',6'-dimethoxydiphenyl

Physical data

Certain physical data have appeared which support the non-coplanar conception. From an x-ray study Clark and Pickett (46) drew the conclusion that in certain $2,2',6,6'$ derivatives of diphenyl, the two rings were in planes turned from each other at an angle not greater than $45°$, while the rings in diphenyl itself were coplanar.[15]

Bergmann and Engel (17) made dipole measurements upon optically active $2,2'$-diamino-$6,6'$-dimethyldiphenyl (LIV). Of the three possible formulas given below, LIVb, which is coplanar, should give no moment, while LIVc, also coplanar, gives a calcu-

[15] These data of Clark and Pickett have been criticized as insufficient to establish this particular truth, owing to the complexity of the organic molecules (45, 61), but just recently, after more experimental work in the laboratories of the Royal Institute in London, the conclusions of Clark and Pickett appear to be correct.

lated moment of 1.99×10^{18}. The value actually found was 1.66 $\times 10^{18}$ thus offering evidence for formula LIVa. These authors calculated from their measurements that the angle of the two planes in this molecule was 67°.
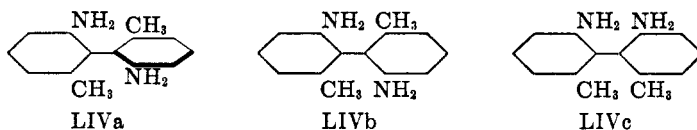
VII. EXPERIMENTAL EVIDENCE RELATIVE TO THE SIZE OF THE 2,2',6,6' GROUPS

The next important problem resolves itself into the determination of the mechanism by which various groups located in the 2,2',6,6' positions can prevent free rotation of the nuclei. The most obvious factors to be considered are (1) the size of the 2,2',6,6' groups, (2) the electrical nature of these groups, (3) the influence of atoms or groups not in the 2,2',6,6' positions. This section deals with the first two of these and the third is discussed in the following section.

On the basis of the obstacle theory, it should be possible merely by properly modifying the size of the 2,2',6,6' groups to prepare optically active diphenyls with widely varying degrees of stability to racemization. The racemization of active diphenyl derivatives or mutarotation of their salts may be explained on the basis of the theory of restricted rotation, in that thermal agitation causes the groups in the 2,2',6,6' positions to slip by each other and thus to result in complete rotations of the two nuclei.

The study of the comparative rates of racemization of different active diphenyls offers a semi-quantitative approach to the determination of the importance of the size of the groups in relation to the blocking effect. Up to 1930 all the known ortho-tetrasubstituted resolvable diphenyls were found to be highly antipodally stable, for instance, XXXI, LIV, LXIX, and LXXVII could not be racemized in boiling acid, alkaline or neutral solution. On the other hand XLIV, XLV, and Schultz's acid, the trisubstituted compounds, were found to racemize in boiling solutions.

The difference between these two sets of compounds is rather to be expected from the obstacle theory. The small volume of the hydrogen atom present in the trisubstituted diphenyls should lend much more chance for the nuclei to pass through the common plane and thus for one active form to change into the mirror image. Moreover, Stearns and Adams (163) pointed out the greater possibility in trisubstituted compounds of the rings bending toward each other when approaching the same plane so as to allow free rotation. This may be a factor in the gradual racemization of such compounds at higher temperatures.

Four pertinent and interesting phases of this problem have been studied experimentally. (A). It should be possible to prepare $2,2',6,6'$-tetrasubstituted diphenyls which, unlike those at first studied, are nonresolvable or resolvable but easily racemized, provided the substituents are not sufficiently large or barely large enough to restrict the free rotation. On the other hand, a trisubstituted compound with large groups should be immune to racemization. (B). A comparison of the rates of racemization of a series of diphenyls in which two of three substituents or three of four substituents in the $2,2',6,6'$ positions remain constant and the third or fourth is varied, should furnish the method for a reasonably quantitative study. The rates of racemization should become greater as the sizes of the groups become smaller. (C). $2,2'$-Disubstituted diphenyls or even 2-monosubstituted diphenyls should be capable of existing in optically active forms, provided the substituent or substituents are sufficiently large to collide with the hydrogen atoms, which appear to have a smaller size and blocking effect than any other atom or group. (D). In groups containing more than a single atom, the steric influence of that whole group should be affected to a greater or less extent by the size and character of those atoms or groups combined to the atom which is attached to the ring.

Each of these lines of attack will be discussed in order. From the practical standpoint the problem of studying the desired effects lies in the selection of the proper groups to substitute in the diphenyl and the preparation of such molecules. Evidence from many sources indicates the fluorine and hydroxyl or methoxyl

to be two of the smallest atoms or groups except hydrogen, with the amino and carboxyl groups not much larger.
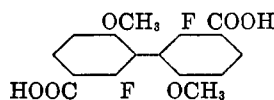
Nonresolvable 2,2',6,6'-tetrasubstituted compounds

(A). The following representatives of Type A (LXXXIV, LXXXV, LXXXVI, LXXXVII), have been prepared by Adams and his students (77, 49, 9), and their resolution has been attempted by means of various alkaloid salts—brucine, strychnine, morphine, cinchonine, and quinine.
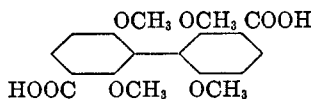
Cl F   F   COOH   OCH₃ F COOH
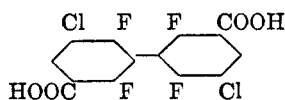
HOOC   F   F   Cl   HOOC   F   OCH₃
        LXXXIV   LXXXV
  2,2',6,6'-Tetrafluoro-3,3'-   2,2'-Difluoro-3,3'-dicarboxy-
dichloro-5,5'-dicarboxydiphenyl   6,6'-dimethoxydiphenyl

    OCH₃ OCH₃ COOH   OCH₃ OCH₃ NH₂
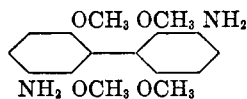
HOOC   OCH₃ OCH₃   NH₂ OCH₃ OCH₃
        LXXXVI   LXXXVII
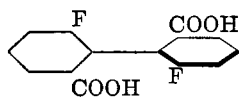 2,2',6,6'-Tetramethoxy-   2,2',6,6'-Tetramethoxy-
  3,3'-dicarboxydiphenyl   3,3'-diaminodiphenyl

In no instance was more than a single salt obtained and none of these showed mutarotation even at low temperatures or gave an active acid on decomposition. A possible exception was the observation of a very slight mutarotation at low temperatures in the camphor sulfonate of LXXXVII. It appears, then, that these are truly representatives of 2,2',6,6'-tetrasubstituted diphenyls in which the ortho groups do not interfere sufficiently to allow resolution.

*Resolvable but easily racemized diphenyls*

The preparation of analogous molecules containing one or more somewhat larger substituents followed. Stanley and Adams (158), on the basis of the interference data (table 2, p. 284), predicted the resolvability and easy racemization of LXXXVIII and of LXXXIX (161, 75). Both of these compounds were synthesized and found to racemize very easily on warming them in a

neutral solvent, and thus they stood out in sharp contrast to the stable active diphenyls studied in the earlier development of the field. Greater stability was expected in XC and actually was found.
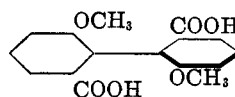

LXXXVIII
2,2'-Difluoro-6,6'-dicarboxydiphenyl
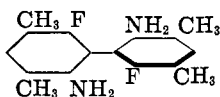
LXXXIX
2,2'-Difluoro-3,5,3',5'-tetramethyl-6,6'-diamino-diphenyl

XC
2,2'-Dimethoxy-6,6'-dicarboxy-diphenyl

Comparison of size of ortho groups and rates of racemization

To make certain that the size was of primary importance and that no specific effect of the fluorine or methoxyl groups was involved, still larger groups along with the fluorine and methoxyl groups were introduced into the molecule. Kleiderer and Adams (76) prepared XCI and found that the active forms did not racemize. In a similar manner XCII and XCIII gave relatively stable active forms which racemized only slowly at higher temperatures (8, 185).
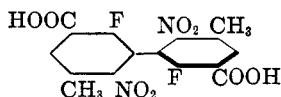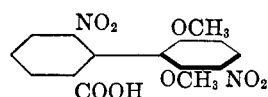

XCI
2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl
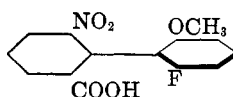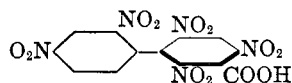
XCII
2-Nitro-6-carboxy-2'-fluoro-6'-methoxydiphenyl

XCIII
2-Nitro-6-carboxy-2'-fluoro-6'-methoxydiphenyl

Although the 2,2',6-trisubstituted diphenyls previously studied could be racemized at high temperatures, Stearns and Adams (163) found that the active forms of XCIV were perfectly stable to the usual means of racemization.
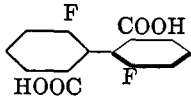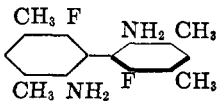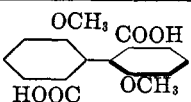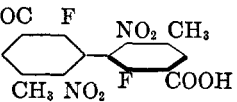

XCIV
2,4,6,2',4'-Pentanitro-3-carboxydiphenyl

The comparison of several of these compounds is given in table 3.

By considering the last three compounds in the table, the racemization of which was carried out in the same solvent, it can be seen that the values for the relative interferences of the groups as deduced from x-ray data fit in surprisingly well with the experimental data on the rates of racemization.

TABLE 3

Rates of racemization and interference values of four diphenyls

GROUPS AT 2,2' 6,6'	INTER-FERENCE OVER 2.90 Å.	REPRESENTATIVE COMPOUND	ANTIPODAL STABILITY
F, COOH	0.05		Complete racemization after 10 minutes boiling in acetic anhydride.
F, NH₂	0.05		Complete racemization after 30 minutes boiling in acetic acid.
OCH₃, COOH	0.11		Half-life period 78 minutes in boiling glacial acetic acid.
F, NO₂	0.41		No racemization in boiling acid, alkaline, or neutral solution

(B). A direct comparison of the effect of different groups might be obtained if the racemization rates of a series of 2,2',6,6'-tetrasubstituted diphenyls were studied in which merely the group in one position only was modified from member to member of the series. To obtain such compounds, however, is extremely difficult, since it is necessary as well that the other groups present

be of such a character that the resulting compounds are more or less readily racemized. Such conditions are more readily obtainable in the 2,2',6-trisubstituted diphenyls and the synthesis of the proper compounds is more feasible. Adams and his students investigated various compounds in this group. They (57, 166) selected for study the two following sets of compounds: (a) 2-x-2'-nitro-6'-carboxydiphenyl (XCV), where x = methoxyl, methyl, carboxyl, or nitro, and (b) 2-y-5-methyl-2'-nitro-6-carboxydiphenyl (XCVI), where y = fluorine, chlorine, or bromine.

