Synthesis of Nitropolymethylbiphenyls by Nitrative Cross Coupling of Polymethylbenzenes

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Nitration of mixtures of *o*-xylene or hemimellitene with more basic methylbenzenes gave nitropolymethylbiphenyls, formed to a considerable extent by cross coupling. Although yields were usually below 30% at about 60% conversion, the reaction produced new biphenyl derivatives in a single step. Coupling preceded nitration.

The formation from *o*-xylene, *o*-diethylbenzene, *o*-ethyltoluene, hemimellitene, and pseudocumene of alkyl homologs of 2-nitrobiphenyl under the influence of nitric acid has been described.[1] For *o*-xylene and hemimellitene the yields were sufficiently good to be of preparative significance. In the proposed mechanism, the intermediate nitroaronium ion had to fulfill certain stability and steric conditions for coupling by electrophilic attack; nitro-*o*-xylonium and the nitrohemimellitonium ions best fitted these conditions.

On the basis of the mechanism we expected to expand the nitrative coupling reaction to a greater variety of biphenyls by intercepting the nitro-*o*-xylonium ion or the nitrohemimellitonium ion intermediates by different alkylbenzenes in a cross-coupling reaction. More basic polyalkylbenzenes—which themselves do not couple alone—would be preferentially attacked by the nitro-*o*-xylonium or nitrohemimellitonium ion. To investigate this possibility, mixtures of *o*-xylene or hemimellitene with methyl aromatics were nitrated as described in the first paper,[1] and the products were determined by gas chromatography, elemental analysis, and ultraviolet, mass, and nmr spectrometry. Although cross coupling was observed as anticipated on the basis of our guiding ideas, during the course of the work we found experimental evidence for a different mechanism in which coupling precedes nitration.

Results and Discussion

Table I summarizes the results of screening experiments. As predicted, only hydrocarbon pairs containing either *o*-xylene or hemimellitene gave coupled products. Homo coupling of *o*-xylene or hemimellitene also occurred. *o*-Xylene and mesitylene formed only one cross-coupled product in substantial yield, which made its isolation easy.

TABLE I

YIELDS OF COUPLED PRODUCTS FROM THE REACTION OF NITRIC ACID WITH MIXTURES OF METHYLBENZENES

Hydrocarbon pair (1:1 molar ratio)	Mole % yield Homo coupling[a]	 Cross coupling[a]
o-Xylene–*m*-xylene	5.9 (2)	19.1 (3)
o-Xylene–*p*-xylene	8.2 (2)	3.8 (3)
o-Xylene–hemimellitene	8.0 (4)[b]	29.1 (3)
o-Xylene–pseudocumene	1.7 (4)	22.2 (2)
o-Xylene–mesitylene	1.0 (2)	25.4 (2)
o-Xylene–prehnitene	0.9 (2)	12.3 (1)
o-Xylene–isodurene	2.0 (2)	12.0 (2)
Hemimellitene–*m*-xylene	5.4 (2)	6.2 (1)
Hemimellitene–mesitylene	6.5 (2)	5.8 (2)
Hemimellitene–prehnitene	5.1 (2)	15.2 (1)

[a] Numbers in parentheses indicate the number of isomers. [b] Nitrobixylyls (two isomers), 1.9%, and nitrobihemimellityls (two isomers), 6.1%.

The effect of the molar ratio of the hydrocarbons on the coupling yield has not been studied in detail. Only in one case did we depart from the usual 1:1 molar ratio to 1:1.5 with the *o*-xylene–*m*-xylene pair at −10°; this resulted in lower coupling yield owing to excessive nitration of *m*-xylene. Fortunately, at such low temperatures hydrocarbons of different basicity nitrated at nearly the same rate so that the reaction mixtures were not exhausted of one of the hydrocarbon components. This was unexpected on the basis of generally accepted views that more highly methylated benzenes nitrate more readily.[2]

Surprisingly, the yield of coupling varies only slightly over a wide temperature range with *o*-xylene–*m*-xylene, *o*-xylene–mesitylene, and *o*-xylene–pseudocumene combinations. On the other hand, the coupling yield of the reactions involving tetramethylbenzenes is very sensitive to the reaction temperature.

