Effects of *para*-Substituents on the Rates of Inversion of Biphenyl Derivatives. II. 2-Isopropyl-2′-methoxybiphenyls

Michinori Ōki and Gaku Yamamoto

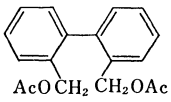
Department of Chemistry, Faculty of Science, The University of Tokyo, Bunkyo-ku, Tokyo

(Received August 22, 1960)

Nine 4,4′-substituted 2-isopropyl-2′-methoxybiphenyls were synthesized and temperature dependence of the NMR spectra of these compounds was examined. The effects of the substituents on the energy barrier to inversion of the biphenyl skeleton can be interpreted in terms of both resonance stabilization and out-of-plane bending of the axis bond at the transition state. In the latter, an electron-donating substituent makes the bond bendig easier and lowers the barrier, whereas an electron-withdrawing group raises the barrier.

In a preceding paper[1] we reported that, in an *o,o′*-bridged biphenyl system where dynamic NMR technique (DNMR) could be applied, the energy barrier to inversion was really affected by the *para*-substituents. We postulated that the effects of the substituents on the barrier might be interpreted in terms of resonance stabilization and out-of-plane bending of the axis bond at the transition state. However, no definite conclusion could be given, because of the limited number of examples due to synthetic and other difficulties.

In this paper we wish to report on a study of the effects of *para*-substituents on the energy barrier to inversion of the non-bridged biphenyl system. There has been only one case where the energy barrier to inversion of non-bridged biphenyl is examined using DNMR. Meyer and Meyer[2] reported on the DNMR of 2,2′-bis(acetoxymethyl)biphenyl (I), where methylene protons showed AB quartet signal ($\delta_{AB}=3.5$, $J_{AB}=12.6$ Hz, in CS_2) at room temperature, and coalesced

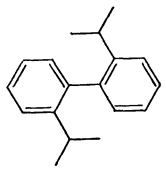


I

at 94°C into a singlet, the result indicating the activation energy of about 13 kcal/mol. A small chemical shift difference seemed to prevent precise line-shape analysis, hence this system did not seem suitable for our purpose.

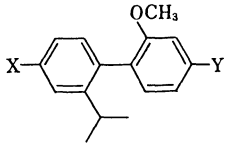
o,o′-Diisopropylbiphenyl (II), possessing geminal dimethyl groups instead of methylene groups in *ortho* positions, was considered. The NMR spectrum of II at room temperature showed double doublets corresponding to the methyl protons of isopropyl groups, indicating that the inversion is slow on the NMR time scale. That the double doublets neither broadened nor coalesced up to 180°C (in hexachloro-1,3-butadiene) indicated that the free energy of activation for rotation about the axis bond is higher than 27 kcal/mol, and that this system also was unsuitable for DNMR study.

2-Isopropyl-2′-methoxybiphenyl (III), derived by replacement of one of the isopropyl groups in II by a less bulky methoxyl group, was considered for study



II

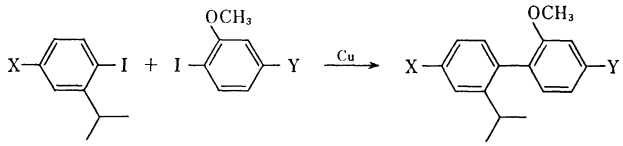
by means of DNMR. Replacement by methoxyl was chosen considering the synthetic ease. III and its 4,4′-substituted derivatives (IV—XI) were thus synthesized and their NMR spectra were examined over a wide range of temperature.



III: X=Y=H
IV: X=H, Y=OCH_3
V: X=H, Y=NO_2
VI: X=OCH_3, Y=H
VII: X=Y=OCH_3
VIII: X=OCH_3, Y=NO_2
IX: X=NO_2, Y=H
X: X=NO_2, Y=OCH_3
XI: X=Y=NO_2

Results and Discussion

Nine derivatives of 2-isopropyl-2′-methoxybiphenyl were synthesized by the Ullman reaction, *viz.*, the coupling of 2-iodocumenes (XII—XIV) and 2-iodoanisoles (XV—XVII) in the presence of copper bronze (Scheme 1).