Series a	Series b
XCV	XCVI
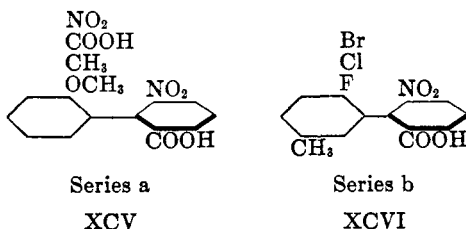
In this connection it may be pointed out that Kuhn and Albrecht (83, 84) demonstrated that the decrease in optical activity of diphenyls obeyed the law of a first order reaction and expressed the rate of racemization in terms of half-life periods.[16] This furnished at least a convenient semi-quantitative measure of stability of such compounds under different conditions, and was adopted in the discussion of the series of compounds with varying rates of racemization.

The presence of the 5'-methyl group in Series b, as will be discussed in a later chapter, probably had very little effect upon

[16] From the rotation values at different time intervals, the constant K of the rate of racemization can be calculated by the formula

$$K = \frac{1}{t} \log \frac{\alpha_0}{\alpha_t}$$

where t is the time in minutes, α_0 the initial rotation, α_t the rotation at time t. The half-life period is calculated from the equation

$$T = \frac{1}{K} \log 2$$

the racemization rates and, therefore, a direct comparison of the compounds in Series a and Series b was permissible.

The methoxyl and the fluorine derivatives showed an interesting phenomenon. Only one alkaloidal salt could be isolated in each instance. The brucine salt of the 2-nitro-6-carboxy-2'-methoxy-diphenyl (XCV) mutarotated in solution at room temperature and the mutarotation undoubtedly was due to the racemization of the acid portion in the salt. The active acid obtained from the brucine salt racemized rapidly at room temperature.

The brucine or quinine salt of 2-nitro-6-carboxy-2'-fluoro-5'-

TABLE 4

Comparison of rates of racemization and the relative interference values from the x-ray data

SUBSTITUTED 2-NITRO-6-CARBOXYDIPHENYL	SOLVENT	TEMPERATURE	HALF-LIFE PERIOD	AVERAGE INTERFERENCE ON EACH SIDE Å.
		degrees C.	*minutes*	
2'-Br, 5'-CH$_3$	Acetic acid	118	3240	0.36
2'-CH$_3$	Acetic acid	118	179	0.18
2'-Cl, 5'-CH$_3$	Acetic acid	118	154	0.26
2'-NO$_2$	Acetic acid	118	125	0.27
2'-COOH	Acetic acid	118	91	0.09
2'-OCH$_3$	Absolute alcohol	25	9.4	0.04
2'-F, 5'-CH$_3$	No active acid obtained			0.01

methoxydiphenyl (XCVI) showed no mutarotation at room temperature but did show it at 0°C.; an equilibrium value resulted at that temperature identical with that obtained by dissolving the salt at room temperature and cooling to 0°C. At room temperature the mutarotation was obviously so rapid that it could not be followed experimentally. The acid from this salt certainly would be extremely sensitive to racemization and in spite of all precautions, no active acid could be obtained by decomposition of the salt even at −5°C.

The other five compounds had normal properties. Both salts were isolated and both active forms of each compound were obtained. The active acids could be racemized only at higher

temperatures. The rates of racemization are given in table 4, with the estimated interference values (158) for comparison.

From the half-life periods it appeared that the relative interference effects of the seven groups studied would be in the following order—Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. Racemization tests in other solvents showed practically the same order. It is noticeable how closely the order followed that of the calculated interference values. The discrepancy between half-life periods and calculated interferences of the nitro and methyl or chlorine groups probably may be attributed to an error in the estimation of the internuclear distance to the center of the methyl group, since many experiments have indicated the methyl as larger than the other two. Moreover, there was always a certain experimental error in the determination of the half-life periods.

2,2'-Disubstituted diphenyls

(C). The possibility of optically active 2,2'-disubstituted diphenyls is of particular interest, because several investigators simultaneously directed their attention to the solution of this problem. After the resolution of 2,2'-dinitro-6,6'-dicarboxydiphenyl, several attempts to resolve 2,2'-disubstituted compounds were made without success (see Section IV).

Bell and Robinson (14) pointed out the theoretical possibility of resolution of 2,2'-disubstituted diphenyls as a logical consequence of the obstacle theory. Suitable derivatives for testing this point were not obtained however. Stanley and Adams (160) were unable to resolve XCVII which, from the standpoint of estimated interferences, offered some possibility of resolution. The compound yielded very insoluble alkaloidal salts which were impossible to fractionate and which gave no active acid on decomposition; moreover, the dimenthyl ester could not be fractionated into stereoisomers. From x-ray experimentation it is known that the carbon–sulfur distance is large and Stanley and Adams (159) consequently attempted the resolution of XCVIII. Owing to the procedure followed in attempts at resolution, they obtained and reported negative results.
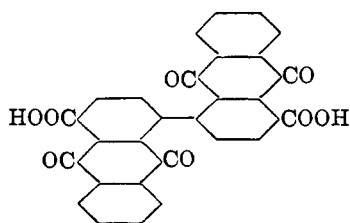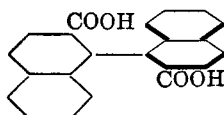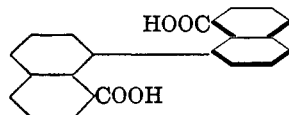
XCVII

4,4'-Dicarboxy-1,1'-
dianthraquinonyl
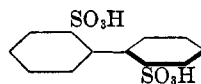
XCVIII
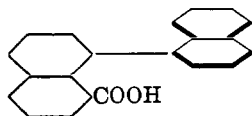
Diphenyl-2,2'-
disulfonic acid

Shortly after, the successful resolution of XCIX was published independently by Stanley (156), by Corbellini (47), and by Meisenheimer and Beisswenger (120). This compound could
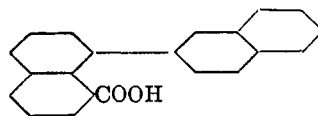
LXVII

2,2'-Dicarboxy-
1,1'-dinaphthyl

XCIX

8,8'-Dicarboxy-
1,1'-dinaphthyl

C

8-Carboxy-1,1'-dinaphthyl

CI

8-Carboxy-1,2'-dinaphthyl

be considered as a disubstituted diphenyl with two C—COOH groups in the 2 and 2' positions. The existence of optical isomers indicated that these groups were sufficiently large to interfere with the hydrogen atoms even though the active acids were readily racemized. The instability of this active compound as compared with that of its very stable isomer (LXVII) was striking.

Meisenheimer and Beisswenger (120) also described the preparation and resolution of C. Its active forms were less stable than those of XCIX. A third compound, CI, was found nonresolva-

ble and it appeared that with only one substitution the molecule
was much more mobile.

Since there is a difference between derivatives of 1,1'-dinaph-
thyl and those of diphenyl, in that the groups attached to the 8
and 8' positions in the dinaphthyl have a spatial orientation
which cannot be reproduced in the diphenyl series, the results
are not directly comparable with those in the diphenyl series.
Nevertheless, the results offered a further indication that 2,2'-
disubstituted diphenyls with proper groups should be resolvable.
Lesslie and Turner (104) reported the optical resolution of CII.
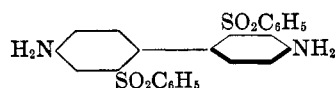
CII

Diphenyl ester of 4,4'-diamino-
diphenyl-2,2'-disulfonic acid
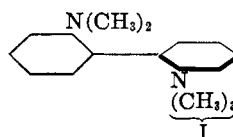
CIII

Monomethiodide of 2,2'-*bis*-
(dimethylamino)-diphenyl

Moreover, these same investigators (105) resolved diphenyl-2,2'-
disulfonic acid (XCVIII) a compound which Stanley and Adams
(159) predicted might resolve but which they failed to obtain in
active forms because of the method employed in attempting resolu-
tion.   Turner (177) also separated CIII into active components.
The cold aqueous solution of the active forms in which the ioniza-
tion was practically complete, retained its activity for indefinite
periods.   Turner considered that the asymmetry of the molecule
was due to the dynamic effect of the two methyl groups attached
to the nitrogen atoms.

Corbellini (48) obtained a mutarotating salt from CIIIa, and
also from the corresponding compound having two methyls in
place of the phenyls attached to the carbon holding the hydroxyl
group (48a).   Stanley and Adams (159) predicted the resolvability
of derivatives of 2,2'-diiododiphenyl and possibly of 2,2'-di-
bromodiphenyl.   This prediction was realized when Searle and
Adams (142, 143) were able to separate CIV into enantiomorphs
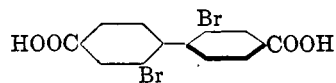and to obtain mutarotation in the salt of CV.
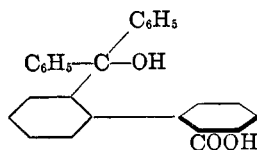
CIIIa

2-(Diphenylhydroxy-
methyl)-2'-carboxy-
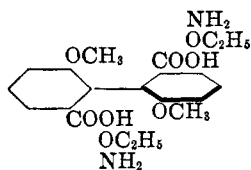diphenyl
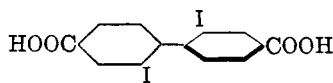
CIV

2,2'-Diiodo-4,4'-
dicarboxydiphenyl

CV

2,2'-Dibromo-4,4'-
dicarboxydiphenyl

Steric effects of nuclei combined to the atom attached to the ring

(D). The steric effect of the hydrogens in the hydroxyl, the amino, or the methyl groups might be expected to be appreciable. Moreover, such an effect would be greater, probably, in the methyl than in the amino, and, in turn, greater in the amino than in the hydroxyl group. An estimate of these interferences was made in the calculation of the internuclear distances by Stanley and Adams. Such influences undoubtedly would vary widely though, in general, probably would be small on account of the free rotation existing between the atom holding the hydrogens and the carbon atom of the ring to which it is attached. With larger nuclei combined to the atom attached to the ring, greater influences might be exerted, depending upon the sphere of influence and character of the atoms present.

No systematic study along these lines has been, as yet, completed. An indication of what may be expected can be seen in a comparison of the racemization rates of the active acid, ester, and amide of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl (CVI) (161). In glacial acetic acid the half-life periods of the acid, ester, and amide were 78, 88, and 240 minutes, respectively. The amino in the —$CONH_2$ group was sterically much more effective than the hydroxyl or the ethoxyl.

