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A Study of Reactions Directed Toward the Preparation of Some
Alkoxybiphenyls by the Williamson Synthesis

A Senior Thesis

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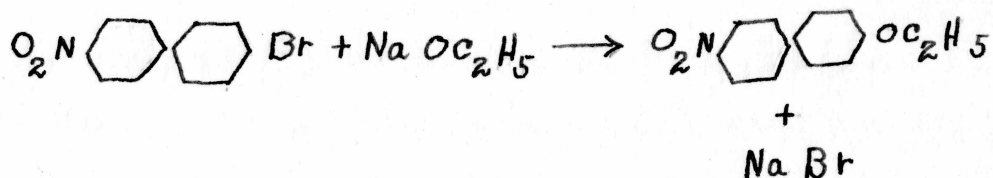
Introduction

There is a large group of substituted ethers among the biphenyls which needs to be synthesized, particularly with a view toward obtaining asymmetric carbons in alkyl groups attached to the biphenyl nucleus. This necessitates the use of antipodes of previously resolved alcohols, and those ethers with asymmetric carbons joined directly to oxygen are of particular interest because of the difference in effect which optically active solvents of the alcohol type might have on their ultraviolet absorption spectra.

This work is directed toward the preparation of the methoxy—ethoxy—, and sec-butoxybiphenyls, by a means which can be extended to the preparation of several optically active ethers. The preparation of the optically active ethers is to be accomplished by using one antipode of a previously resolved alcohol.

Problem

The problem is to prepare an alkoxybiphenyl by means of the Williamson Synthesis. The position which the alkoxy group is to occupy on the biphenyl ring must be sufficiently activated so that the alkoxy group may be substituted into the molecule. The starting product in each of the experiments of this work was a 4-nitro-4'-bromobiphenyl. It is to be determined whether the nitro group in the 4-position will sufficiently activate bromine in the 4'-position, to allow substitution with an alkoxy group.



Activation of the 4'-Position of 4-Substituted Biphenyls

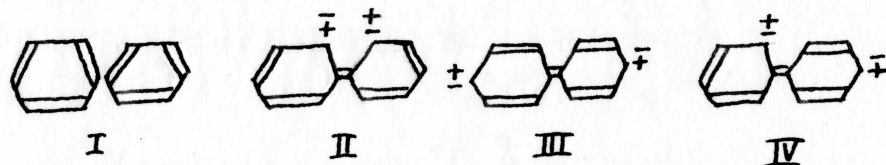
It is found that the bond distance between the carbon atoms joining the two benzene nuclei of the biphenyl molecule is 1.48 \AA , which is between that of a double bond and a single bond.³

Table 1

Carbon to Carbon Bond Distances of Pertinent Organic Substances

Substance	Bond Distance \AA	Bond Character	Method of Determination
diamond	1.542 ± 0.001	C-C	X-ray
ethane	1.55 ± 0.03	C-C	electron diffraction
biphenyl	1.48	C-C ₁	X-ray
ethylene	1.34 ± 0.02	-C=C-	electron diffraction
vinyl-chloride	1.38	X-C=C	electron diffraction
benzene	1.40 ± 0.01	C-C	electron diffraction

This is attributed to resonance within the biphenyl molecule,⁴ of which there are fourteen chief resonance contributors, four each for structures I, II, and IV, and two for structure III.



The relationship between the carbon to carbon interatomic distance and the amount of double bond character for a single bond-double bond resonance may be illustrated by Figure 2.²⁴