XII: X=H
XIII: X=OCH_3
XIV: X=NO_2
XV: X=H
XVI: X=OCH_3
XVII: X=NO_2
III—XI

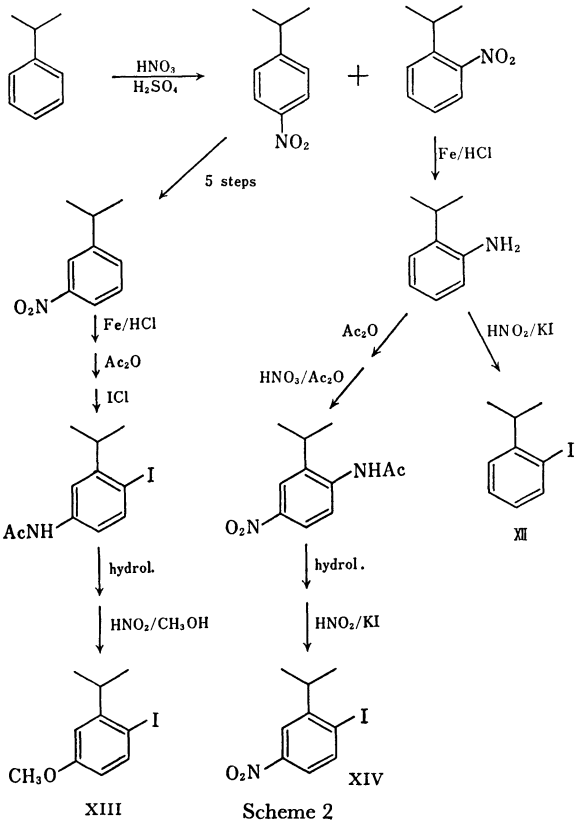
Scheme 1

The desired unsymmetrical biphenyls were isolated by distillation and/or column-chromatography. Nine biphenyls (III—XI) as well as two 2-iodocumenes (XIII and XIV) are new compounds. Elementary analyses and NMR spectra of these compounds were consistent with the expected ones.

5-Methoxy- (XIII) and 5-nitro-2-iodocumene (XIV)

1) M. Ōki, H. Iwamura, and G. Yamamoto, This Bulletin, **44**, 262 (1971).

2) W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, **85**, 2170 (1963).



Scheme 2

were synthesized from cumene as described in Scheme 2. The positions of the introduced iodine in XIII and of the nitro group in XIV were confirmed by analysis of the aromatic proton signals in their NMR spectra, and further by comparison of the spectra with those of the corresponding toluene derivatives; XIII *vs.* 2-iodo-5-methoxytoluene and XIV *vs.* 2-iodo-5-nitrotoluene, each pair of spectra showing the same pattern of the aromatic proton signals.

The NMR spectra were measured as 15% solutions in 1,1,2,2-tetrachloroethane over a range from −10 to +150°C. Methyl protons of each compound showed a pair of doublets ($J\sim7$ Hz), with a separation of about 10 Hz at room temperature. This magnetic nonequivalence of the two methyls of the isopropyl groups indicated that inversion of the biphenyl skeleton is slow on the NMR time scale.

As the temperature was raised, the double doublet signal gradually broadened accompanying the gradual decrease in apparent chemical shift difference. The signal then became a broad single peak. The temperature at which this line shape was attained was regarded as the coalescence temperature T_c. With a further rise of temperature the signal split into two peaks, which gradually sharpened. At 150°C a sharp doublet was observed indicating fast inversion. A typical example, the case of V, is shown in Fig. 1.

The apparent chemical shift difference of the two methyl groups below T_c changed as shown in Fig. 2. The "intrinsic" chemical shift difference without exchange varied almost linearly with temperature. This phenomenon may be explained as follows. The "intrinsic" chemical shift difference is a weighed average of the chemical shift differences in conformations arising