Identification of Products.—Known compounds were identified by their gas chromatographic retention times. Unknown compounds formed in low yield were trapped out from the gas chromatograph and identified by mass spectrometry. In these cases the molecular weights and nature of the compounds were definitely established but the positions of substituents could not be assigned with certainty. Several cross-coupled products were isolated for complete characterization; the physical constants and elemental analyses are compiled in Table II. Table III gives the nmr absorptions to infer the positional assignment of the substituents from the spectroscopic criteria that have been discussed in detail.[1] In addition, there was a remarkable feature in the ultraviolet spectra which can also help in the positional assignment of the substituents. In 2-nitro-2′-methylbiphenyls the molar absorptivity of the end absorption at a specified wavelength (*e.g.*, 240 mμ) was much higher if the 3 position was unsubstituted (11,400–12,400 in compounds II and VI; 7100–7900 in compounds I, V, and VIIb), apparently because contribution to the biphenyl absorption of the nitro-group resonance is sterically hindered.[3]

In two cases the interpretation of the nmr spectra was not in accord with the expected structures. Thus, from the nitrative cross coupling between *o*-xylene and mesitylene we expected 2-nitro-2′,4,4′,5,6′-pentamethylbiphenyl (VIII) as the major product since the homo coupling of *o*-xylene was previously found[1] to

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[1] I. Puskas and E. K. Fields, *J. Org. Chem.*, **31**, 4204 (1966).

[2] A. V. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds," Pergamon Press Inc., New York, N. Y., 1959, p 12.

[3] Compare with the effect of alkyl substituents on nitrobenzene: W. G. Brown and H. Reagan, *J. Am. Chem. Soc.*, **69**, 1032 (1947).

TABLE II
PHYSICAL CONSTANTS AND ELEMENTAL ANALYSES OF NEW NITROPOLYMETHYLBIPHENYLS

No.	Compd	Mp, °C (cor)	Formula[a]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
I	2-Nitro-2′,3,4,4′-tetramethylbiphenyl	94.0–94.7	$C_{16}H_{17}NO_2$	75.29	74.63	6.66	6.90	5.49	5.44
II	2-Nitro-2′,4,4′,5-tetramethylbiphenyl	74.5–76.0	$C_{16}H_{17}NO_2$	75.29	75.57	6.66	6.86	5.49	5.40
III	3-Nitro-2,3′,4,4′,6-pentamethylbiphenyl	103.8–104.8	$C_{17}H_{19}NO_2$	75.81	75.82	7.11	7.10	5.20	...
IV	2-Nitro-2′,3′,4,4′,5-pentamethylbiphenyl	*b*	$C_{17}H_{19}NO_2$	...	...	...	...	...	...
V	2-Nitro-2′,3,4,4′,5′-pentamethylbiphenyl	114–116	$C_{17}H_{19}NO_2$	75.81	75.53	7.11	7.08	5.20	5.57
VI	2-Nitro-2′,4,4′,5,5′-pentamethylbiphenyl	119–120	$C_{17}H_{19}NO_2$	75.81	75.16	7.11	6.85	5.20	...
VII	2-Nitro-3,3′,4,4′,5,6-hexamethylbiphenyl	151–152	$C_{18}H_{21}NO_2$	76.29	75.66	7.47	7.51	4.94	5.04
(or VIIb)	(or 2-nitro-2′,3,3′,4,4′,5′-hexamethylbiphenyl)								

[a] Confirmed by mass spectrometric molecular weight determinations. [b] A eutectic mixture melting at 75–78° and containing approximately 77% of this compound was isolated which could not be purified further.

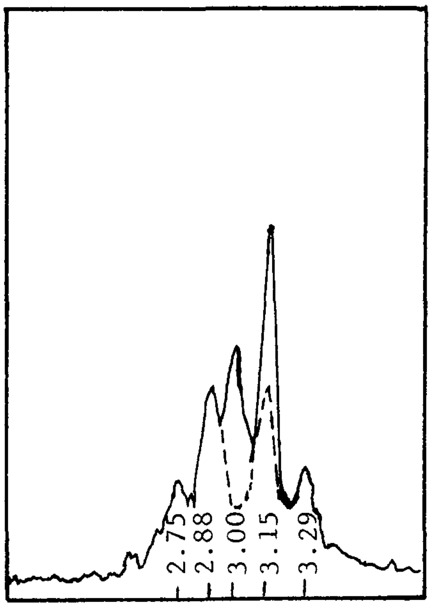
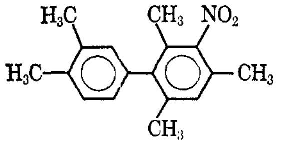