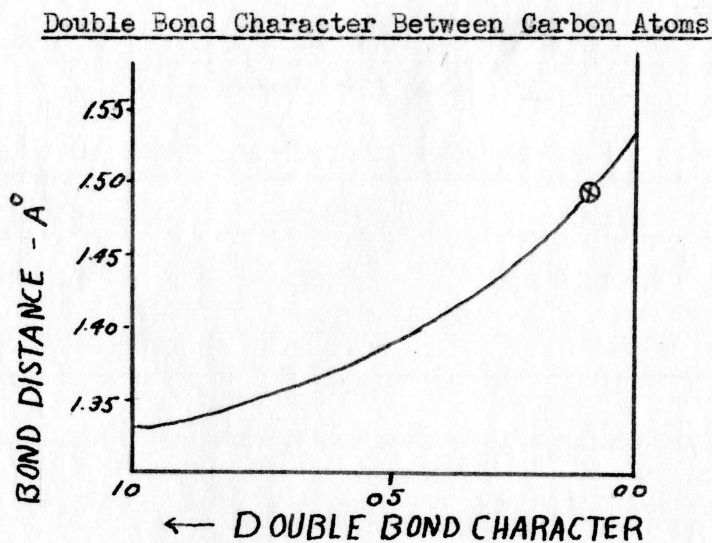
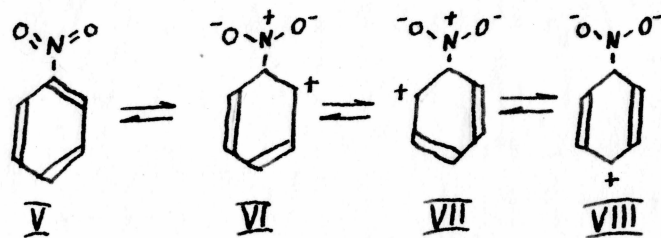


Figure 2

Biphenyl has a bond corresponding to about 14% double bond character.⁵

The effect of a nitro group substituted in the 4-position of the biphenyl molecule should enhance the double bond form of the biphenyl molecule, as the nitro group tends to draw electrons from the ring through four principal resonance forms.⁶



This is evidenced in part by an examination of the effect of the nitro group upon the dipole moment of the molecule.

Table 2

Dipole Moments (Debye Units)

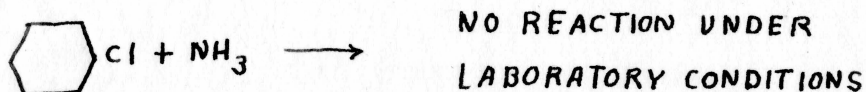
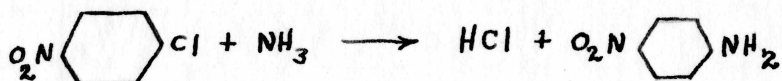
Compounds and State of Aggregation⁷

Compounds	Solution	Vapor
benzene	0.00 D	0.00 D
nitrobenzene	3.97 D	4.24 D

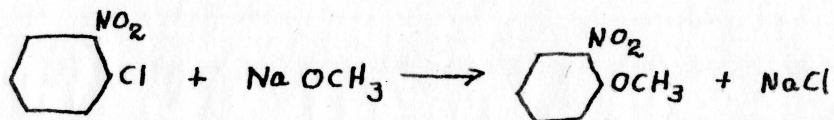
The effect of the electronegative nitro group substituted in the ring is to make electrons less available to the ortho and para positions, thus activating halogens in those positions. Considering chlorobenzene under laboratory conditions, the exchange of NH₂ for Cl cannot be

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effected.¹⁰ However, with a nitro group substituted on the ring, ortho or para to the chlorine atom, the reaction will take place under conditions of moderate heat and pressure.






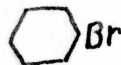






Similarly, chlorobenzene will not enter into a Williamson Synthesis with ease, but when a nitro group is introduced ortho or para to the chlorine atom, the reaction will take place.¹¹



Through earlier investigations^{22, 17} it was concluded that the two nuclei of the biphenyl derivatives resonated independently. However, more recent investigations by C. G. Le Févre and R. J. W. Le Févre,²⁰ reveal that the independent resonance of the benzene nuclei is not so complete as first thought. These investigations were made on a number of comparisons of the dipole moments of para substituted benzene derivatives and the 4-4' substituted biphenyls.