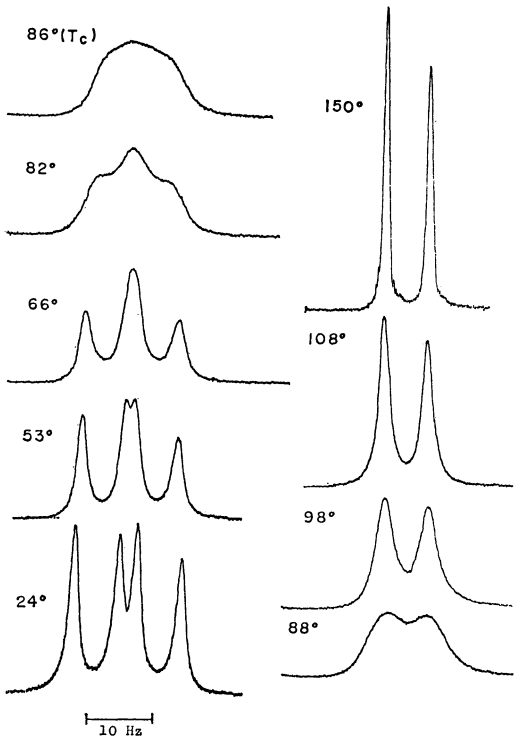


Fig. 1. The temperature dependence of the methyl proton signal of V.

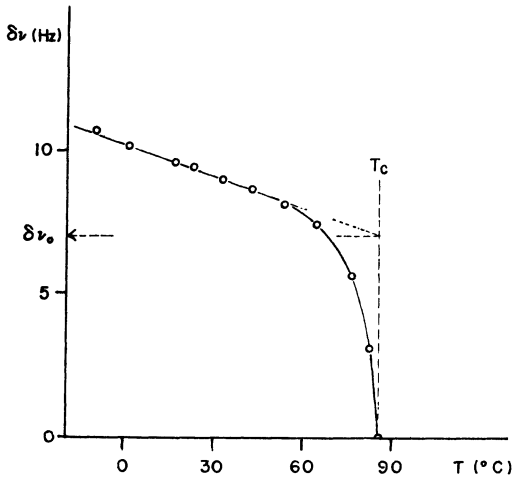


Fig. 2. The temperature dependence of the apparent chemical shift difference of the methyl protons of III.

from rotation about the bond between the isopropyl group and the benzene ring. The relative populations of these conformations may change with temperature because of the difference in potential energies, and this causes the observed change in chemical shift difference.

The same phenomenon was observed in the NMR spectra of *o,o′*-diisopropylbiphenyl (II). The methyl protons of II showed a chemical shift difference of 5.2, 4.9 and 4.5 Hz at 80, 120 and 180°C, respectively, at 60 MHz.

In order to obtain the kinetic parameters for inversion, these spectral changes were analyzed regarding them as two overlapping doublets, each coalescing into a singlet.

Inversion rate, k_c, at T_c was calculated using the

equation[3]

$$k_c = \frac{\pi\delta\nu_0}{\sqrt{2}} \quad (1)$$

where $\delta\nu_0$ represents the chemical shift difference of the two methyl groups without exchange. $\delta\nu_0$ was obtained by extrapolating the chemical shift differences at various temperatures to T_c.

Approximate inversion rate k at temperatures above T_c was calculated following the fast exchange approximation

$$k = \frac{\pi(\delta\nu_0)^2}{2(W - W_0)} \quad (2)$$

where W and W_0 are the signal width at half height at a given temperature and at a free exchange on the NMR time scale, respectively. W value at the highest temperature was used as W_0. The same numerical value as was used for the $\delta\nu_0$ in Eq. (1) was used for the $\delta\nu_0$ in Eq. (2). Uncertainty of the value inevitably gives rise to a considerably large error in k values.

The k values were plotted against the reciprocal temperature, which gave fairly good linearity. The inversion rate at 86°C was obtained graphically from this plot and $\Delta G_{86}^{\ddagger}$, the free energy of activation at 86°C, was calculated for each compound. The results are given in Table 1.