CVI

2,2'-Dimethoxy-6,6'-dicarboxydiphenyl and derivatives

All these experimental results favor the obstacle theory.   Some confusion regarding the interpretation of the theory appears to exist, since Bergmann (16) suggested the obstacle theory as unnecessary and yet considered the "mutual influence of the electron shells of the atoms or groups" to be the chief consideration, and Bretscher and Wolf (24) expressed a similar view.   Their conception, however, is similar to that of other previous investigators in the field (159) who have used the term "obstacle."

An occasional objection is raised to the obstacle theory.   Turner (175) argued that if steric effects were large, it would be expected that 2-nitrodiphenyl would nitrate to a larger extent in position 4' and less in position 2', than would 4-nitrodiphenyl. Actually it was found that 2-nitrodiphenyl nitrated 39 per cent in position 2', and 4-nitrodiphenyl only 37 per cent in this position. Turner considered this as evidence that steric effects of one group were not of first importance.   But in this case the steric effects would appear to be of somewhat different character and the value of this conclusion is dubious.

Electrical effects of groups

The experimental evidence in this last section has been discussed merely from the standpoint of the size of the atoms or groups.   What is the evidence in regard to the electrical effects of the groups?   In attempting to answer this question it is pertinent to consider diphenyls in which all four ortho groups are identical.   The diphenyl molecules containing four methyls, four chlorines, four nitros, four methoxyls, and four fluorines in the ortho position, have been studied from the standpoint of resolution, and when resolved, their racemization rates have been determined.   The compounds containing the four chlorines and four nitro groups which are polar in character were very resistant to racemization.   But the compound with four methyl groups, which are essentially nonpolar and approximately the same size as the chlorines, was also very resistant to racemization.   On the other hand, the tetrafluoro and tetramethoxy compounds were neither of them even resolvable.   In fact, by considering all of the large variety of compounds already studied, it is impossible to correlate electrical characteristics and interference effects of

the individual groups.   Steric influences due to the polarity of groups probably produce no more than a secondary effect.

VIII. EFFECT OF FACTORS OTHER THAN THE SIZE OF ORTHO GROUPS

The foregoing experimental facts present a preponderance of evidence that the size of ortho groups is a major factor in the resolvability or nonresolvability of certain diphenyl compounds and in the stability of the active molecules.   But in such a complex molecule as a substituted diphenyl, it is not surprising that other factors exist which may affect more or less the stability of the active isomers.

Substituents in positions other than the 2,2',6,6' positions

It was first noted by Kuhn and Albrecht (84) that the half-life period of active CVII in 2 N sodium hydroxide solution at 98°C. was eighteen minutes, and that of CVIII, under the same conditions, was fifty minutes.   Thus antipodally the latter was three times as stable as the former.   This was inexplicable if the 2,2', 6,6' groups were the only factors which affected the stability to racemization of the active molecules.
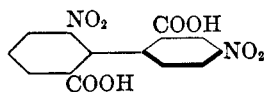
CVII

2,4'-Dinitro-2',6'-
dicarboxydiphenyl
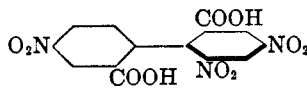
CVIII

2,4,4'-Trinitro-6,6'-
dicarboxydiphenyl

Later, Adams and his students started a systematic study on this particular phase of the diphenyl stereochemistry.   Yuan and Adams (194, 195) prepared a series of compounds, each of which was a 5'-substituted 2-nitro-6-carboxy-2'-methoxydiphenyl with the 5' group successively methoxyl, methyl, chloro, bromo, and nitro (CIX).   These were compared with the unsubstituted
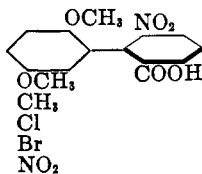
CIX

2-nitro-6-carboxy-2'-methoxydiphenyl which racemized readily at room temperature and thus made possible a fairly accurate polariscopic study of the rate of racemization. The determination of the effect of each of a variety of groups in the 5' position was thus possible. For each compound merely one alkaloidal salt could be isolated and all of these mutarotated in solution. The active acids obtained from the salts racemized readily in organic solvents at room temperature. The half-life periods of the various molecules varied from compound to compound (table 5).

A comparison of the rates of racemization of the free acids indicated that the stabilities of the unsubstituted, the 5'-methoxyl

TABLE 5

Half-life periods at 26°C. of the active forms of substituted 2-nitro-6-carboxy-2'-methoxydiphenyls and their salts

COMPOUND	HALF-LIFE PERIOD IN MINUTES	
	Free acid in alcohol	Brucine salt in chloroform
	minutes	*minutes*
No substituent	9.4	12.0
5'-OCH₃	10.8	16.7
5'-CH₃	11.5	15.8
5'-Cl	31.0	16.7
5'-Br	32.0	16.7
5'-NO₂	35.4	7.7

and the 5'-methyl derivatives were practically the same, the stabilities of the 5'-chloro and 5'-bromo were also identical and more stable than the first three. The 5'-nitro appeared to be somewhat more stable than the 5'-halogen derivatives.

Only a few results on analogous compounds (58) with substituents in the 4' and 3' positions are as yet available, but it is clear that the effect of groups in these positions will be different from that in the 5' position. The 4'-nitro (CX) racemized less readily than the corresponding 5' derivative, and the 4'-methoxyl (CX) more readily than the corresponding 5' derivative. The 3'-methyl (CXI) homolog (38) unlike the 5' derivative could not be obtained in active forms nor did the alkaloidal salts mutarotate.

CH$_3$O, NO$_2$ 〈 〉 — 〈 〉 OCH$_3$ NO$_2$ COOH

CH$_3$ OCH$_3$ NO$_2$ 〈 〉 — 〈 〉 COOH

CX   CXI
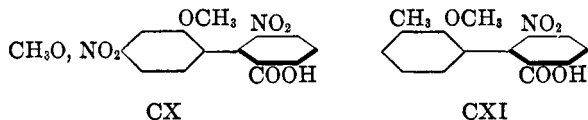
From these data it becomes obvious that groups other than the 2,2′,6,6′ do affect the stereoisomeric stability of the active diphenyl compounds. The theoretical basis for and the exact mechanism of this phenomenon are still obscure, but it may involve one or more, or possibly all, of the following causes (195). (1) The variation of the valency angle at which the ortho substituent on the ring is attached, thus changing the effective size of the group; (2) the slowing down of the semicircular oscillation of the two phenyl rings by substituents, thus diminishing the chances of the complete rotation; (3) the modification of the distance between 1,1′ carbon atoms with the nature of substituents; (4) the bending of the linkage between the two rings in such a way that the rings are no longer coaxial. There appears also to be some parallelism between the rates of racemization of these diphenyls and the dipole moments of the corresponding substituted anisoles, which comprise half of the respective molecules. The experimental results are perhaps significant in leading to the conclusion that cause 2 is not a factor, since the substitution of two atoms of similar polarity but of different weight, such as chlorine and bromine, resulted in essentially identical effects on the rate of racemization.

Comparison of isomeric 2,2′,6-trisubstituted compounds

Another interesting comparison is that of the stability of three 2,2′,6-trisubstituted diphenyls where the groups are the same but differ in their relative positions. If the two rings remain symmetrically placed as they approach the same plane, the rate of racemization would be determined by the ease with which the group of position 2′ could pass the smaller or less interfering of the groups at positions 2 and 6. Thus, in CXII, where R$_3$ is the largest group, R$_2$ the next in size, and R$_1$ the smallest or least interfering group, the rate of racemization would depend chiefly on the ability of the group R$_1$ to pass the group R$_2$. The passing

of the groups R_1 and R_3 would be more difficult, so would have less effect on the rate of racemization.

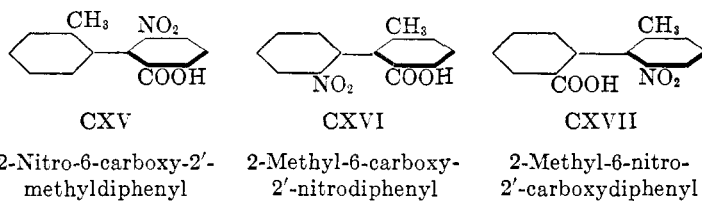

CXII   CXIII   CXIV
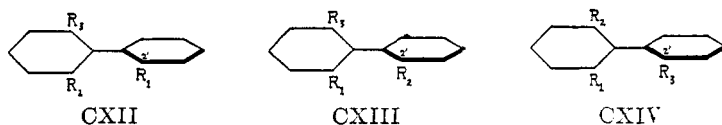
In compound CXIII, where the groups have been interchanged, the ability of the groups R_1 and R_2 to pass each other would again be the largest factor determining its rate of racemization. These two compounds then would be expected to racemize at about the same rate.

A third interchange of groups resulting in compound CXIV should produce a more stable system than either of the above two, because here the group R_1 would have to pass the largest group R_3 in order for the compound to racemize.

On the other hand, if the molecule is mobile, then an average interference is the significant factor, and the rate of racemization of each should be approximately the same.

Actually, three substituted diphenyls illustrating the above types were prepared and studied (57, 165). They were CXV, CXVI, and CXVII.

CXV   CXVI   CXVII

2-Nitro-6-carboxy-2'-   2-Methyl-6-carboxy-   2-Methyl-6-nitro-
   methyldiphenyl   2'-nitrodiphenyl   2'-carboxydiphenyl

Since the methyl was the largest group as determined by racemization values, compounds CXV and CXVI should be of about the same stability, and compound CXVII should be less stable. Experimentally, it was found that compound CXV racemized most readily, CXVI the next, and CXVII the least readily of all. The interchange of ortho substituents must, therefore, involve certain relative influence factors which affect the stability of the active molecules.

It is desirable here to point out other unexpected phenomena which must be attributed to some factors in the molecule other than the size of ortho groups. The mutarotation of the salts of the series of acids previously mentioned in which a variable 5' group was involved, did not run parallel to the rates of racemization of the acids. The sodium salts of many optically active diphenyl derivatives racemized in aqueous solution more readily than the free acid racemized in organic solvents. This was assumed to be due, possibly, to ionization and the smaller size of the COO⁻ group. It was found, however, that the sodium salts of all the substituted 2-nitro-6-carboxy-2'-methoxydiphenyls in water racemized less readily than the free acids in organic solvents (195). The sodium salts in absolute alcohol, however, racemized more readily than the free acids in the same solvent.

It might appear at first from the relatively large change in the racemization rates caused by substituents in positions other than the 2,2',6,6', that such substituents play a very important rôle. Nevertheless, it must be considered that the amount of change is something about which no quantitative information is available. It is quite possible that small changes in interference have a large observed effect, particularly on those molecules which are sensitive to racemization under mild conditions.

So far the experimental data are not sufficient to give a clue as to the nature of these phenomena.