Figure 1.—Nmr spectrum of 3-nitro-2,3′,4,4′,6-pentamethylbiphenyl in the aromatic proton range (in deuteriochloroform).

give 2-nitro-3′,4,4′,5-tetramethylbiphenyl (IX) as the main isomer. However, to our surprise, the nmr spectrum of the isolated nitropentamethylbiphenyl did not show a low-field aromatic proton in the τ 2.00–2.50 region for an *o*-nitro proton (Table III). The unsymmetrical multiplet (Figure 1) appears to be composed of two slightly perturbed doublets (dotted lines) and two singlets. We ascribe the singlets to one proton in the mesityl portion of the biphenyl and another in the *o*-xylyl portion. The doublets might be the result of the AB type of coupling in the *o*-xylyl portion. The coupling constant (7.0 cps) indicates coupling by *ortho*



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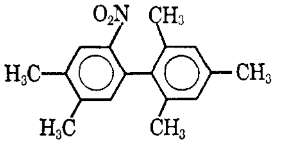
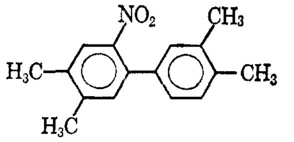
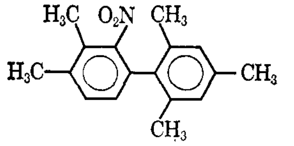


VIII



IX



X

TABLE III
NMR ABSORPTIONS OF THE NEW NITROPOLYMETHYLBIPHENYLS

	Nmr τ values		
	In deuteriochloroform		In benzene,
Compd	Aromatic protons[a]	Methyl protons[a]	methyl protons[a]
I	from 2.66 to 3.02 (partially resolved)	7.65 (3) 7.69 (3) 7.78 (3) 7.90 (3)	7.88 (3) 7.94 (3) 8.18 (3) 8.23 (3)
II	2.21 (1) 2.96 (2) 3.03 (2)	7.67 (9) 7.97 (3)	7.94 (3) 8.03 (3) 8.32 (6)
III	Multiplet[b] from 2.75 to 3.29	7.73 (9) 8.00 (3) 8.06 (3)	7.95 (3) 8.00 (3) 8.02 (3) 8.11 (3) 8.18 (3)
IV[c]	2.46 (1) 2.89 (1) 3.05 (2)	7.61 (3) 7.66 (3) 7.70 (6) 7.95 (3)	
V	Multiplet from 2.87 to 3.20	7.69 (3) 7.74 (6) 7.84 (3) 7.93 (3)	
VI	2.26 (1) 2.98 (1) 3.04 (1) 3.18 (1)	7.71 (6) 7.81 (6) 8.01 (3)	7.97 (6) 8.02 (3) 8.21 (6)
VII (or VIIb)	Multiplet[d] from 2.84 to 3.33	7.78 (12) 7.86 (3) 8.00 (3)	

[a] Numbers in parentheses indicate number of protons. [b] For interpretation see Figure 1. [c] Although the compound was only 77% pure the nmr spectrum is given for the pure compound. Peaks corresponding to impurities are omitted. [d] For interpretation see Figure 2.

protons[4] which would be in agreement with the 3-nitro-2,3′,4,4′,6-pentamethylbiphenyl (III) assignment. The alternative formula of 2-nitro-2′,3,4,4′,6′-pentamethylbiphenyl (X) is unlikely on the basis of the ultraviolet spectrum. In such a sterically hindered tri-*ortho*-substituted biphenyl the 3-nitro-*o*-xylene portion should absorb separately showing a peak or at least a well-observable inflection with an expected λ_{max} 251 mμ (ϵ_{max} 4210),[5] which is not the case.

Similarly, from the nitrative cross-coupling between *o*-xylene and prehnitene we expected 2-nitro-2′,3′,4,4′,5,5′-hexamethylbiphenyl as the major product,

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[4] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 193–195.

