Nitration of Decamethylbiphenyl and 2,3,4,5,6-Pentamethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl with Fuming Nitric Acid. Exclusive *Ortho* Orientation for the Side-chain Attack[1]

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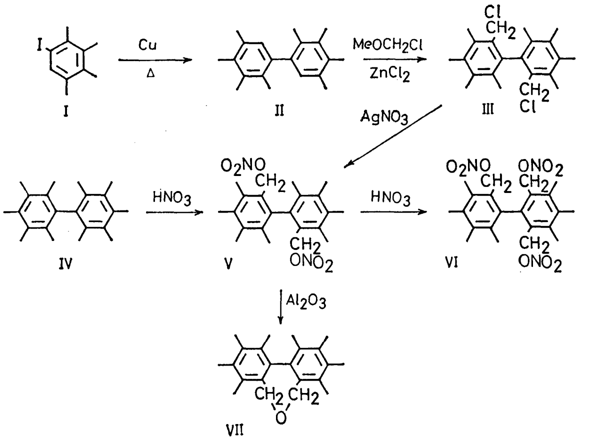
Products obtained by the reaction of the title compounds with fuming nitric acid in dichloromethane were investigated. Decamethylbiphenyl gave 6,6′-bis(nitrooxymethyl)-2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl or 2,6,6′-tris(nitrooxymethyl)-2′,3,3′,4,4′,5,5′-heptamethylbiphenyl as the major product, depending on the amount of nitrating agent. 2,3,4,5,6-Pentamethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl similarly gave 6-nitrooxymethyl-2,3,4,5-tetramethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl or 2,6-bis(nitrooxymethyl)-3,4,5-trimethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl. Some plausible reaction sequences for the exclusive *ortho* attack on the alkyl side-chains of biphenyl systems have been suggested.

On treatment with fuming nitric acid at low temperature, polymethylbenzenes and their derivatives undergo side-chain nitrooxylation to give benzyl nitrates in good yields. The reaction is characterized by a peculiar orientation of the products and high positional selectivity. Substitution will preferentially occur into the side-chain *ortho* to the electron-withdrawing groups and *meta* to the electron-releasing groups.[2] For a facile nitrooxylation there should be a pair of methyl groups situated *para* one another. In order to clarify the mechanism of the reaction, studies were extended to the unusual nitration of the biphenyl systems. So far no report has appeared on the nitration of fully alkylated biphenyl systems.

Decamethylbiphenyl (IV) was treated with five molar proportions of fuming nitric acid (d=1.5) in dichloromethane below 0 °C to give a light brown paste, which upon recrystallization from ligroin yielded a crystalline solid melting at 142—144 °C as the only product (*ca.* 70% yield). The compound has a molecular formula of $C_{22}H_{28}N_2O_6$ and shows strong infrared absorptions due to $-ONO_2$ at 1632, 1275, and 854 cm^{-1}; ^1H NMR peaks at δ 1.82, 2.28, 2.30, and 5.08 with relative areas 3: 3: 6: 2. The peak at higher field (δ 1.82) corresponds to two *ortho* methyl groups. Signals of the methylene protons appear at a considerably high field (δ 5.08) as compared to those of ordinary benzyl nitrates (δ 5.5—5.8).[3] This can be interpreted by the structure 6,6′-bis(nitrooxymethyl)-2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (V) and suggests a configuration in which one phenyl ring lies in a plane nearly perpendicular to that of another ring, each *ortho* methyl and nitrooxymethyl group lying above the adjacent ring and subjected to a diamagnetic shielding effect. Its identity was confirmed by comparison with an authentic specimen prepared from prehnitene by the sequence shown in Scheme 1. The alternative synthesis was initiated by the Ullmann condensation of iodoprehnitene (I). The resulting 2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (II) was bis-chloromethylated with chloromethyl methyl ether in the presence of anhydrous zinc chloride. The chloride (III) so obtained was converted into V by treatment with silver nitrate in acetonitrile. The possibility of the concurrent formation of other isomeric nitrates in a significant amount was rule out by comparison of ^1H NMR spectra of the crude product with those of authentic 5,5′-bis(nitrooxymethyl)-2,2′,3,3′,4,4′,6,6′-octamethylbiphenyl (XV) and 4,4′-bis(nitrooxymethyl)-2,2′,3,3′,5,5′,6,6′-octamethylbiphenyl (XVI), obtained from iodoisodurene and iododurene, respectively, by a similar sequence to that in Scheme 1. No peak could be observed in the region δ 5.6—5.7, ascribed to the absorptions of *meta* and *para* nitrooxymethyl groups.