IX. POLYPHENYL SYSTEMS

Compounds having more than one asymmetric carbon atom possess a number of diastereoisomers, and the same phenomenon is to be expected in derivatives of properly substituted polyphenyls containing several asymmetric centers. The stereoisomerism of p-diphenylbenzenes was first discussed by Stanley and Adams (157, 78).
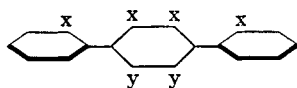
Theoretically, there are four general types of properly substituted p-diphenylbenzenes.
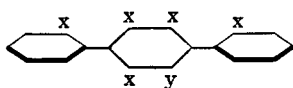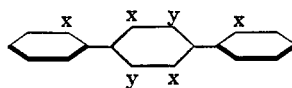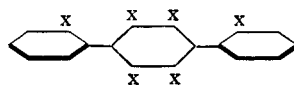

Type 1   Type 2

Type 3   Type 4

Type 1 contains two dissimilar asymmetric centers and should, therefore, exist in two disastereoisomeric forms, each of which is a racemic modification, one *cis* and one *trans*. Compounds of Types 2 and 3 have two similar asymmetric centers and, therefore, should exist in two forms, one meso and one racemic. The meso form of Type 2 is the *trans* form, and the racemic is the *cis* form. On the other hand, the meso form of Type 3 is the *cis* form, and the racemic is the *trans* form. It is of interest that the meso form of Type 2 has not the usual plane of symmetry, but a point of symmetry. In Type 4 the central ring is symmetrically substituted so that there exist no asymmetric centers and consequently no optical isomerism is possible. On the other hand, restricted rotation is still capable of existence and two geometric isomers, *cis* and *trans* forms, result.

Properly substituted *meta-* and *ortho-* diphenylbenzene derivatives yield analogous, though somewhat different, types of stereoisomers. Type 5, with two different asymmetric centers, should exist in two diastereoisomeric racemic forms, one *cis* and the other *trans*. In Type 6 the two asymmetric centers are identical, so that meso and racemic modifications exist. As a plane of symmetry is present in the *cis* modification, it will be the meso, and the *trans* modification will be the racemic. Such a compound corresponds to Type 3 of the *p*-diphenylbenzene series. Similar conditions obtain in Type 7, in which a single group in the central ring acts as an interfering group for both asymmetric centers.
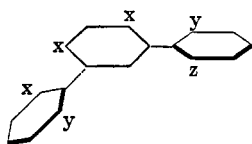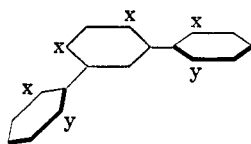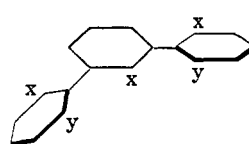
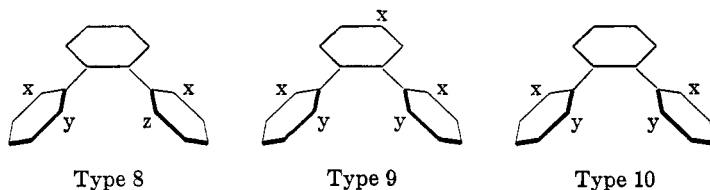Type 5   Type 6   Type 7

In the *o*-diphenylbenzenes three types exist, as shown by Types 8, 9, and 10; it will be observed that two of these, 8 and 10, contain no substitution in the central ring. Such substitution is

Type 8   Type 9   Type 10

unnecessary for restricted rotation because of the fact that one
of the terminal benzene rings acts as the third substituent to
produce restricted rotation between the other terminal ring and
the central ring.   Only if it is desired to render the central ring
unsymmetrically substituted when the two terminal rings are iden-
tical (9) is substitution necessary.   Types 8 and 9 correspond to
Type 5, in that two racemic modifications are possible, one *cis*
and one *trans*.   In Type 10 there are the meso or *cis* form and the
racemic or *trans* form.

But if a model of *o*-diphenylbenzene (11) is constructed with
all the rings coplanar, it can be seen that the distance 'd' between
the ortho carbons in the two terminal rings is the same as that of
an internuclear C—C bond, 1.45Å.   Thus, merely two hydrogen
substituents should collide and isomers should exist provided that
the terminal rings are unsymmetrically substituted.   There are
then three possibilities, represented by Types 12, 13, and 14.

Type 11   Type 12   Type 13
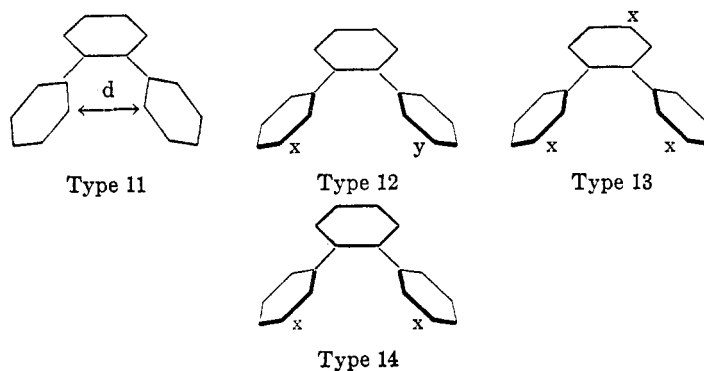
Type 14

In Types 12 and 13 two racemic modifications should exist, one
cis and one *trans*; in Type 14 one racemic, the *trans* form, and one
meso, the *cis* form.   Such isomers as have just been pictured are
dependent on the assumption that the oscillation of the two
terminal rings is not synchronized in such a way as to prevent
collisions.

Properly substituted polyphenyls with more than three nuclei will involve more than two asymmetric centers and, therefore, will make possible the existence of additional stereoisomers. By way of illustration may be cited one general case in which three asymmetric centers are present.
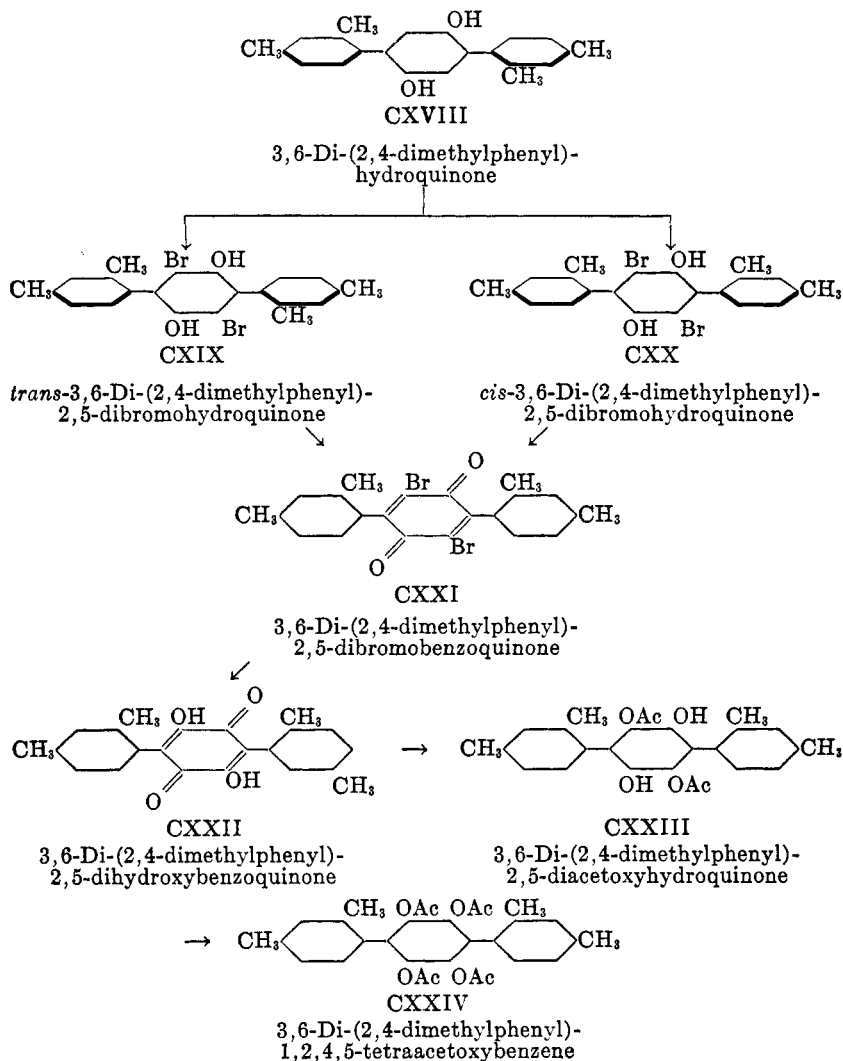
$$1 \qquad 2 \qquad 3 \qquad 4$$
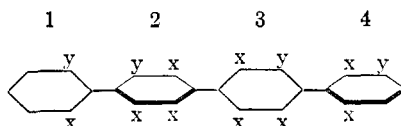
A quaterphenyl of this type should occur in four racemic modifications where the possible configurations of the pairs of rings are as follows:

Rings

1,3	2,4
cis	*cis*
cis	*trans*
trans	*cis*
trans	*trans*

The special cases in the polyphenyls are even more numerous.

Experimentally, only *p*-diphenylbenzene derivatives have as yet been investigated. The possibility for the existence of a meso and a racemic modification of substituted *p*-diphenylbenzenes of Type 2 was demonstrated by the isolation (25) of two stereoisomeric compounds, CXIX and CXX, prepared by bromination of CXVIII, a product from the reaction of *m*-xylene, quinone, and aluminum chloride. Each of the two isomers formed individual series of derivatives but oxidized to the same quinone CXXI. The quinone, in turn, upon reduction always gave a mixture of the two hydroquinones, CXIX and CXX.

Sufficient interference apparently was not present in the quinone to allow the existence of two isomers. From the quinone by treatment with alkali (53), a dihydroxyquinone (CXXII) was formed which, on acetylation and reduction, gave a diacetoxyhydroquinone (CXXIII) which, on acetylation, gave a tetraacetate (CXXIV). This last compound belongs to Type 4 and should occur in *cis* and *trans* modifications. Only one form was obtained, but from the available knowledge that the hydroxyl group or its derivatives had only a very small interfering effect, this was not an unexpected result.