Table 3

Dipole Moments of Substituted Aromatic Compounds

Compound	Dipole Moment	Compound	Dipole Moment
	1.50 D		1.47 D
	1.64 D		1.55 D
	4.17 D		4.03 D
	6.46 D		6.32 D
	3.30 D		2.85 D

Resonance between benzene rings of biphenyl involves π orbitals, directed orbits of electrons of doubly bonded carbon, symmetrical about an axis perpendicular to the plane of the rings. For resonance to exist in the biphenyl molecule, it is necessary that the π orbitals of the adjacent 1,1' carbons be parallel. This requires that the two rings constituting the biphenyl molecule be coplanar. Any influence tending to turn the rings out of coplanarity will thus disrupt the π orbitals and reduce resonance. Groups substituted in the 4,4' positions of the biphenyl molecule offer no steric hindrance to the coplanarity of the molecule. In a study of the ultraviolet absorption spectra of several of the substituted biphenyl compounds,²⁵ Rodebush

and Shaughnessy, showed that in several cases 4,4' substituted biphenyls have greater absorption than unsubstituted biphenyl, as shown in Figures 3 and 4.

Extinction Coefficient of Biphenyl and 4,4' Dimethylbiphenyl in the Ultraviolet Region.

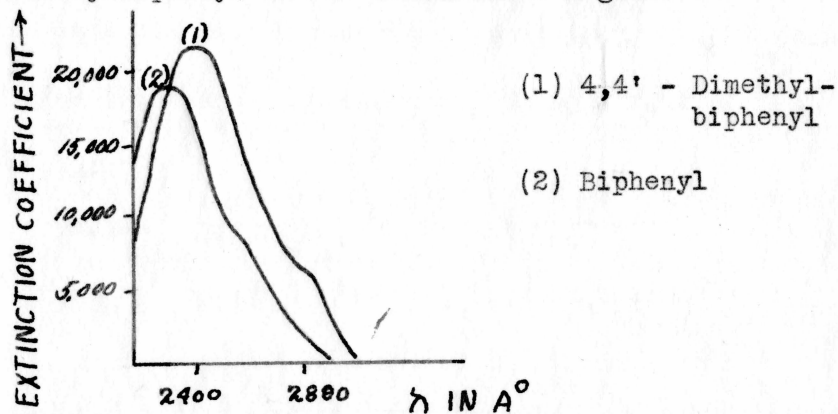


Figure 3

Extinction Coefficient of Biphenyl, 4,4'-Dinitrobiphenyl, and 4,4'-Dibromobiphenyl in the Ultraviolet Region.²⁸

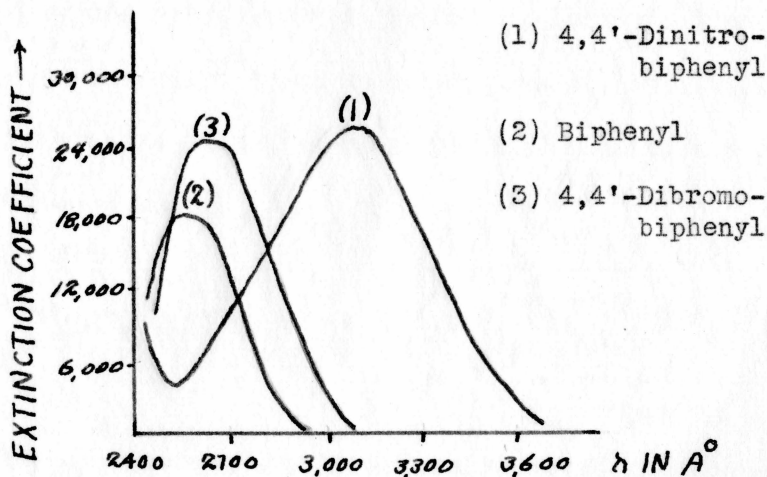
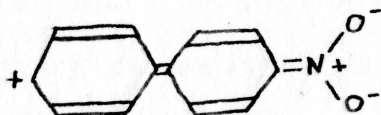