Scheme 1.

When the product mixture was placed on the top of an alumina column and eluted with light petroleum and diethyl ether, successively, large prisms with the composition $C_{22}H_{28}O$ (*m/e* 308) were obtained from the ether eluates in 42% yield. The compound exhibited ^1H NMR peaks at δ 2.04 (2 Me), 2.32 (4 Me), 2.40 (2 Me), 3.72 (2 CH, d; J_{gem}=12 Hz), and 4.82 (2 CH, d; J_{gem}=12 Hz); infrared band at 1036 cm^{-1} (C–O–C). These spectral data are consistent with the formulation of the product as 6,6′-(2-oxapropano)-2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (VII), which was obtained from V by the alumina-catalyzed ring closure during elution. A pair of *geminal* benzylic protons appear as a doublet

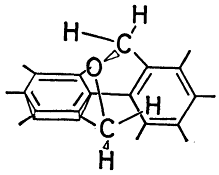
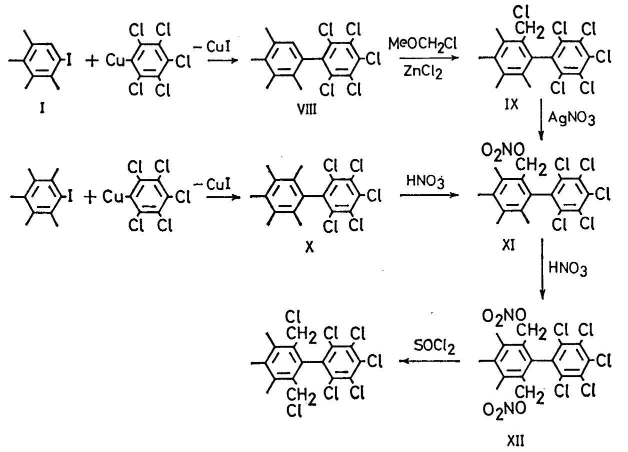


Fig. 1.

at a higher field (δ 3.72). This is ascribed to a greater diamagnetic shielding of the protons due to the induced ring current, suggesting the configuration shown in Fig. 1. Methylene signals of bisbenzyl ethers usually appear in the δ 4.6—4.9 region.[4)]

With the use of a large excess of fuming nitric acid, the major isolable product was found to be 2,6,6'-tris-(nitrooxymethyl)-2',3,3',4,4',5,5'-heptamethylbiphenyl (VI), the structure of which was established by elemental analysis as well as by comparison of the spectra of related compounds. Isolation of VI as pure crystalline solid was difficult. Most of the product (80%) remained as non-crystallizable syrupy substance. This result is in contrast to the nitration of hexamethylbenzene under similar conditions to give predominantly 5,6-bis(nitrooxymethyl)-1,2,3,4-tetramethylbenzene.[5)]

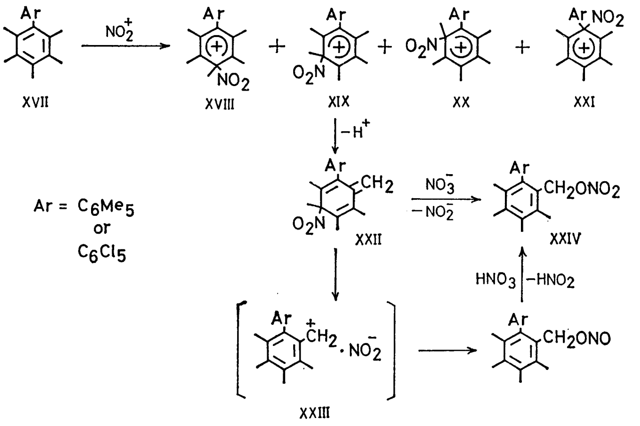
2,3,4,5,6-Pentamethyl-2',3',4',5',6'-pentachlorobiphenyl (X) was comparatively stable towards the action of cold fuming nitric acid in dichloromethane, but readily underwent side-chain nitrooxylation at room temperature to give a nitrate in 84% yield. The nitrate was identified as 6-nitrooxymethyl-2,3,4,5-tetramethyl-2',3',4',5',6'-pentachlorobiphenyl (XI) by direct comparison with the authentic sample prepared from 2,3,4,5-tetramethyl-2',3',4',5',6'-pentachlorobiphenyl (VIII) by chloromethylation to IX followed by treatment with silver nitrate in hot acetonitrile (Scheme 2).