CH₃ OH
CH₃—◯—◯—◯—CH₃
    OH   CH₃
CXVIII
3,6-Di-(2,4-dimethylphenyl)-
hydroquinone

trans-3,6-Di-(2,4-dimethylphenyl)-
2,5-dibromohydroquinone
CH₃ Br OH
CH₃—◯—◯—◯—CH₃
   OH Br CH₃
CXIX

cis-3,6-Di-(2,4-dimethylphenyl)-
2,5-dibromohydroquinone
CH₃ Br OH CH₃
CH₃—◯—◯—◯—CH₃
      OH Br
CXX

CH₃ Br O
CH₃—◯—◯—◯—CH₃
   O   Br
CXXI
3,6-Di-(2,4-dimethylphenyl)-
2,5-dibromobenzoquinone

CH₃ OH O CH₃
CH₃—◯—◯—◯—CH₃
   O   OH CH₃
CXXII
3,6-Di-(2,4-dimethylphenyl)-
2,5-dihydroxybenzoquinone

→

CH₃ OAc OH CH₃
CH₃—◯—◯—◯—CH₃
      OH OAc
CXXIII
3,6-Di-(2,4-dimethylphenyl)-
2,5-diacetoxyhydroquinone

→

CH₃ OAc OAc CH₃
CH₃—◯—◯—◯—CH₃
      OAc OAc
CXXIV
3,6-Di-(2,4-dimethylphenyl)-
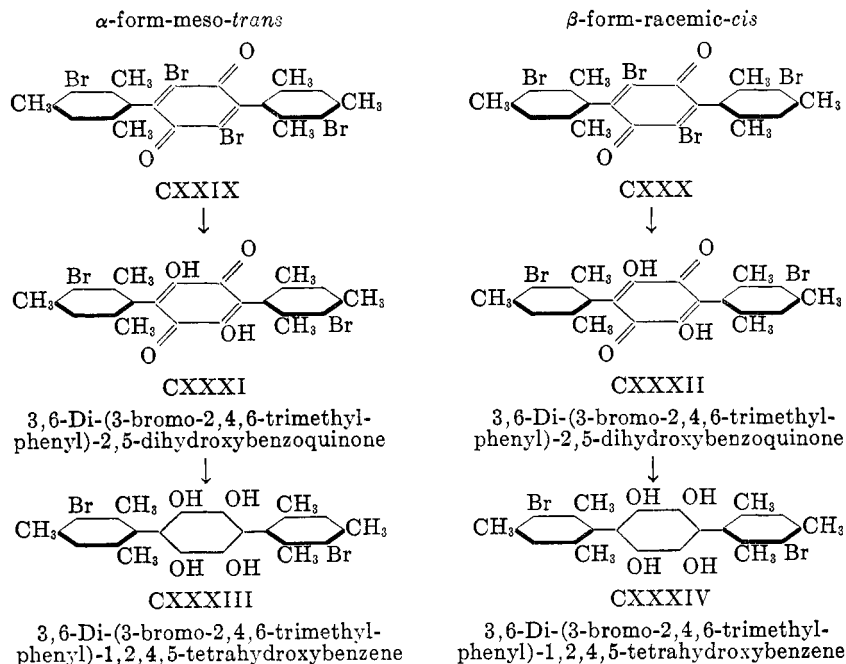1,2,4,5-tetraacetoxybenzene

A second compound (148, 149) in which all of the ortho positions were filled furnished a more suitable compound for testing the validity of the predictions. By brominating CXXV, a product from the reaction of mesitylene, quinone, and aluminum chloride, two stereoisomeric compounds CXXVI and CXXVII were formed. These isomers were converted readily to characteristic derivatives. Upon bromination they produced the same

hexabromo derivative (CXXVIII), thus experimentally confirming the fact that stereoisomers exist only if each of the rings is unsymmetrically substituted.

Each of the two tetrabromodimesitylhydroquinones, CXXVI and CXXVII, unlike the two dibromodixylylhydroquinones, CXIX and CXX, which oxidized to the same quinone, yielded, upon oxidation, the stereoisomeric quinones (CXXIX and CXXX). The additional *o*-methyl group increased the interference sufficiently to produce restricted rotation and thus allowed the formation of isomers in the quinones. Incidentally, these quinones present an example of restricted rotation between a benzene and a quinone ring, the first instance of such isomerism to be found in systems other than diphenyl.

CXXV
3,6-Di-(2,4,6-trimethylphenyl)-
hydroquinone

α-form-meso-*trans*

CXXVI
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

CXXIX
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromobenzoquinone

β-form-racemic-*cis*

CXXVII
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

CXXX
3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dibromobenzoquinone

CXXVIII
3,6-Di-(3,5-dibromo-2,4,6-trimethyl-
phenyl)-2,5-dibromohydroquinone

The two diastereoisomeric dibromoquinones (CXXIX and CXXX) with aqueous sodium hydroxide were converted to two stereoisomeric dihydroxyquinones (CXXXI and CXXXII) (149).

α-form-meso-*trans*   β-form-racemic-*cis*

CXXIX   CXXX

CXXXI   CXXXII
3,6-Di-(3-bromo-2,4,6-trimethyl-   3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-2,5-dihydroxybenzoquinone phenyl)-2,5-dihydroxybenzoquinone

CXXXIII   CXXXIV
3,6-Di-(3-bromo-2,4,6-trimethyl-   3,6-Di-(3-bromo-2,4,6-trimethyl-
phenyl)-1,2,4,5-tetrahydroxybenzene phenyl)-1,2,4,5-tetrahydroxybenzene

Each of these two latter compounds formed the expected individual series of derivatives,—namely, the diacetoxyquinones, the dibutyroxyquinones, the diacetoxyhydroquinones, the tetrahydroxy compounds (CXXXIII and CXXXIV), the tetraacetoxy and tetrabutyroxy compounds. The last three pairs belonged to the *p*-diphenylbenzenes of Type 4 and represented *cis* and *trans* isomers incapable of optical isomerism. On the other hand, the two hydroxyquinones and their derivatives represented pairs of *cis* and *trans* isomers, in each pair of which one is a meso and one a racemic modification.

Owing to the small size of the hydroxyl group, the *cis* form of the dihydroxyquinone (CXXXII) and its diacetate and dibutyrate could be converted, by heating in high-boiling solvents,

into the corresponding *trans* forms.   Similar treatment did not cause the conversion of any of the other *cis* forms in this series.

The high-melting forms in the dimesitylbenzene and dimesityl-quinone series were assumed by analogy to other known pairs of stereoisomers to be the *trans* modifications, and the low-melting forms to be the *cis* modifications.   That this assumption is correct Shildneck and Adams (150) proved experimentally by the isolation of two diastereoisomeric menthoxyacetates (CXXXV and CXXXVI) of the *cis* form and only one such derivative of the *trans* form.
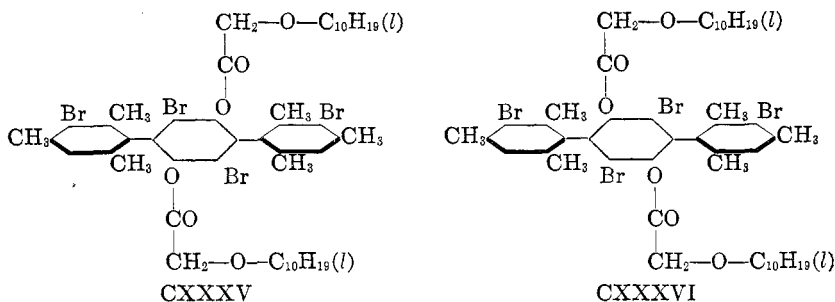
3,6-Di-(3-bromo-2,4,6-trimethylphenyl)-
2,5-dibromohydroquinone dimenthoxyacetate

From the two compounds CXXXV and CXXXVI, the two active forms of the dihydroxy compound (CXXVI) were obtained by hydrolysis.

From these results, though limited in number, it is obvious that in the diphenylbenzene system the exact conditions hold that would be expected from the study of the diphenyl series.

X. EXTENSION INTO NONBENZENOID RING COMPOUNDS

The search for the presence of stereoisomerism in certain substituted molecules containing rings of an aromatic but non-benzenoid type is a natural development from the study of diphenyl compounds.   Such a field includes compounds in the series of the phenylpyridines, dipyridyls, phenylpyrroles, dipyrryls, phenyl-pyrazoles, etc.   The difficulty of synthesis, however, is a severe hindrance to the rapid development of the study of these types.
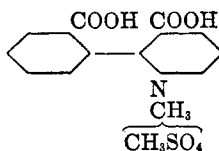
Apparently the first suggestion that the stereoisomerism ob-

served in the diphenyl series might also occur among binuclear heterocyclic substances is due to Kermack and Slater (73), who attempted the resolution of CXXXVII but met with failure.
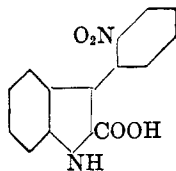

CXXXVII

3-(o-Nitrophenyl)-indole-
2-carboxylic acid

CXXXVIII
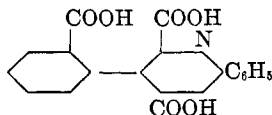
2-(o-Carboxyphenyl)-3-carboxy-
pyridine methylsulfate

Lions and his coworkers (35, 109) made attempts to provide a blocking group in the 2-phenylpyridine series by conversion of the tertiary nitrogen atom into a quaternary salt.   Thus CXXXVIII was examined, but its resolution was not effected.

Steele and Adams (164) prepared two substituted phenyl-pyridines, CXXXIX and CXL, but were unable to resolve them.
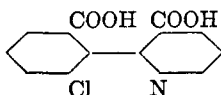
CXXXIX

2-(2-Carboxy-6-chlorophenyl)-
3-carboxypyridine

CXL

3-(2-Carboxyphenyl)-2,4-
dicarboxy-6-phenylpyridine

The negative results were attributed to possible distortion within the molecule with subsequent free rotation, due, possibly, to the character of the pyridine ring or to the electrical attraction of the basic nitrogen and acid carboxyl groups which would disturb the normal interferences.

Phenylquinones, phenylpyrroles, dipyrryls, dipyridyls

In the study of terphenyl derivatives (148) two stereoisomeric diphenylquinones (CXXIX and CXXX) were obtained, and as mentioned previously these compounds represented the first examples of a diphenyl type of isomerism in compounds which have one of the rings not a benzene nucleus.

Later, Hill and Adams (60) prepared and resolved CXLI into optical enantiomorphs. Another substituted phenylquinone (CXLII) of the resolvable type (196) was prepared, but resolution was not effected because attempts to introduce proper salt-forming groups into the molecule resulted in failure.
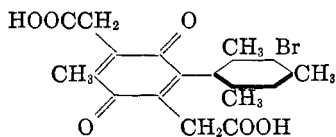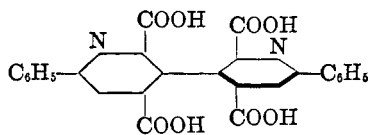

CXLI

2-(3-Bromo-2,4,6-trimethylphenyl)-
5-methylbenzoquinone-3,6-di-
(acetic acid)
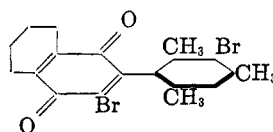
CXLII

2-(3-Bromo-2,4,6-trimethylphenyl)-
3-bromo-1,4-naphthoquinone

In spite of the fact that several attempts to resolve a C—C linked phenylpyridine were unsuccessful, the resolution of a 2,2',6,6'-substituted dipyridyl into optically active isomers was reported by Woodruff and Adams (193). Upon oxidation of phenanthroline with potassium permanganate, CXLIII was obtained and resolved. The active acids were readily racemized by warming for a short time in ethyl alcohol.