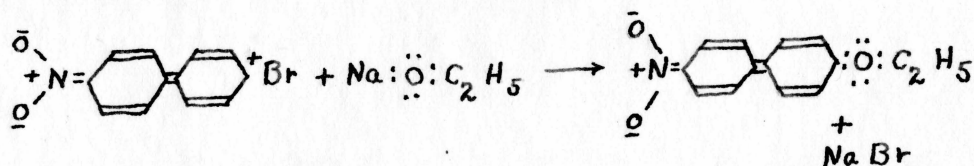
Figure 4

As ultraviolet absorption is an indication of the double bondedness of a compound, the resonance necessitating a double bond between carbons 1- and 1'-in these substituted derivatives must be increased.

The nitro group in the 4-position of the biphenyl molecule will produce an inductive and resonance effect, that is electrons will be drawn from the rings to produce a greater amount of the resonance form:¹³



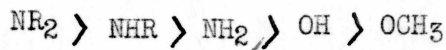
This resonance effect will be at the expense of carbon atoms 3, 5, and 4', thus making those positions relatively vulnerable to electron donating reagents. A bromine atom substituted in the 4'-position would be less strongly bonded to the 4'-carbon due to the resonance effect produced by the nitro group in removing electrons from the 4'-carbon, than if the nitro group were not present, and it is conceivable that an electron donating reagent could replace the bromine in the 4'-position.



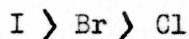
It is the purpose of this problem to determine whether or not such a reaction will take place under moderate conditions of temperature.

Color

4-Nitro-4'-alkoxybiphenyls would be expected to be colored compounds due to the chromophoric nitro group. The alkoxy group in the 4'-position behaves as a color intensifier to the nitro group. It has been recognized that this functions to increase resonance within the molecule,¹⁵ thus shifting the absorption band into lower frequencies and deepening the color. Witt recognized these color-intensifying agents, listed in the order of decreasing effect:¹⁴



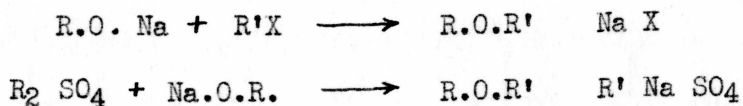
Halogens also increase color in the order:



4-Nitrobiphenyl exists as pale yellow needles and 4-nitro-4'-bromobiphenyl as yellow brown crystals. Bell and Kenyon reported that 4-nitro-4'-methoxybiphenyl crystallized from alcohol in yellow needles,¹ and it may be anticipated that the ethers sought for in this investigation will be colored.

Methods of Preparation of Ethers

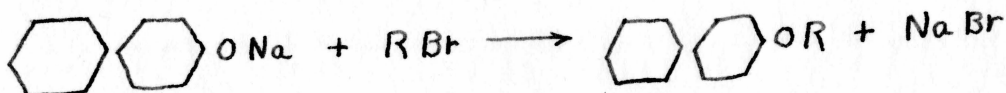
The most widely used method of preparing mixed aryl alkyl ethers is the Williamson Synthesis.¹⁸ It may be represented by the following general equations:



R-aryl group

R'-alkyl group

Experimental conditions vary widely, and are dependent largely upon the reactivities of the substances employed. 4-Ethoxybiphenyl, 4-propoxybiphenyl, and 4-isopropoxybiphenyl were all prepared from 4-hydroxybiphenyl by the reaction:⁸



This method, if applied to the preparation of an optically active ether by using an optically active alkyl halide, might prove ineffectual due to racemization of the alkyl group during the reaction, if the asymmetric center is adjacent to the halide. If at any time the optically active alkyl group exists as a carbonium ion,

the retention of optical properties would depend on the stability of this positive ion, so that racemization of the ion would yield a racemic form of the alkoxybiphenyl.