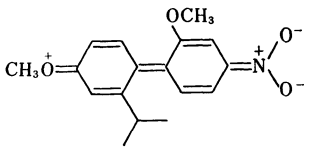
Table 1. Kinetic parameters of the inversion of 2-isopropyl-2′-methoxybiphenyls

Compound	X	Y	T_c (°C)	$\delta\nu_0$[a] (Hz)	$\Delta G_c^{\ddagger}$[b] (kcal/mol)	k_{86} (sec^{-1})	$\Delta G_{86}^{\ddagger}$[b] (kcal/mol)
III	H	H	86	7.2	19.2	16	19.2
IV	H	OCH_3	74	7.8	18.5	33	18.7
V	H	NO_2	86	7.1	19.2	16	19.2
VI	OCH_3	H	70	7.5	18.3	53	18.3
VII	OCH_3	OCH_3	61	7.3	17.9	82	18.0
VIII	OCH_3	NO_2	65	7.8	18.0	65	18.2
IX	NO_2	H	79	7.2	18.8	23	18.9
X	NO_2	OCH_3	58	8.0	17.6	80	18.0
XI	NO_2	NO_2	82	6.6	19.0	19	19.1

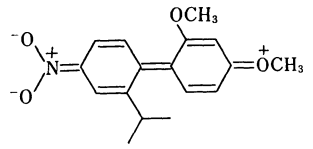
a) Extrapolated value to T_c.
b) The maximum errors for $\Delta G_c^{\ddagger}$ and $\Delta G_{86}^{\ddagger}$ are estimated to be ±0.1 and ±0.3 kcal/mol, respectively.

Enthalpy and entropy of activation derived from NMR line shape analysis, particularly by use of approximate equations were noted to involve serious errors.[4] Thus, in our case it seemed risky to discuss quantitatively using the obtained values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. We will rather discuss assuming that there is no large variation in $\Delta S^{\ddagger}$ values among the compounds in question, that is, the relative order of $\Delta G_{86}^{\ddagger}$ values corresponds to the relative order of the energy barrier to inversion. $\Delta G_{86}^{\ddagger}$ is considered to be reliable within the error of 0.3 kcal/mol.

Low barriers in 4-methoxy-4′-nitro- (VIII) and 4′-methoxy-4-nitro- (X) derivatives are in accordance with the results in 5,7-dihydrodibenzo[*c*,*e*]thiepin system[1] and may be explained in terms of resonance stabilization of the transition state, due to the contribution of canonical structures XVIII and XIX.



XVIII



XIX

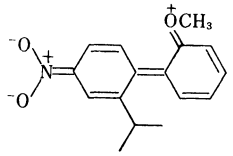
Comparison of the data for compounds IV and V is of interest. The contribution of resonance stabilization by the through conjugation in these compounds is thought to be of the same order. The difference may then be attributed to the difference in the extent of release of steric interactions by the out-of-plane bending of the axis bond. The electron-donating methoxyl group increases the π-electron density at 1,1′-positions, and according to the orbital following theory[5] this makes the out-of-plane bending of the axis bond easier. This means that the steric interactions between the *ortho* positions in the coplanar transition state are more easily released and thus the energy barrier to inversion is lowered.

Decrease in the $\Delta G_{86}^{\ddagger}$ values for IV relative to that for III may be interpreted to be due to the sum of the small conjugation effect and the bond bending effect.

The ease of the bond bending is reasonably expected to increase with the increasing number of the methoxyl groups: 2′-(III)<2′,4′-(IV)<4,2′-(VI)<4,2′,4′-(VII). The obtained data clearly agree with this prediction. It is interesting that the 4,4′-dimethoxy derivative (VII) has almost the same barrier as the 4-methoxy-4′-nitro one (VIII), which indicates that the bond bending factor is as important as the resonance stabilization factor in lowering the barrier.

On the other hand, the orbital following theory predicts that the electron-withdrawing nitro group lowers the π-electron density at 1,1′-positions and makes the out-of-plane bending of the axis bond less easy. The reason why V has the same barrier as III is ascribed to two compensating factors, *viz.*, resonance stabilization and destabilization due to the difficulty of the out-of-plane bending at the transition state. A small decrease in the barrier for IX relative to that for III may be interpreted as the conjugation effect represented

3) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).
4) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).
5) R. D. Kross, V. A. Fassel, and M. Margoshes, *J. Amer. Chem. Soc.*, **78**, 1332 (1956). J. M. Linnett and P. J. Wheatley, *Trans. Faraday Soc.*, **45**, 33 (1949).



XX

by the canonical structure XX exceeding the destabilization effect of the nitro group. It seems that an *o*-quinoid structure such as XX is much less important in stabilizing the transition state than *p*-quinoid structures such as XVIII and XIX. Increased double bond character of $C_{2'}$-O bond makes the in-plane bending of this bond difficult, which otherwise could release the non-bonded interactions at the transition state. In compound XI an almost complete compensation of the two factors is observed.