CXLIII

2,4,2',4'-tetracarboxy-
6,6'-diphenyl-3,3'-di-
pyridyl

Perhaps the most fruitful and interesting results in the field of binuclear compounds other than diphenyls was obtained from the study of compounds of N-phenylpyrrole and N,N'-dipyrryl types. Different from all the compounds previously studied where the attachment of one ring to the other is through carbon linkages, substituted N-phenylpyrroles represent a class of bicyclic compounds with carbon–nitrogen linkages between the rings.

Bock and Adams (19) prepared and resolved CXLIV. The active forms were exceedingly stable and did not racemize upon boiling for eight hours in ethyl alcohol, and were only completely racemized by boiling for twenty-four hours in 0.1 N sodium hydroxide solution. Then a dipyrryl (CXLV) was resolved by Chang and Adams (37) and the active forms were found to be unusually resistant to racemization.
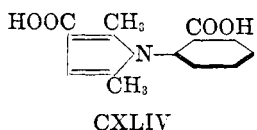

CXLIV

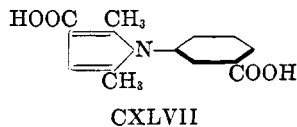N-2-carboxyphenyl-2,5-dimethyl-3-carboxypyrrole

CXLV
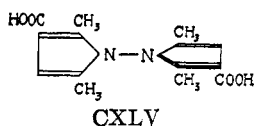
N,N'-2,5,2',5'-tetramethyl-3,3'-dicarboxydipyrryl

If the usual explanation of the phenomenon in the diphenyl series is applied here, it may be said that there is restricted rotation between the benzene ring and the pyrrole ring or between the two pyrrole rings, owing to the interference of the ortho groups. In this case, the three valences of each nitrogen must be assumed to be in a single plane or at least to oscillate through a configuration in which the two rings are coaxial. With these assumptions, more or less the same conditions should hold for optical isomerism in phenylpyrroles as in the diphenyl series, namely, two or more groups of proper size substituted in the ortho positions and unsymmetrical substitution in each of the rings. Experimental facts have conformed to this view.
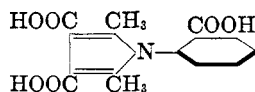
Bock and Adams (20) were unable to resolve any of the following compounds—CXLVI, CXLVII, and CXLVIII. These represent two examples of o-disubstitution and one of symmetry in one ring.
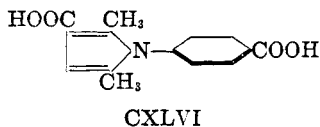
CXLVI

N-(4-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole

CXLVII

N-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole

HOOC CH₃ COOH

HOOC CH₃

CXLVIII

N-(2-carboxyphenyl)-
2,5-dimethyl-3,4-
dicarboxypyrrole

If a fixed tetrahedral structure for nitrogen and at the same time restricted rotation are assumed, formula CXLIX would represent the appearance of such a molecule. Under these conditions unsymmetrical substitution in one ring only would be necessary to produce optical isomerism, but this does not agree with the facts (CXLVIII).
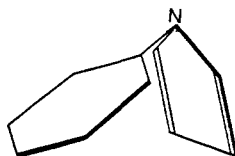
CXLIX

That optical isomerism in phenylpyrroles might be due to an asymmetric nitrogen atom is also very improbable, first because of the lack of positive results of many investigators in resolving trivalent nitrogen compounds, and second because it is difficult to see how such slight changes from formula CXLIV in the molecules CXLVI and CXLVII would eliminate optical isomerism if it were due to the nitrogen.

Analogous to N-phenylpyrroles are the phenylcarbazoles. Patterson and Adams (135) were unable to resolve CL which contained the symmetrical carbazole ring, but obtained optical isomers from CLI which contained the unsymmetrically substituted carbazole.

COOH

NO₂

COOH
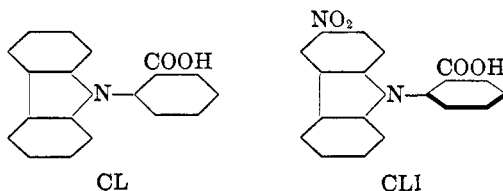
CL

N-(2-carboxyphenyl)-
carbazole

CLI

N-(2-carboxyphenyl)-
3-nitrocarbazole

Dipyrrylbenzenes

As the experimental results indicate that the isomerism is very similar to that in the diphenyl series, an extension could, therefore, be made to dipyrrylbenzenes, which should exhibit isomerism similar to that of the diphenylbenzenes. This was confirmed experimentally and it was possible to distinguish the meso and the racemic modifications by resolution studies. Chang and Adams (36) prepared the diastereoisomeric forms of the *m*-dipyrrylbenzenes (CLII). The less soluble, presumably the *trans* form, was racemic and was resolved into its highly active, stable enantiomorphs, while the more soluble, presumably *cis* form, was meso and preliminary experiments indicated that it could not be resolved. The corresponding *p*-dipyrrylbenzenes (CLIII) were also prepared, but in this case the less soluble, presumably *trans* form, is meso, and although the experimental work is still incomplete it apparently cannot be resolved, whereas the more soluble, presumably the *cis* form, is racemic and should be resolvable.
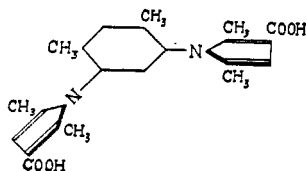
CLII

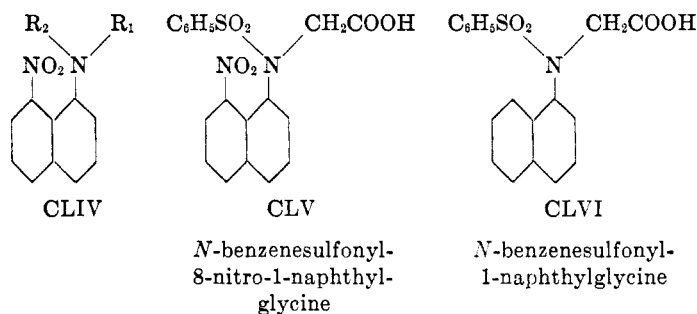2,5-Di-*N*-(2,5-dimethyl-3-carboxypyrryl)-1,3-dimethylbenzene
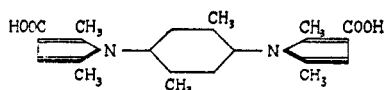
CLIII

2,6-Di-*N*-(2,5-dimethyl-3-carboxypyrryl)-1,4-dimethylbenzene

XI. FURTHER STUDIES IN RESTRICTED ROTATION

The conception of restricted rotation has been applied to the stereochemistry of molecules other than diphenyls or bicyclic compounds, and the results will be described briefly in this résumé.
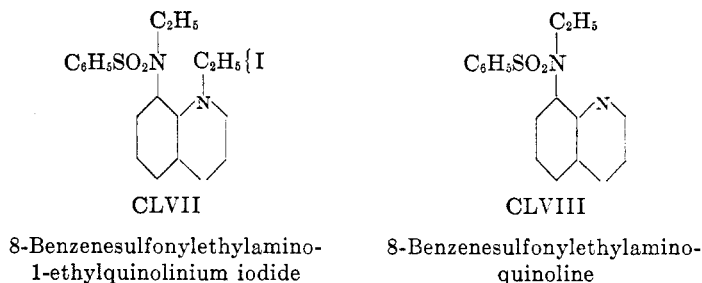
Mills and Elliott (129) predicted that steric hindrance similar to that which prevents free rotation of the two nuclei in diphenyl

might be exhibited in peri-substituted naphthalenes (CLIV). They showed that the nitro derivative (CLV) could be resolved into rather easily racemized enantiomorphic forms, whereas the un-nitrated compound (CLVI) could not be. This was explained

R₂ R₁ C₆H₅SO₂ CH₂COOH C₆H₅SO₂ CH₂COOH

NO₂ N NO₂ N N

CLIV CLV CLVI

N-benzenesulfonyl-8-nitro-1-naphthyl-glycine

N-benzenesulfonyl-1-naphthylglycine

by these authors as molecular asymmetry due to restricted rotation about the C—N bond because of the collision of the R_1R_2N— group and the nitro group in the 8 position. No such obstacle existed in the un-nitrated compound (CLVI), and hence no optical activity.

A second analogous illustration of restriction was described by Mills and Breckenridge (127, 128), the resolution of CLVII in contrast to the nonresolvability of the corresponding tertiary base (CLVIII) or the corresponding 1-methylquinolinium iodide.

C₂H₅ C₂H₅

C₆H₅SO₂N C₂H₅{I C₆H₅SO₂N

N N

CLVII CLVIII

8-Benzenesulfonylethylamino-1-ethylquinolinium iodide

8-Benzenesulfonylethylamino-quinoline

Adams and coworkers (62, 119) suggested the possibility of the resolution of other types of compounds which might be asymmetric if steric hindrance prevented free rotation. Such types are represented by the general formulas 1, 2, and 3, where R stands for groups of proper size.

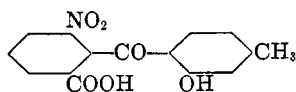|		
1	2	3
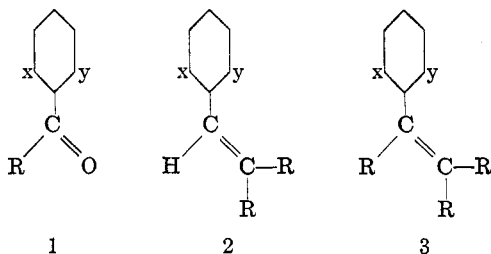
Compounds representing types 1 and 2 were prepared. They were CLIX, CLX, CLXI, CLXII, CLXIII, CLXIV, and CLXV.
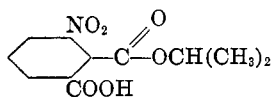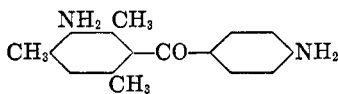

CLIX

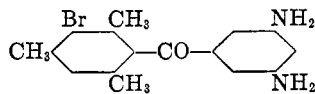2-Carboisopropoxy-
3-nitrobenzoic acid

CLX

2-(2-Hydroxy-4-methylbenzoyl)-
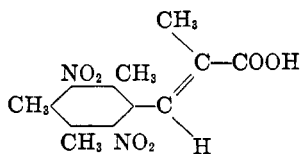3-nitrobenzoic acid
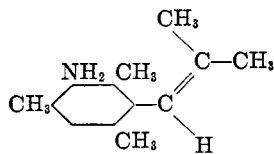

CLXI

v-Aminobenzoyl-
bromomesitylene

CLXII

3,5-Diaminobenzoyl-
bromomesitylene

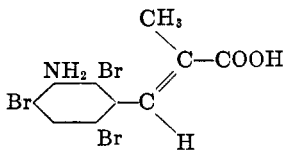

CLXIII

2,3,4,6-Tetramethyl-
2,5-dinitrocinnamic acid


CLXIV

3-Aminoisobutenyl-
mesitylene

CLXV

α-Methyl-3-amino-2,4,6-
tribromocinnamic acid

In carrying out the fractional crystallization, there was no definite separation, nor did the relative size of the fractions give any indication of salts of different solubilities. In no case were optically active compounds obtained by decomposition of the salts. Substituted stilbenes were examined for optical activity by Pfeiffer and coworkers (136), but the results were all negative.