Wallis and Adams,²⁷ submitted evidence to show that carbonium ions of the type: $\left[\begin{array}{c} R \\ R_2 \cdot \ddot{C} : \\ R_3 \end{array} \right]^-$ are spatially sufficiently stable to maintain an asymmetric configuration during a reaction. Also that carbonium ions of the type $\left[\begin{array}{c} R \\ R_2 \cdot \ddot{C} : \\ R_3 \end{array} \right]^+$ are optically unstable, except in the absence of a special mechanism which leads to a Walden inversion. Evidence was also submitted to demonstrate the optical instability of free radicals of the type $\left[\begin{array}{c} R \\ R_2 \cdot \ddot{C} \cdot \\ R_3 \end{array} \right]$. Thus any preparation of an alkyl aryl ether involving either carbonium ions or free radicals will result in an optically inactive product.

In the preparation of an aryl alkyl ether, it is conceivable that an inversion might take place, as in Figure 5.

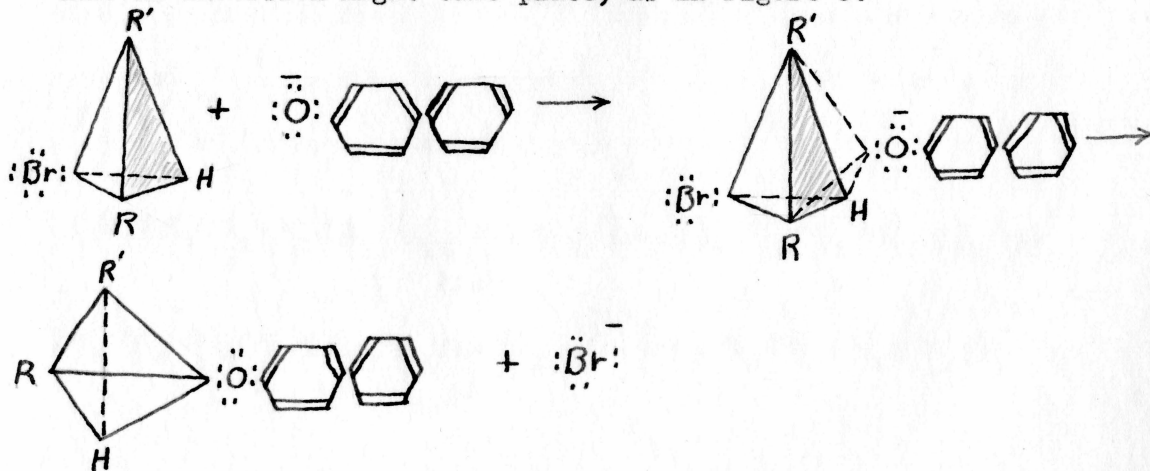

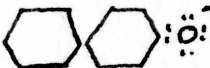
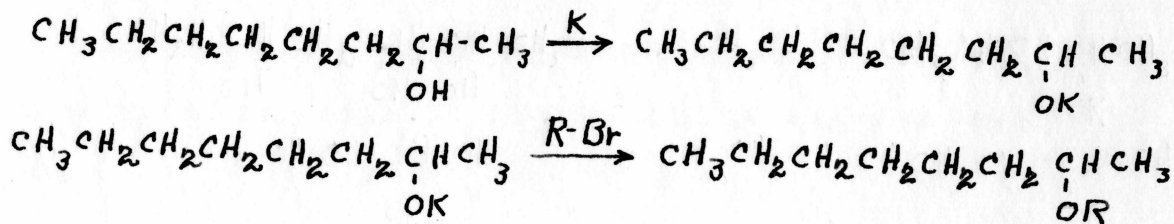


Figure 5

This represents a nucleophilic, or electron pushing attack by the aryloxyl ion on the molecule. Lewis²³ accounts for inversion by assuming that the entering radical, in this case, 

becomes temporarily attached to the central carbon atom, at the tetrahedral face opposite to the bromine atom. A slight shift of the asymmetric carbon would make it the center of a new tetrahedron, while the bromine atom becomes detached. Thus, the new molecule is the mirror image of the original, with the exception that the  ion has replaced $:\ddot{\text{Br}}:^-$

Kenyon and Mc Nicol¹⁹ in their investigations of the normal aliphatic ethers of d-2-octanol, advanced a general method for the preparation of optically active ethers. To d-2-octanol was added potassium metal. The potassium 2-octoxide showed $\left[\alpha \right]_{5461}^{16} + 19.36^\circ$ whereas the original alcohol showed $\left[\alpha \right]_{5461}^{16} + 19.40^\circ$. Thus it was concluded that no racemization of the optically active component resulted. The d-potassium-2-octoxide was refluxed with an alkyl halide. The product obtained was an optically active ether.