Of course, the bond bending factor may be operating also in compounds VIII and X, but here the resonance stabilization factor may be far more important in lowering the energy barrier.

Harris and Cheung King Ling[6] have proposed that the dependence of the racemization rates of optically active 2,2′-diiodobiphenyls on the *para*-substituents could be interpreted on the assumption that the axis bond bent out of the plane of the benzene rings at the transition state.

The possibility of such bond bending could be attributed to the extreme bulkiness of the *ortho* substituents. But the present study seems to show that out-of-plane bending of the axis bond contributes in lowering the energy barrier to inversion in biphenyl systems possessing as low a barrier as can be studied by DNMR.

Experimental

Spectra. NMR spectra were obtained on a JNM C-60H or a Hitachi R-20A spectrometer both operating at 60 MHz. The temperatures were read with ethylene glycol sample and are accurate to ±2C°. Approximately 15% (w/w) solutions in 1,1,2,2-tetrachloroethane were employed.

Materials.[7] o-*Iodocumene (XII)*: *o*-Isopropylaniline, prepared by reduction of *o*-nitrocumene, was diazotized and treated with potassium iodide. Slightly colored oil was obtained; bp 116—117°C/12 mmHg (lit,[8] 84—85°C/2 mmHg).

3-Isopropyl-4-iodoacetanilide: Freshly prepared iodine monochloride (16.2 g, 0.1 mol) in acetic acid (10 m*l*) was added to a stirred solution of *m*-isopropylacetanilide (13.5 g, 0.1 mol) in acetic acid (15 m*l*) at room temperature over a period of 1 hr. The reaction mixture was poured into water containing a small amount of sodium bisulfite. The solidified mass, after recrystallization from methanol - water (5 : 1), gave colorless plates; yield 20 g (60%), mp 130—131°C.

Found: C, 43.40; H, 4.58; N, 4.68%. Calcd for $C_{11}H_{14}ONI$: C, 43.58; H, 4.66; N, 4.62%.

3-Isopropyl-4-iodoanisole (XIII): 3-Isopropyl-4-iodoacetanilide (18.2 g, 0.06 mol) was hydrolyzed with alcoholic potassium hydroxide. The resulting aniline was dissolved in 100 m*l* methanol containing sulfuric acid (15 m*l*), diazotized with sodium nitrite (5 g) in minimal amount of water with ice-cooling. The diazotized solution was warmed on a water bath until boiling and finally heated under reflux for 15 min. After evaporation of the major portion of methanol, the residue was poured into water and extracted with ether. The ethereal solution was shaken with dilute sodium hydroxide solution to separate the phenol from the anisole. The aqueous layer was treated with dimethyl sulfate and the resulting oil was extracted with ether. The two ethereal solutions were combined, washed with dilute alkali and water, and dried with potassium carbonate. Vacuum distillation gave colorless oil; yield 14 g (80%), bp 110—111°C/2 mmHg.

Found: C, 43.36; H, 4.72%. Calcd for $C_{10}H_{13}OI$: C, 43.50; H, 4.74%.

2-Isopropyl-4-nitroacetanilide: *o*-Isopropylaniline (40.5 g, 0.3 mol), dissolved in acetic anhydride (300 m*l*), was cooled down to −50°C with dry ice-alcohol, and freshly distilled nitric acid (specific gravity 1.51) was added dropwise during the course of 3 hr. Stirring was continued further 4 hr during which period the temperature was kept below −40°C. The reaction mixture was poured onto ice-water affording an oil. Repeated recrystallizations from methanol gave colorless needles; yield 12 g (18%), mp 159—161°C.

Found: C, 59.28; H, 6.65; N, 12.74%. Calcd for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60%.