Several attempts to prepare compounds of Type 3, which showed the analogy to substituted diphenyls most completely, met with failure. The probability of isomerism of selected representatives of these compounds is supported by the more recent results of Meisenheimer upon certain oximes.

Meisenheimer, Theilacker, and Beisswenger (122) pointed out that formulas CLXVI and CLXVII represented two forms of a substituted aromatic oxime. In the molecule of the β-form of the ketoxime (CLXVII), both the hydroxyl and the R groups have the possibility of colliding with the x and y groups on the benzene ring. Thus, the rotation of the radical R—$\overset{|}{\text{C}}$=NOH would be restricted and the compound would be able to exist in antipodal forms. As for the α-form (CLXVI), there should be no interference between the hydroxyl group and the x and y groups, so that the molecule should not be resolvable.

CLXVI
α-form
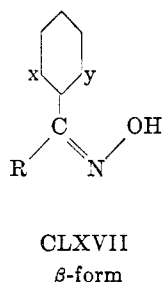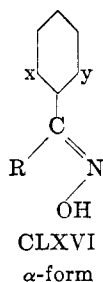
CLXVII
β-form

Experimentally, these authors found that neither form of CLXVIII could be resolved. Of the α- and β-forms of CLXIX, the α-form could not be separated into enantiomorphs. The β-oxime of the same ketone (CLXIX) yielded coniine, cinchonine, and strychnine salts, all of which exhibited mutarotation in pyridine; hence asymmetry of the molecules was inferred even

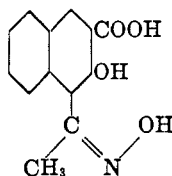though the optically active acid could not be isolated. The corresponding ether (CLXX), however, formed a cinchonine salt which mutarotated in solution and upon decomposition at 0°C. gave an active ether.
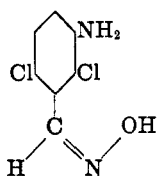
CLXVIII	CLXIX (β-form)	CLXX
2,6-Dichloro-3- aminobenzaldoxime	2-Hydroxy-3-carboxy- 1-naphthyl methyl ketoxime	2-Hydroxy-3-carboxy- 1-naphthyl methyl ketoxime *N*-methyl ether
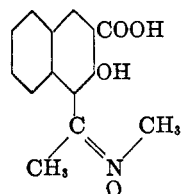
The resolution of these compounds was used as evidence for the correctness of the Hantzsch-Werner theory for the structure of oximes, and offered a new instance of optical isomerism due to restricted rotation.

The search for stereoisomerism in substituted diphenylmethane compounds was also made. The 3,3'-diamino derivatives of dimesitylmethane (CLXXI), dimesitylsulfone (CLXXII), and dimesityl ketone (CLXXIII) were prepared and examined for optical activity by Maclean and Adams (113). Using a similar method for calculation of interferences as in the diphenyl series, the adjacent methyl groups in CLXXI should collide, provided that the rings are coplanar and provided that the valence angles of the central carbon atom remain undistorted.
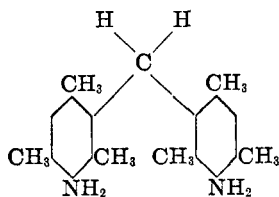
CLXXI	CLXXII	CLXXIII
3,3'-Diamino- dimesitylmethane	3,3'-Diamino- dimesitylsulfone	3,3-Diamino- dimesityl ketone

Experimentally, none of the above three compounds could be resolved. This indicates, in all probability, a distortion of the carbon tetrahedral structure or a synchronizing of the two rings during rotation.

Hayashi (59) reported the existence of two stereoisomeric benzoylbenzoic acids (CLXXIV), and discussed the possibility of the diphenyl type of isomerism. From the present knowledge of diphenyl stereochemistry, however, this explanation appears very unlikely, and it is more reasonable to suppose that the two substituted benzoylbenzoic acids are position isomers.

CLXXIV
2-(5-Chloro-2-hydroxybenzoyl)-
3-methylbenzoic acid

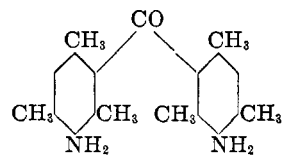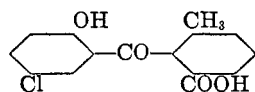In 1907, Lees and Thorpe (93) reported isomeric N,N'-dimethyl-1,3-diamino-2-phenylnaphthalenes to which, later, Gibson and coworkers (54) assigned stereochemical formulas based on restricted rotation. Upon reinvestigation by Lesslie and Turner (101), the two compounds were shown to be position isomers.

Many substituted diphenyls have been reported by Van Alphen (184) as existing in dimorphic forms, but there appears to be no association between this phenomenon and diphenyl stereoisomerism.

XII. SUMMARY AND CONCLUSIONS

In the foregoing pages an attempt has been made to give an account of all the important investigations in the field of diphenyl stereochemistry, and it is of interest to note how an erroneous hypothesis stimulated various experimental researches and opened a new field with striking and fruitful results. Without the incentive provided by the Kaufler formula, the resolution of diphenyl compounds might not have been attempted.

The present status of the problem can be summarized in the following four points, which have been intensively studied experimentally.

(1). There is no reason to believe that diphenyl derivatives have the Kaufler folded formula.

(2). The resolution of certain substituted diphenyls and the nonresolution of others can be satisfactorily explained on the assumption that the two benzene rings in a resolvable diphenyl possess a common axis, but lie in different planes, owing to the restriction of free rotation about the axis because of the ortho substituents. The resulting configuration is asymmetric. The degree of inhibition of rotation, as manifested by the ease of racemization, depends primarily upon the size of the groups.

(3). The phenomenon persists in terphenyl compounds and binuclear compounds other than diphenyls. The restriction of free rotation about a single bond has also been found in other classes of compounds.

(4). There are factors other than the size of ortho groups affecting the optical stability of active diphenyls, but these are of lesser significance.

In concluding this résumé a brief discussion of those points upon which our knowledge is still incomplete and uncertain, may be of interest.

(1). As the accumulation of experimental information increases, the factors which influence the interfering effects of the groups appear to be numerous. The possibility of obtaining strictly quantitative information on the effect of a specified ortho substituent in any particular molecule, therefore, seems remote.

(2). It has been demonstrated experimentally that groups other than those in the 2,2',6,6' positions affect the rate of racemization of an active diphenyl. From the data it is impossible to distinguish whether the other groups cause (a) a variation in the size of the ortho groups *per se*, or (b) a change in the angle of attachment.

The trisubstituted diphenyls appear to have, in general, a greater tendency to racemize than the tetrasubstituted, even after taking into account the character and size of the ortho groups. The correct explanation of these phases of the problem is not clear.

(3). There have been two different methods suggested for

calculating the approximate interfering effects of ortho groups. Stanley and Adams (158) accepted the values of the internuclear distances as probably best representing the relative interference effects. Relative "interference values" of a pair of groups were obtained by comparing the sum of the two internuclear distances of the 2,2'-substituted groups with the known vertical distance between the 2,2' carbon atoms, 2.90Å. Lesslie and Turner (104) preferred to predict the resolvability by using the values of the atomic radii of the 2,2' atoms or groups and by constructing a model for each molecule.

(4). There appears to be no absolute and sharp distinction between the resolvable and nonresolvable substituted diphenyls. Bell and Robinson (15) observed that the quinine salt of 4-dinitro-2,2'-dicarboxydiphenyl, which is regarded as nonresolvable, had abnormal positive rotation. Kuhn and Albrecht (83) made a similar observation on the quinine salt of 4,4'-dinitro-2,2'-dicarboxydiphenyl, and the effect was later named by Kuhn (82) as the "asymmetric transformation of the first order." Lesslie and Turner (178) found similar properties in quinine diphenate and Hyde and Adams (62) in certain substituted aryl aliphatic compounds. The phenomenon has been accepted by some chemists as evidence of labile optical isomerism. This explanation may be the proper one and may involve the effect of the presence of the two large alkaloid nuclei. The work of Hilditch (60a), however, must not be overlooked. He observed just such anomalous effects in a large variety of salts of various alkaloids with definitely inactive acids.

(5). The nonresolvability of certain phenylpyridine derivatives needs elucidation.

The development of the stereochemistry of diphenyls has stimulated the use of optical rotation for studying dynamic effects within certain molecules and has offered new methods of attack to other stereochemical problems. Bell (9a) has suggested that a cycle of the type shown below, if carried out with an optically active base, might reveal a new type of Walden inversion or perhaps give information about the mechanism of replacement of one group by another.
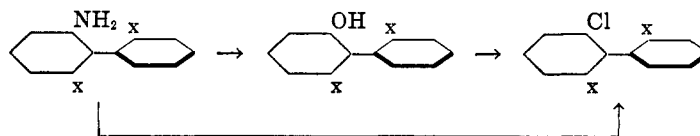
Lesslie and Turner (102) have reported the asymmetric synthesis of 2,4-dinitro-6-carboxy-2'-methyldiphenyl; the extension of their line of work may lead to interesting results. Just as Mills (127, 128, 129) and Meisenheimer (122) have applied the knowledge obtained in the study of the diphenyl field to the structure of peri-substituted naphthalenes and to the structure of oximes, still more applications to other fields may confidently be expected in the future.

The authors wish to express their sincere thanks to Dr. F. Bell of the Battersea Polytechnic, London, to Dr. W. H. Carothers of the duPont Company, and to Drs. R. L. Shriner and R. C. Fuson of the University of Illinois for their kindness in reading the manuscript and offering many pertinent suggestions.

XIII. CLASSIFICATION OF SUBSTITUTED DIPHENYLS WHICH HAVE BEEN INVESTIGATED

Before concluding this résumé it is desirable to list together the substituted diphenyls and analogous compounds which have been investigated from the stereochemical point of view. From this list the reader may get a bird's-eye view of the present status of the problem and information as to which types of compounds have not yet been studied. Certain compounds not mentioned in the previous discussion because they have no bearing on the theoretical aspects of the problem have been included.