Scheme 2.

When either X or XI was treated with a large excess of fuming nitric acid in an ice bath and the mixture was left to stand for several hours, the temperature of the system being allowed to gradually rise to room temperature, the only product was 2,6-bis(nitrooxymethyl)-3,4,5-trimethyl-2',3',4',5',6'-pentachlorobiphenyl (XII), which was obtained almost quantitatively and resisted further reaction even on prolonged contact with the nitrating agent. Proof of the symmetrical structure of XII was obtained from the ^{1}H NMR spectrum which contained the expected sharp bands at δ 2.37, 2.43, and 5.17 in a 3: 6: 4 ratio of intensities. Thus, irrespective of the electronic nature of substituent groups on the opposite ring, the side-chain substitutions in the polymethylated biphenyl systems are found to occur exclusively on the methyl groups adjacent to the phenyl-phenyl bond. The nitrooxymethyl group is a versatile unit, and the present reaction provides an attractive entry into some polysubstituted biphenyls with functionalized substituents at *ortho* positions.

The exclusive *ortho* orientation for the side-chain attack might be rationalized as follows: electrophilic attack of nitronium ion on biphenyl (XVII) can theoretically lead to a mixture of four benzenium ions (XVIII to XXI) (Scheme 3). Although the attack of nitronium ion at C_4 will be most favored with unsubstituted biphenyl due to the electromeric diffusion of positive charge into the adjacent ring, the ion XVIII can not enjoy such stabilizing effect, because it exists in a non-planar configuration to minimize the steric interaction of four *ortho* substituents. Contribution of ions XX and XXI is supposed to be much less important, since the access of the nitronium ion to the ring positions C_1 and C_2 to form these ions would undergo considerable steric hindrance. Thus, ion XIX in which the charge is most effectively dissipated by three methyl groups seems to be the most favored intermediate ion, from which the proton release would occur preferentially on the methyl group bonded to the more positively polarized ring carbon at the 6-position, giving a methylene cyclohexadiene (XXII). Heterolytic scission of the carbon-nitrogen bond in XXII will form a benzyl cation-nitrite ion pair (XXIII); recombination at benzylic carbon atom *via* carbon-oxygen bond followed by oxidation will afford the nitrate (XXIV). A possible alternative mechanism for the conversion of XXII into XXIV involves the attachment of the nitrate ion to the terminal methylene carbon of XXII, redistribution of electrons to regain the aromatic system, and concurrent departure of the nitro group as an anion, leading to the formation of XXIV.[6)] It is not clear which course is actually followed.



Scheme 3.

Experimental

All melting points were determined with a hot-stage apparatus and are uncorrected. Infrared spectra were obtained as Nujol on a Jasco 402G spectrophotometer. ^{1}H NMR measurements were carried out in deuteriochloroform solutions on a Varian T-60 spectrometer at probe temperatures against internal tetramethylsilane.

Decamethylbiphenyl (IV)[7)] was prepared by the Ullmann reaction of iodopentamethylbenzene and purified by chromatography on alumina with light petroleum as an eluant. Mp 259—262 °C.

2,3,4,5,6-Pentamethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl (X). A Grignard reagent was prepared from magnesium (1.3 g) and hexachlorobenzene (14 g) in tetrahydrofuran (40 ml). Cuprous iodide (9.6 g) was added to this solution, and the mixture was stirred for some hours at room temperature. Iodopentamethylbenzene (13.7 g) was then added and the reaction mixture was heated under reflux for 8 hr and poured into water. The insoluble solid was filtered off and extracted with benzene with a Soxlhet extractor. The extract was concentrated and passed over alumina to give pentachlorobenzene from light petroleum eluates and X (5.1 g; 25.7%) from benzene eluates. Mp 276—278 °C.

Found: C, 51.02; H, 3.70%. Calcd for $C_{17}H_{15}Cl_5$: C, 51.49; H, 3.81%.

2,3,4,5-Tetramethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl (VIII) was prepared in a similar manner from iodoprehnitene (I). Mp 281—283 °C.

Authentic specimens of nitrooxymethyl compounds XIII, XIV, and IX were prepared by essentially the same procedure involving chloromethylation of the respective biphenyls with chloromethyl methyl ether, followed by treatment of the chlorides with silver nitrate in acetonitrile. Physical properties of a series of polysubstituted biphenyls prepared in the context of the present work are summarized in Table 1.