This method was employed successfully in the preparation of the following ethers:

Methyl d-sec-octyl ether

Ethyl d-sec-octyl ether

n-Propyl d-sec-octyl ether

n-Butyl d-sec-octyl ether

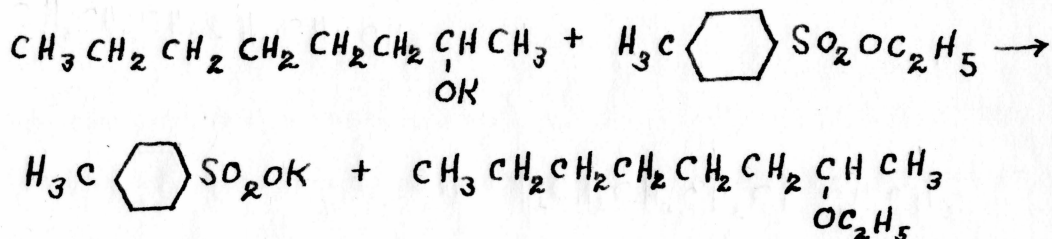
n-Butyl d-sec-octyl ether

n-Hexyl d-sec-octyl ether

n-Octyl d-sec-octyl ether

Thus it seems evident that the optical activity of the asymmetric carbon atom is preserved by the presence of the oxygen atom. It is reasonable to assume that this method can be extended to the preparation of an optically active aryl alkyl ether, by using the sodium or potassium alkoxide of an antipode of a previously resolved alcohol, and an aryl halide.

Ferns and Lapworth¹² described another general method by which optically active ethers may be prepared. This method employs the potassium alkoxide of one antipode of the optically active alcohol and the p-toluenesulfonate of the other component of the ether. An example of this method is the preparation of ethyl d-sec-octyl ether.

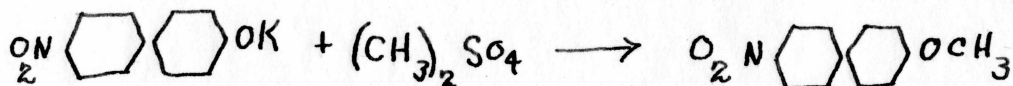


Kenyon and Mc Nicol used this method in the preparation of the ethyl d-sec-octyl ether. They found that the ether thus prepared had $\left[\alpha \right]_{5461}^{19^\circ} + 8.03$ This figure compares very closely with that of the same ether prepared by using ethyl bromide, which has a value $\left[\alpha \right]_{5461}^{17.8^\circ} + 8.08$ It may be assumed that optically active ethers may be prepared equally as effectively by either of the two methods.

In this work, the method advanced by Kenyon and Mc Nicol was adapted for the preparation of the aryl alkyl ethers.

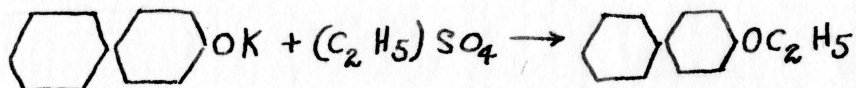
Historical Background

Bell and Kenyon² prepared 4-nitro-4'-methoxybiphenyl by adding small quantities of methyl sulfate and potassium hydroxide to a hot solution of 4-nitro-4'-hydroxybiphenyl in dilute aqueous potassium hydroxide until the red color disappeared. When filtered hot, this crystallized from alcohol in yellow needles, M.p. 111°.



4-Methoxybiphenyl, on direct nitration, yields about 80% of the 3-nitro-4'-methoxybiphenyl, and about 15% of the 4-nitro-4'-methoxybiphenyl.