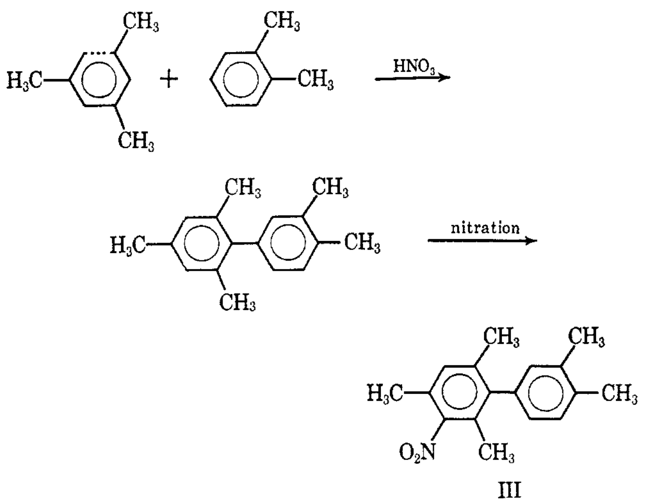
[5] J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Visser, and B. M. Wepster, *Rec. Trav. Chim.*, **77**, 493 (1958).

whereas according to the nmr spectrum it is either 2-nitro-3,3′,4,4′,5,6-hexamethylbiphenyl (VII) or 2-nitro-2′,3,3′,4,4′,5′-hexamethylbiphenyl (VIIb). The spectrum of the aromatic protons (Figure 2) appears to be composed of two perturbed doublets (dotted line in Figure 2), which are assigned to the two protons of the *o*-xylene portion of the biphenyl derivative, and a singlet proton which might come from any part of the biphenyl. The coupling constant (7.2 cps) indicates coupling by *ortho* protons. Unfortunately, ultraviolet spectroscopy cannot differentiate between VII and VIIb; *o,o*-disubstituted and *o,o′*-disubstituted biphenyls exhibit very similar ultraviolet spectra.[6]

The structural assignments of the rest of the compounds of Table II are straightforward, although in several cases alternative structures cannot be ruled out with certainty, *e.g.*, 2-nitro-2′,3,3′,4,5′-pentamethylbiphenyl as the structure of compound V.

Mechanistic Implications.—Among the by-products of the reaction we also found polymethylbiphenyls. Their presence immediately suggested that these compounds might be intermediates in the formation of nitropolymethylbiphenyls. Indeed, we found that at low reaction temperatures the yield of polymethylbiphenyls was quite good and that of the nitropolymethylbiphenyls poor; this product distribution was drastically reversed at somewhat higher temperatures. This is evidence for the reaction path exemplified in Scheme I by the coupling reaction between *o*-xylene and mesitylene. According to this mechanism, coupling precedes nitration. In fact, at low temperatures polymethylbiphenyls accumulated in such concentrations as to permit isolation. Although these observations cannot entirely rule out the possibility of the simultaneous occurrence of another mechanistic path such as originally suggested,[1] the predominant—if not the sole—reaction path is coupling followed by nitration.

Scheme I



III

The new mechanism, by fortuitous coincidence, with a few exceptions, gives isomeric distribution of the coupled products similar to that expected on the basis of the previously defined rules of coupling.[1] Since mononitration of biphenyl gives mixtures of 2-nitro- and 4-nitrobiphenyl,[7] nitration of the polymethylbiphenyls should also give 4-nitropolymethylbiphenyls unless the *para* positions are blocked. The isolated coupled products on the basis of spectroscopic evidence have their nitro groups in the 2 positions (and in one case in the 3 position) because the 4,4′ positions are occupied by methyl groups. However, formation of a biphenyl with 4-nitro group such as XI could be possible in the cross coupling of *o*-xylene and pseudocumene. Similarly, nitration of unsymmetrical polymethylbiphenyl may take place anywhere, but in the nitropolymethylbiphenyls derived from cross-coupling of *o*-xylene with a more basic hydrocarbon the nitro group in most cases entered the *o*-xylene ring, probably because of steric and substituent effects. However, the cross-coupled product from *o*-xylene and mesitylene (III) has its nitro group not only in the mesitylene ring but also in a *meta* position of the biphenyl, which is somewhat unusual.

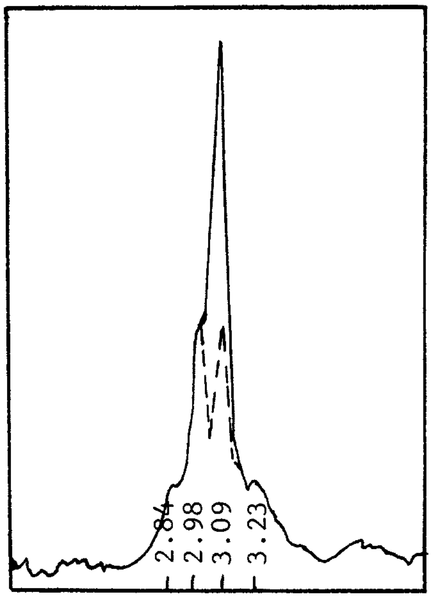
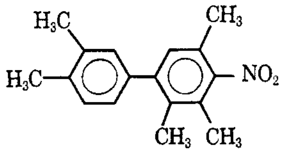


Figure 2.—Nmr spectrum of 2-nitro-3,3′,4,4′,5,6-hexamethylbiphenyl in the aromatic proton range (in deuteriochloroform).