6,6′-Bis(chloromethyl)-2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (III). A mixture of 2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (II; 0.30 g),[8] chloromethyl methyl ether (3 g), and anhydrous zinc chloride (0.04 g) was heated with stirring at 40—50 °C for 1 hr, and then poured into water to give III (0.28 g; 68%), which was crystallized from ligroin in the form of fine needles, mp 205—206 °C.

Found: C, 72.46; H, 7.65%. Calcd for $C_{22}H_{28}Cl_2$: C, 72.72; H, 7.77%.

By a similar treatment, 2,2′,3,3′,4,4′,6,6′-octamethylbiphenyl[9] was converted into *5,5′-bis(chloromethyl)-2,2′,3,3′,4,4′,6,6′-octamethylbiphenyl (XIII)*, mp 211—213 °C; 2,2′,3,3′,5,5′,6,6′-octamethylbiphenyl[10] and 2,3,4,5-tetramethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl (VIII) were converted into *4,4′-bis(chloromethyl)-2,2′,3,3′,5,5′,6,6′-octamethylbiphenyl (XIV)*, mp 246—247 °C, and *6-chloromethyl-2,3,4,5-tetramethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl (IX)*, mp 265—268 °C, respectively. VIII required an extended reaction period to obtain satisfactory conversion into IX.

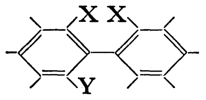
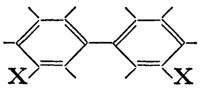
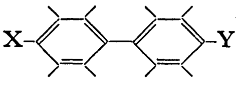
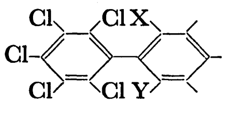
XIII: Found: C, 72.84; H, 7.62%. Calcd for $C_{22}H_{28}Cl_2$: C, 72.72; H, 7.77%.

XIV: Found: C, 72.68; H, 7.82%. Calcd for $C_{22}H_{28}Cl_2$: C, 72.72; H, 7.77%.

IX: Found: C, 47.21; H, 3.19%. Calcd for $C_{17}H_{14}Cl_6$: C, 47.37; H, 3.27%.

6,6′-Bis(nitrooxymethyl)-2,2′,3,3′,4,4′,5,5′-octamethylbiphenyl (V). A warm solution of silver nitrate (0.75 g) in acetonitrile (20 ml) was added all at once with stirring to a hot solution of III (0.31 g) in the same solvent (30 ml). The mixture was stirred with heating for several hours, silver chloride being separated by filtration. Evaporation of the solvent *in vacuo*, followed by crystallization of the residue

TABLE 1. PHYSICAL PROPERTIES OF SOME POLYSUBSTITUTED BIPHENYLS

Compound		X	Y	Mp (°C)	¹H NMR Spectra (δ)
	II	H	H	138—140	1.97 (2 Me), 2.25 (6 Me), 6.88 (2 aromatic H)
	III	CH_2Cl	Me	205—206	1.86 (2 Me), 2.28 (2 Me), 2.32 (2 Me), 2.41 (2 Me), 4.28 (2 CH_2)
	IV	Me	Me	259—262	1.80 (4 Me), 2.26 (4 Me), 2.30 (2 Me)
	V	CH_2ONO_2	Me	144—146	1.82 (2 Me), 2.28 (2 Me), 2.30 (4 Me), 5.08 (2 CH_2)
	VI	CH_2ONO_2	CH_2ONO_2	154—160	1.83 (Me), 2.27 (Me), 2.31 (3 Me), 2.35 (Me), 2.37 (Me), 5.07 (CH_2), 5.13 (2 CH_2)
	VII	CH_2OCH_2	Me	252—253	2.04 (2 Me), 2.32 (4 Me), 2.40 (2 Me), 3.72 (2 CH; J_{gem}=12 Hz), 4.82 (2 CH; J_{gem}=12 Hz),
		H	H	121—122	1.84 (4 Me), 2.21 (2 Me), 2.32 (2 Me), 6.96 (2 aromatic H)
	XIII	CH_2Cl	CH_2Cl	211—213	1.80 (2 Me), 1.92 (2 Me), 2.25 (2 Me), 2.43 (2 Me), 4.78 (2 CH_2)
	XV	CH_2ONO_2	CH_2ONO_2	178—179	1.83 (2 Me), 1.88 (2 Me), 2.26 (2 Me), 2.38 (2 Me), 5.67 (2 CH_2)
		H	H	136—138	1.74 (4 Me), 2.26 (4 Me), 6.99 (2 aromatic H)
	XIV	CH_2Cl	CH_2Cl	246—247	1.76 (4 Me), 2.35 (4 Me), 4.81 (2 CH_2)
	XVI	CH_2ONO_2	CH_2ONO_2	178—179	1.76 (4 Me), 2.33 (4 Me), 5.67 (2 CH_2)
	VIII	H	Me	281—283	2.16 (Me), 2.25 (2 Me), 2.38 (Me), 6.95 (aromatic H)
	IX	CH_2Cl	Me	265—268	1.89 (Me), 2.27 (Me), 2.31 (Me), 2.40 (Me), 4.25 (CH_2)
	X	Me	Me	276—278	1.84 (2 Me), 2.24 (2 Me), 2.28 (Me)
	XI	CH_2ONO_2	Me	177—178	1.88 (Me), 2.32 (2 Me), 2.35 (Me), 5.16 (CH_2)
	XII	CH_2ONO_2	CH_2ONO_2	230—231 (decomp.)	2.37 (Me), 2.43 (2 Me), 5.17 (2 CH_2)
		CH_2Cl	CH_2Cl	292—294	2.35 (Me), 2.44 (2 Me), 4.24 (2 CH_2)