Dains, Andrews, and Roberts⁹ prepared 4-ethoxybiphenyl by adding diethyl sulfate to a solution of p-phenylphenol and potassium hydroxide. Upon nitration of the 4-ethoxybiphenyl with fuming nitric acid, two products were obtained. The greater fraction, 3-nitro-4'-ethoxybiphenyl, M.p. 110°, and a lesser fraction of the 4-nitro-4'-ethoxybiphenyl, M.p. 65-70°.



No information could be found concerning the methods of preparation or physical characteristics of 4-nitro-4'-sec-butoxybiphenyl.

Experimental Work

A. Preparation of 4-Nitro-4'-Bromobiphenyl

According to the method of Le Févre and Turner,²¹ a mixture of 100 grams of 4-nitrobiphenyl and 200 cc of glacial acetic acid was heated on a water bath at 100°. Fifty cubic centimeters of bromine was added over a period of 1½ hours, and heating was continued for 2 hours. The product was cooled, filtered, and recrystallized from glacial acetic acid. This yielded 4-nitro-4'-bromobiphenyl, pale yellow crystals, M.p. 169-171°, in a 38% yield.

B. Attempted Synthesis of 4-Nitro-4'-Methoxybiphenyl

Sodium methoxide was prepared by adding 2 grams of sodium metal to 60 cc of absolute methyl alcohol¹⁶. The reaction was assumed to be complete when the evolution of hydrogen ceased. Ten grams of 4-nitro-4'-bromobiphenyl were added, and the mixture refluxed with constant stirring for 7½ hours. The product was cooled and filtered, and the filter cake washed with boiling distilled water. A small portion of the water filtrate was acidified with nitric acid, and silver nitrate was added. There was a negative test for bromine. The substance consisted of brilliant yellow crystals,

M.p. 170°-172°, in nearly quantitative yield, and gave a deep red color with concentrated sulfuric acid.²⁶

Reduction of the Reaction Product of Sodium Methoxide and
4-Nitro-4'-Bromobiphenyl

Five grams of the reaction product of sodium methoxide and 4-nitro-4'-bromobiphenyl, and 40 cc of 95% ethyl alcohol were brought to boiling on a water bath at 100°. A solution of 18 grams of stannous chloride in 20 cc of concentrated hydrochloric acid was added slowly. Heating was continued for 1 hour. Upon cooling, a white gelatinous precipitate formed. A slight excess of 20% potassium hydroxide was added, and the product was recrystallized from 90% ethyl alcohol, pale yellow crystals, M.p. 143°-144°. The melting point of the reduction product corresponds to the melting point of 4-amino-4'-bromobiphenyl. Tests for bromine are positive.

C. Attempted Synthesis of 4-Nitro-4'-Ethoxybiphenyl

Sodium ethoxide was prepared by adding 2 grams of metallic sodium to 100 cc of absolute ethyl alcohol. The reaction was assumed to be complete when the evolution of hydrogen ceased.

Ten grams of 4-nitro-4'-bromobiphenyl were added, and the mixture was refluxed with constant stirring on a water bath at 100°, for 5 hours. The reaction mixture was cooled and filtered, and the filter cake washed with boiling distilled water. A small portion of the water filtrate was acidified with nitric acid, and silver nitrate added. There was a negative test for bromine. The substance consisted of dark brown crystals, M.p. 238°-240°, in nearly quantitative yield, and gave a brown-violet color with concentrated sulfuric acid.²⁶

Reduction of the Reaction Product of Sodium Ethoxide and
4-Nitro-4'-Bromobiphenyl

Five grams of this solid, and 40 cc of 95% ethyl alcohol were brought to boiling on a water bath at 100°. A solution of 18 grams of stannous chloride and 20 cc of concentrated hydrochloric acid was added slowly. Heating was continued for 2 hours, and the mixture was cooled, and a slight excess of 20% potassium hydroxide was added. Upon addition of the potassium hydroxide, a fine gray precipitate was obtained. Extraction with 95% ethyl alcohol yielded a substance which upon being recrystallized twice from 95% ethyl

alcohol, formed light brown crystals, M.p. 138^o-140^o. Sodium fusion tests for bromine were positive.