XI

Experimental Section

Melting points are corrected. Ultraviolet spectra were obtained on a Cary Model 11 recording spectrophotometer; nmr spectra were measured on a Varian Associates HR-60 spectrometer at 52 Mc with trimethylsilane as an internal standard; and mass spectra were taken on a modified CEC Model 21-130 mass spectrometer.

Gas chromatographic analyses were performed as described previously.[1] Based on that experience we assigned arbitrary correction factors to different types of compounds to correct for the thermal conductivity differences and for possible thermal decomposition of the higher boiling components.[1]

General Procedure.—The reaction vessel was a round-bottomed, three-necked flask equipped with a stirrer, a thermom-

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[6] See examples: G. H. Beaver and E. A. Johnson, *Spectrochim. Acta*, **14**, 72 (1959).

[7] R. Taylor, *J. Chem. Soc.*, *Phys. Org. Chem. Sect.*, 727 (1966), and references cited therein.

eter, and a dropping funnel. In most experiments, the flask containing 0.1 mole of each hydrocarbon was immersed in a thermostated bath and brought to the desired temperature. Then 28.2 ml of 90% nitric acid (about 0.6 mole) was added dropwise, slowly enough to control the exothermic reaction. After all the acid had been added (usually 40–50 min), the mixtures was stirred for an additional 10–20 min and poured onto a mixture of ethanol-free ether and ice to quench the reaction. Products were extracted into the ether layer, which was then washed with a 10% sodium hydroxide and with water, and dried with saturated sodium chloride solution, and the ether was removed in a Rotavapor (Rinco Instrument Co.) at room temperature. The residues were analyzed by gas chromatography.

In the preparative scale experiments larger amounts of reactants (up to 1.0 mole of each hydrocarbon) were used with correspondingly longer reaction times.

Experiments involving tetramthylbenzenes suddenly became violent and got out of control after most of the acid had been added, if the reaction temperature was too high. Such an accident occurred with the *o*-xylene–isodurene pair at 0 to −2°.

Isolation of Cross-Coupled Products. *o*- and *m*-Xylenes.—The crude reaction mixture from the reaction of 1.0 mole of each hydrocarbon at −5 ± 5° was distilled at 0.1 mm. Nitrobixylyls distilled at 145–165°; high-vacuum fractionation of the mixture did not give satisfactory separation. From hexane solution at 0° crystals separated slowly which were recrystallized from ethanol and again from hexane to give pale yellow **2-nitro-2′,4,4′,5-tetramethylbiphenyl** (II, 7.3 g), mp 74.5–76.0°.

Treatment of the mother liquors of the crude II with methanol at 0° yielded crystals. Recrystallization from methanol gave white needles of **2-nitro-2′,3,4,4′-tetramethylbiphenyl** (I), mp 94.0–94.7°.

***o*-Xylene and Mesitylene.**—The crude reaction mixture (209 g) from the reaction of 0.75 mole of each hydrocarbon at −1 ± 2° was distilled at 0.1 mm. The fraction boiling at 167–168° solidified in contact with methanol. Recrystallization from methanol gave off-white crysals of **3-nitro-2,3′,4,4′,6-pentamethylbiphenyl** (III, 14.6 g), mp 103.8–104.8°. The yield of pure product was 8.1% not taking account of the recoverable unreacted hydrocarbon.

***o*-Xylene and Hemimellitene.**—The crude reaction mixture (197 g) from the reaction of 0.75 mole of each hydrocarbon at −5 ± 2° was distilled at 0.1–0.2 mm. The fractions boiling at 172–183° were mixtures of coupled products (46.5 g). Several recrystallizations from ethyl acetate-methanol gave some pure 2-nitro-2′,3,3′,4,4′,5-hexamethylbiphenyl.[1] The major cross-coupled product could not be isolated by fractional crystallization from many solvents. A fraction containing 77.3% of IV, 21.3% 2-nitro-2′,3,3′,4,4′,5-hexamethylbiphenyl, and 1.4% unidentified minor component was used for structure determination by nmr spectroscopy; the peaks owing to 2-nitro-2′,3,3′,4,4′,5-hexamethylbiphenyl[1] were subtracted from the spectrum of the mixture.