I. *Compounds which have been resolved or of which mutarotating salts have been obtained*

(A) 2,2'-Disubstituted.
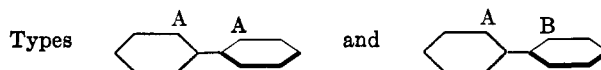
2,2'-Diiodo-4,4'-dicarboxydiphenyl (142)
2,2'-Dibromo-4,4'-dicarboxydiphenyl (143)

Diphenyl-2,2'-disulfonic acid (105)
4,4'-Diaminodiphenyl-2,2'-di-(phenylsulfonate) (104)
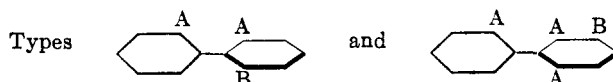Monomethiodide of 2,2'-*bis*-(dimethylamino)-diphenyl (177)
2-(Diphenylhydroxymethyl)-2'-carboxydiphenyl (48)
2-(Dimethylhydroxymethyl)-2'-carboxydiphenyl (48a)
8,8'-Dicarboxy-1,1'-dinaphthyl (47, 156, 120)
8-Carboxy-8'-carboethoxy-1,1'-dinaphthyl (120)
8-Carboxy-1,1'-dinaphthyl (120)

(B) 2,2',6-Trisubstituted.

Types

 and

2-Nitro-6,6'-dicarboxydiphenyl (14)
2,4,4'-Trinitro-6,6'-dicarboxydiphenyl (42)
2,4'-Dinitro-6,6'-dicarboxydiphenyl (39)
2,4,6,2',4'-Pentanitro-3-carboxydiphenyl (163)

Type
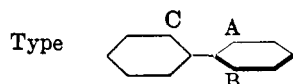
2,4-Dinitro-2'-methyl-6-carboxydiphenyl (102)
2-Methyl-6-*nitro*-2'-carboxydiphenyl (165)
2-Nitro-6-carboxy-2'-bromo-5'-methyldiphenyl (166)
2-Nitro-6-carboxy-2'-chloro-5'-methyldiphenyl (166)
2-Nitro-6-carboxy-2'-methoxydiphenyl (166)
2-Nitro-6-carboxy-2'-methyldiphenyl (57)
2-Nitro-6-carboxy-2'-nitrodiphenyl (57)
2-Methyl-6-carboxy-2'-nitrodiphenyl (57)
2-Nitro-6-carboxy-2',4'-dimethoxydiphenyl (194)
Substituted 2-nitro-6-carboxy-2'-methoxydiphenyl with methyl, methoxyl,
    chloro, bromo, and nitro groups at 5' position (195)
2-Nitro-6-carboxy-2',4'-dimethoxydiphenyl (58)
3,5-Dinitro-2,α-naphthylbenzoic acid (103)

(C) 2,2',6,6'-Tetrasubstituted.

Types

 and
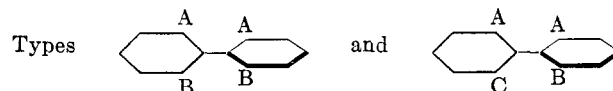
2,2'-Dinitro-6,6'-dicarboxydiphenyl (41)
2,4,2',4'-Tetranitro-6,6'-dicarboxydiphenyl (41)
2,2',4-Trinitro-6,6'-dicarboxydiphenyl (43)
2,2'-Dichloro-6,6'-dicarboxydiphenyl (40)
2,2'-Dimethoxy-6,6'-dicarboxydiphenyl (72, 161)
2,2'-Difluoro-6,6'-dicarboxydiphenyl (161)
2,2'-Dinitro-4,4'-dicarboxy-6,6'-dichlorodiphenyl (68)

2,2'-Dimethoxy-5,5'-dicarboxy-6,6'-dimethyldiphenyl (108)

2,2'-Dimethyl-6,6'-diaminodiphenyl and derivatives (121, 114, 141a)

7,8-Dimethyl-2-phenyldiphenylimidine (141a)

7,8-Dimethyl-2-keto-2,3-dihydrodiphenylimidine (141a)

2,2'-Difluoro-6,6'-diamino-3,5,3',5'-tetramethyldiphenyl (75)

2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl (76)

2,2'-Diamino-1,1'-dinaphthyl (87)

2,2'-Dicarboxy-1,1'-dinaphthyl (86)

2,2'-Dihydroxy-3,3'-dicarboxy-1,1'-dinaphthyl (157)

2,2'-Dinitro-1,1'-dinaphthyl-5,5'-disulfonic acid (134)

2,2'-Dicarboxy-1,1'-dianthraquinonyl (85)

2-Amino-2'-nitro-6,6'-dimethyldiphenyl (4)

2-Amino-2'-chloro-6,6'-dimethyldiphenyl (3)

Types and
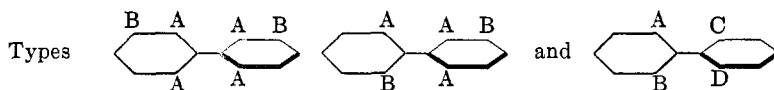
2,4,6,2',4',6'-Hexamethyl-3,3'-diaminodiphenyl (133)

2,4,6,2',4',6'-Hexanitro-3,3'-dicarboxydiphenyl (21)

2,4,6,2',4',6'-Hexachloro-3,3'-dicarboxydiphenyl (191)

2,3'-Dinitro-6-carboxy-2',6'-dimethoxydiphenyl (185)

2-Nitro-6-carboxy-2'-fluoro-6'-methoxydiphenyl (8)

(D) Phenylquinones.

    2-(3-Bromo-2,4,6-trimethylphenyl)-5-methylbenzoquinone-3,6-di(acetic acid) (60)

(E) N-phenylpyrroles.

    N-(2-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (19)

    N-(2-carboxyphenyl)-3-nitrocarbazole (135)

    1,3-Di-N-(2,5-dimethyl-3-carboxypyrryl)-2,4-dimethylbenzene (36)

(F) N, N'-Dipyrryls.

    N,N'-2,5,2',5'-Tetramethyl-3,3'-dicarboxydipyrryl (37)

    2,5-Di-N-(2,5-dimethyl-3-carboxypyrryl)-1,3-dimethylbenzene (36)

(G) Dipyridyls.

    2,4,2',4'-Tetracarboxy-6,6'-diphenyl-3,3'-dipyridyl (193)

II. *Diphenylbenzene derivatives (cis and trans forms)*

Types and
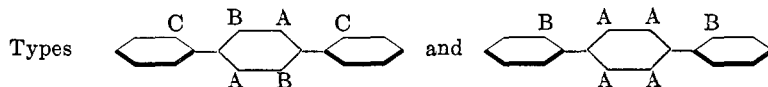
2,5-Di-(2,4-dimethylphenyl)-3,6-dibromohydroquinones and their derivatives (25)

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinones and the corresponding quinones (148)

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinone-di-menthoxy acetates (150)

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrahydroxybenzenes (149)

III. *Compounds upon which resolution has been unsuccessfully attempted*

(A) No ortho substituents.
  5,5'-Dichloro-3,3'-dicarboxydiphenyl (110)
(B) Ortho-monosubstituted.
  2-Carboxydiphenyl (11)
  2-Aminodiphenyl (11)
  1,2'-Dinaphthyl-8-carboxylic acid (120)
(C) Ortho-disubstituted.
  2,4-Dinitro-6-carboxydiphenyl (102)
  2,4-Dinitro-6-carboxy-3'-methyldiphenyl (102)
  3-Methoxy-5-methyl-2,6-dicarboxydiphenyl (70)
  Diphenic acid (63, 12)—Mutarotation of the quinine salt (178)
  4-Nitro-2,2'-dicarboxydiphenyl (10)
  4,4'-Dinitro-2,2'-dicarboxydiphenyl (44)—Dextrorotation of the quinine
   salt
  5,5'-Dinitro-2,2'-dicarboxydiphenyl (138)
  5,5'-Dibenzoyldiamino-2,2'-dicarboxydiphenyl (138)
  1,1'-Diamino-2,2'-dinaphthyl (115)
  2,2'-Dinitro-4,4'-dicarboxydiphenyl (15)
  4,4'-Dicarboxy-1,1'-dianthraquinonyl (160)
  2,2'-Diaminodiphenyl (114)
  2,2'-Diamino-4,4'-dimethyldiphenyl (114)
  2,2'-Diamino-5,5'-dimethyldiphenyl (114)
(D) 2,2',6-Trisubstituted.
  2-Nitro-6-carboxy-2'-fluoro-5'-methyldiphenyl (166)—Mutarotation of al-
   kaloidal salts at 0°C.
  2-Nitro-6-carboxy-2'-methoxy-3'-methyldiphenyl (38)
(E) 2,2',6,6'-Tetrasubstituted.
  2,2',6,6'-Tetrafluoro-3,3'-dichloro-5,5'-dicarboxydiphenyl (77)
  2,2'-Difluoro-6,6'-dimethoxy-3,3'-dicarboxydiphenyl (9)
  2,2',6,6'-Tetramethoxy-3,3'-dicarboxydiphenyl (49)
  2-Nitro-6-carboxy-2',6'-dimethoxydiphenyl (185)
  2,4,6,2',4',6'-Hexanitro-3,3'-dihydroxydiphenyl (118)[17]
(F) Phenylpyrroles, phenylindoles, phenylpyridines, diquinolyls, etc.
  N-(4-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (20)
  N-(3-carboxyphenyl)-2,5-dimethyl-3-carboxypyrrole (20)
  N-(2-carboxyphenyl)-2,5-dimethyl-3,4-dicarboxypyrrole (20)
  N-(2-carboxyphenyl)-carbazole (135)
  3-(2-Nitrophenyl)-2-carboxyindole (73)
  2-(2-Carboxyphenyl)-3-carboxypyridine (109)
  2-(2-Carboxy-6-chlorophenyl)-3-carboxypyridine (164)
  3-(2-Carboxyphenyl)-2,4-dicarboxy-6-phenylpyridine (164)
(G) Phenylketones, phenylethenes, etc.
  2-Carboisopropoxy-3-nitrobenzoic acid (62)

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[17] This compound should be capable of resolution. The experimental technic
may be the difficulty.

2-(2-Hydroxy-4-methylbenzoyl)-3-nitrobenzoic acid (62)

p-Aminobenzoylbromomesitylene (62)

3,5-Diaminobenzoylbromomesitylene (62)

α,3,4,6-Tetramethyl-2,5-dinitrocinnamic acid (119)

4-Amino-2-isobutenylmesitylene (119)

α-Methyl-3-amino-2,4,6-tribromocinnamic acid (119)

3,3'-Diaminodimesitylmethane (113)

3,3'-Diaminodimesitylketone (113)

3,3'-Diaminodimesitylsulfone (113)

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