D. Attempted Synthesis of 4-Nitro-4'-sec-Butoxybiphenyl

Sodium sec-butoxide was prepared by adding 2 grams of metallic sodium to 90 cc of absolute sec-butyl alcohol. The reaction was assumed to be complete when the evolution of hydrogen ceased. Ten grams of 4-nitro-4'-bromobiphenyl were added, and the mixture refluxed with constant stirring for 5 hours. The mixture was cooled and filtered, and the filter cake washed with boiling distilled water. A small portion of the water filtrate was acidified with nitric acid, and silver nitrate added. Tests for bromine were negative. The product consisted of orange-brown crystals, M.p. above 300^o, in nearly quantitative yield, and gave a brown-violet color with concentrated sulfuric acid.²⁶

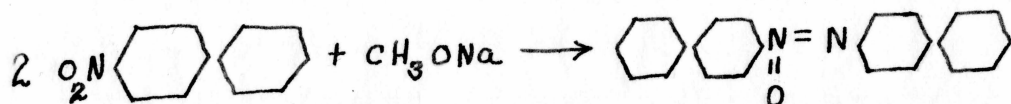
Reduction of the Reaction Product of Sodium sec-Butoxide and 4-Nitro-4'-Bromobiphenyl

Five grams of this solid, and 40 cc of 95% ethyl alcohol were brought to boiling on a water bath at 100^o. A solution of 18 grams of stannous chloride in 20 cc of concentrated hydrochloric acid

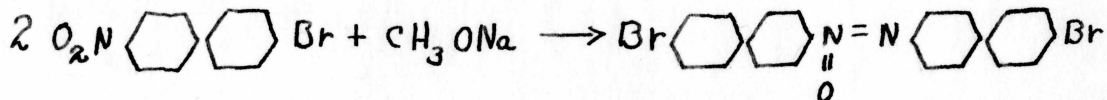
was added slowly. Heating was continued for 2 hours, and the mixture was cooled, and a slight excess of 20% potassium hydroxide was added. Upon addition of the potassium hydroxide, a fine pink precipitate was obtained. Extraction with 95% ethyl alcohol and recrystallization twice from ethyl alcohol yielded golden-brown crystals, M.p. above 300°. Sodium fusion tests for bromine were positive.

Conclusion

D. Vorländer²⁶ prepared p-azoxybiphenyl by the following method: 0.5 grams of p-nitrobiphenyl dissolved in 15 cc of absolute methyl alcohol, was added to a solution of 0.3 grams of sodium in 10 cc of absolute methyl alcohol, and boiled.



By analogy, the product prepared by the action of sodium methoxide on 4-nitro-4'-bromobiphenyl might possibly be the bromo-azoxy compound.



This is further verified by the continued reduction of the reaction product of sodium methoxide and 4-nitro-4'-bromobiphenyl, to yield

a compound whose melting point is identical with that of 4-amino-4'-bromobiphenyl. Thus it may be assumed that the preparation of the methoxy-biphenyl ether cannot be effected under the conditions of this experiment.

The reaction products of sodium ethoxide on 4-nitro-4'-bromobiphenyl, and sodium sec-butoxide on 4-nitro-4'-bromobiphenyl, are both highly colored compounds, indicating that a partial reduction might have taken place. However, by further reduction, the 4-amino-4'-bromobiphenyl cannot be isolated in either case. From the experimental data, it is possible to say that the primary products in all three cases are different, and it is apparent that some form of reduction has taken place in all three cases.

Summary

Not all possible reaction conditions for the preparation of an alkoxybiphenyl by the Williamson Synthesis, using 4-nitro-4'-bromobiphenyl and a sodium alkoxide, have been explored. However, at conditions of moderate temperature and atmospheric pressure, such a synthesis cannot be effected.

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