2-Iodo-5-nitrocumene (XIV). 2-Isopropyl-4-nitroacetanilide (22.2 g, 0.1 mol) was heated under reflux with sulfuric acid (30 m*l*) in water (100 m*l*) for 3 hr. The solution was cooled with ice-bath, and diazotized with sodium nitrite (8 g) solution. After decomposition of excess nitrous acid with urea, aqueous potassium iodide (20 g, 0.12 mol) was added. The reaction mixture was kept at room temperature for 10 min, at 60°C for 15 min and cooled to room temperature. After extraction with ether, the ether layer was washed successively with sodium bisulfite solution, dilute sodium hydroxide solution and water and dried with potassium carbonate. Distillation gave 19.5 g (67%) of an oil, bp 128—129°C/2 mmHg.

Found: C, 37.21; H, 3.59; N, 4.82%. Calcd for $C_9H_{10}O_2NI$: C, 37.14; H, 3.46; N, 4.81%.

General Procedure of the Ullman Reaction. *o*-Iodocumene (or its 4-substituted derivative) and 1 to 5 molar equivalent of *o*-iodoanisole (or its 4-substituted derivative) were mixed and heated at 150°C. Approximately the same weight of copper bronze as the iodine compounds was added to the mixture, which was then gradually heated up to 220—250°C and kept for 1 to 2 hr. The reaction mixture was cooled to room temperature and extracted with acetone. The evaporated extract contained symmetrically substituted biphenyls, 2,2′-dimethoxybiphenyl and 2,2′-diisopropylbiphenyl, as well as the decomposition products of low molecular weight, in addition to the desired unsymmetrical biphenyl. In most cases the desired product was isolated by distillation under reduced pressure and/or column chromatography followed by repeated recrystallizations.

2-Isopropyl-2′-methoxybiphenyl (III) was obtained after recrystallization from methanol as colorless crystals, mp 36°C.

Found: C, 84.93; H, 8.31%. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02%.

2-Isopropyl-2′,4′-dimethoxybiphenyl (IV) was collected as a fraction boiling at 142—145°C/2 mmHg which resisted crystallization. Repeated distillation gave a colorless oil.

Found: C, 79.82; H, 7.65%. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%.

2-Isopropyl-2′-methoxy-4′-nitrobiphenyl (V) was obtained as pale

6) M. M. Harris and C. Cheung King Ling, *J. Chem. Soc.*, **1964**, 1825.

7) All the melting points and boiling points are uncorrected.

8) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, **79**, 1897 (1957).

yellow crystals, mp 101—102°C (from methanol).

Found: C, 70.98; H, 6.50; N, 5.04%. Calcd for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16%.

2-Isopropyl-4,2'-dimethoxybiphenyl (VI) was obtained as a colorless oil, bp 142—145°C/2.5 mmHg.

Found: C, 79.70; H, 7.68%. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%.

2-Isopropyl-4,2',4'-trimethoxybiphenyl (VII) crystallized from methanol as colorless granules, mp 56—57°C.

Found: C, 75.35; H, 7.95%. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74%.

2-Isopropyl-4,2'-dimethoxy-4'-nitrobiphenyl (VIII) was recrystallized from petroleum ether (bp 50—60°C) affording yellow orange granules, mp 73.5—74.5°C.

Found: C, 67.63; H, 6.40; N, 4.44%. Calcd for $C_{17}H_{19}O_2N$: C, 67.76; H, 6.36; N, 4.65%.

2-Isopropyl-2'-methoxy-4-nitrobiphenyl (IX) was obtained by recrystallization from methanol as pale yellow crystals, mp 72—73°C.

Found: C, 70.84; H, 6.61; N, 5.09%. Calcd for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16%.

Chromatography of the reaction mixture also afforded 2,2'-diisopropyl-4,4'-dinitrobiphenyl as orange crystals, mp 172—174°C (from methanol).

Found: C, 65.93; H, 6.20; N, 8.45%. Calcd for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53%.

2-Isopropyl-2',4'-dimethoxy-4-nitrobiphenyl (X) was obtained by repeated recrystallizations from ethanol as yellow crystals, mp 108—110°C.

Found: C, 68.06; H, 6.84; N, 4.66%. Calcd for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36; N, 4.65%.

2-Isopropyl-2'-methoxy-4,4'-dinitrobiphenyl (XI) was obtained by repeated recrystallizations from acetone as orange yellow plates, mp 139—140°C.

Found: C, 60.56; H, 5.25; N, 8.75%. Calcd for $C_{16}H_{16}O_5N_2$: C, 60.76; H, 5.10; N, 8.86%.