The distillation residue was dissolved in hot methanol-acetone, treated with active carbon, and allowed to stand at 0°. After a couple of days crystals separated. These were recrystallized from dioxane to give pure 2,2′-dinitro-3,3′,4,4′,5,5′-hexamethylbiphenyl,[1] mp 281–282°.

***o*-Xylene and Pseudocumene.**—The crude reaction mixture (206 g) from the reaction of 0.75 mole of each hydrocarbon at −8 ± 7° was vacuum distilled at 0.4 mm. The fraction distilling at 163–176° from methanol gave yellow crystals of **2-nitro-2′,4,4′,5,5′-pentamethylbiphenyl** (VI, 10.3 g), mp 114–116°. These were recrystallized from methanol to raise the melting point to 119–120°.

The mother liquors of VI were taken down to dryness and crystallized from hexane at 0°. The impure crop gave colorless **2-nitro-2′,3,4,4′,5′-pentamethylbiphenyl** (V) by recrystallization from methanol (2.1 g), mp 114–116°.

***o*-Xylene and Prehnitene.**—The reaction mixture (79.5 g) from 0.3 mole of each hydrocarbon at −11 to −14° was vacuum distilled at 0.1 mm. The fraction boiling at 171–180° (5.9 g) solidified on cooling. Recrystallization from methanol containing small amounts of ethyl acetate gave colorless crystals of **2-nitro-3,3′,4,4′,5,6-hexamethylbiphenyl** (VII) (or 2-nitro-2′,3,3′,4,4′,-5′-hexamethylbiphenyl (VIIb) in several crops, mp 151–152° (3.5 g).

The solvent was removed from the mother liquors of VII. Syrupy residue from acetic acid gave a few milligrams of colorless crystals, mp 142–144°, 96.1% pure according to gas chromatography. A better recovery of this compound from the solution failed because it tends to form mixed crystals. It has been identified by mass spectroscopy as **octamethyldiphenylmethane.** The reported melting point for octamethyldiphenylmethane is 150°.[8]

Registry No.—I, 7540-83-2; II, 7540-84-3; III, 7540-85-4; IV, 7540-86-5; V, 7540-87-6; VI, 7540-88-7; VII, 7540-89-8; VIII, 7540-90-1; 2,2′-dinitro-3,3′,4,4′-5,5′-hexamethylbiphenyl, 7540-91-2.

Acknowledgments.—The spectroscopic analyses by S. Meyerson, E. M. Banas, and R. R. Hopkins are gratefully acknowledged. M. C. Hoff is thanked for samples of the polymethylbenzenes.

(8) C. L. Hewett and R. H. Martin, *J. Chem. Soc.*, 1396 (1940); C. M. Welch and H. A. Smith, *J. Am. Chem. Soc.*, **73**, 4391 (1951).

The Nuclear Magnetic Resonance Spectra of Some Polyphenyldialkylbenzenes and -anthracenes. Long-Range Shielding by Benzene Rings

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Several polyphenyldialkylbenzenes and -anthracenes were examined to determine the effect of a phenyl substituent on the nmr absorption of alkyl protons held near the axis perpendicular to the plane of the phenyl group. A set of empirical shielding constants is derived and shown to be generally consistent although anomalies exist. Some of the shielding constants are compared with values calculated on the basis of a previously described theoretical model, and discrepancies between theory and experiment are noted.

The concept of a local magnetic field generated by a ring current arising from the interaction of an externally applied magnetic field and a system of π electrons has been invoked to account for the low-field nuclear magnetic resonance (nmr) absorption of aromatic protons. Theoretical calculations of the magnitude of this effect have been made on the basis of a model invented by Pauling[1] and explicitly stated for the nmr problem by Pople[2] and Waugh and Fessenden,[3] and modified by Johnson and Bovey.[4] Quantitative predictions based on this theory have agreed with experimental values for some simple compounds (ethylbenzene and dibenzyl), but failed to agree for others (diphenylmethane and β-CH$_2$ of tetralin).[4]

(1) L. Pauling, *J. Chem. Phys.*, **4**, 673 (1936).

(2) J. A. Pople, *ibid.*, **24**, 1111 (1956).

(3) J. S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, **79**, 846 (1957).

(4) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).