from hot ligroin gave V as white prisms (0.22 g; 62%), mp 144—146 °C; slightly soluble in cold ligroin and readily soluble in chloroform.

Found: C, 63.24; H, 6.61%. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78%.

The above procedure applied to XIII, XIV, and IX gave *5,5′-bis(nitrooxymethyl)-2,2′,3,3′,4,4′,6,6′-octamethylbiphenyl (XV)*, mp 140—141 °C; *4,4′-bis(nitrooxymethyl)-2,2′,3,3′,5,5′,6,6′-octamethylbiphenyl (XVI)*, mp 178—179 °C; and *6-nitrooxymethyl-2,3,4,5-tetramethyl-2′,3′,4′,5′,6′-pentachlorobiphenyl (XI)*, mp 177—178 °C, respectively.

XV: Found: C, 63.77; H, 6.90%. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78%.

XVI: Found: C, 63.48; H, 6.65%. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78%.

XI: Found: C, 44.39; H, 3.12; N, 3.25%. Calcd for $C_{17}H_{14}Cl_5NO_3$: C, 44.62; H, 3.08; N, 3.06%.

Procedure for Nitration of Fully Substituted Biphenyls. A mixture of a biphenyl (IV or X; 0.005 mol) and dichloromethane (10 ml) was vigorously stirred and fuming nitric acid (d=1.5; 1.6 g) in the same solvent (5 ml) was added dropwise at −5 to 0 °C to give a dark brown solution. The mixture was allowed to stand at room temperature for several hours, during the course of which the initial dark color faded to light yellow. It was then poured into water and the organic layer was thoroughly washed with water. Evaporation of the solvent left a light brown paste (in the case of IV) or a white crystalline solid (in the case of X), which was inspected by IR, ^{1}H NMR, or thin-layer chromatography. Nitrates were obtained by crystallization of the crude product from a mixture of dichloromethane and light petroleum, and identified by their spectra and elemental analyses, or by direct comparison with the authentic specimens.

Chromatography on alumina of the crude nitration product obtained from IV gave unchanged material and nitrooxymethyl compounds from light petroleum eluates, and a cyclic ether VII (42%) from diethyl ether eluates. Recovery of nitrooxymethyl compounds was very unsatisfactory.

VI: Found: C, 56.29; H, 5.78; N, 8.59%. Calcd for $C_{22}H_{27}N_3O_9$: C, 55.34; H, 5.70; N, 8.80%.

IR: 1624, 1274, and 857 cm^{-1} (-ONO_2).

VII: Found: C, 85.47; H, 9.09%. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15%.

XI: Found: C, 44.52; H, 3.11; N, 3.08%. Calcd for $C_{17}H_{14}Cl_5NO_3$: C, 44.62; H, 3.08; N, 3.06%.

IR: 1632, 1277, and 855 cm^{-1} (-ONO_2).

XII: Found: C, 39.46; H, 2.55; N, 5.28%. Calcd for $C_{17}H_{13}Cl_5N_2O_6$: C, 39.37; H, 2.53; N, 5.40%.

IR: 1632, 1276, and 842 cm^{-1} (-ONO_2).

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