[CONTRIBUTION NO. 2512 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Further Evidence for Benzyne as an Intermediate in Nucleophilic Aromatic Substitution Reactions[1]

BY M. PANAR AND JOHN D. ROBERTS

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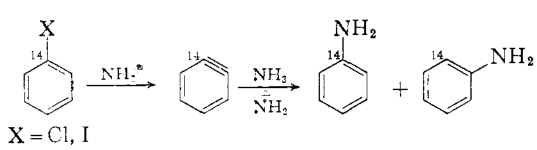
Some alternatives to the "benzyne" (elimination–addition) mechanism for aminations of non-activated halobenzenes have been disproved by the finding that the amination of iodobenzene-1-^{14}C-2,4,6-^{2}H$_3$ gives the same extent of ^{14}C rearrangement in the resulting aniline as does iodobenzene-1-^{14}C. The intermediacy of substituted benzynes in non-rearranging aminations of 3-substituted halobenzenes has been confirmed by a study of the hydrogen–deuterium kinetic isotope effect in reactions of 3-bromoanisole-2,4,6-^{2}H$_3$.

Introduction

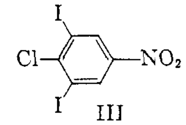
The elimination–addition mechanism (eq. 1) postulated[2] for nucleophilic substitutions of non-activated halobenzenes provided the first coherent explanation of the rearrangements which frequently accompany these reactions. Thus, both chlorobenzene-1-^{14}C- and iodobenzene-1-^{14}C yield, upon amination with amide ion in liquid ammonia,



(1)

a nearly 1:1 mixture of aniline-1-^{14}C and aniline-2-^{14}C in agreement with the exclusive operation of the benzyne mechanism.

Alternative mechanisms, however, can account for the rearrangements observed in these amination reactions. For example, the 1:1 ratio of aniline-1-^{14}C to aniline-2-^{14}C could conceivably result from a combination of two reactions proceeding at nearly identical rates: one reaction being a direct displacement and the other leading to rearrangement. This possibility may be regarded as unlikely in view of the nearly identical product mixtures obtained from the amination of iodobenzene-1-^{14}C and chlorobenzene-1-^{14}C, which halides should hardly have the same ratio of "direct" to "abnormal" reactions. However, the argument involves a value judgment which, in some quarters, might be regarded as less reasonable than the postulation of benzyne as an intermediate. To be sure, the dual-path mechanism is also inconsistent with the demonstrated requirement of these amination reactions for hydrogens to be present *ortho* to the leaving halide group, as witnessed by the fact that bromodurene (I) and bromomesitylene (II) are not aminated by sodium amide in liquid ammonia. The lack of reactivity of I and II could be ascribed to steric hindrance provided by the *ortho* groups but this can, in turn, be countered by the finding that two *o*-iodines only slightly decrease the reactivity of the activated chlorobenzene III toward substitution by piperidine.[3] Furthermore, if the dual mechanism were correct, the over-all hydrogen–deuterium kinetic isotope effect[2] of nearly 6 found for amination of bromobenzene-2-^{2}H would mean an isotope effect of almost 12 for the rearranging mechanism because, by all rights, the direct mechanism would have at most 10–20% hydrogen kinetic isotope effect.



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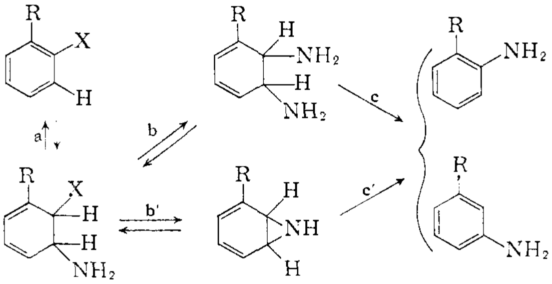
A further explanation for the 1:1 ratio of isomeric products resulting from these amination reactions involves addition–substitution–elimination (eq. 2).[2] This formulation is rendered



(2)

unlikely by virtue of the large (5.5–5.8) kinetic isotope effect found in aminations of bromobenzene-2-^{2}H and chlorobenzene-2-^{2}H. The argument is as follows. The hydrogen kinetic isotope effect implies that the bond to the *o*-hydrogen is broken in the rate-determining step; therefore, the slow step in (2) would have to be the final, probably exothermic, step (c) involving loss of ammonia or rearrangement of a proton and re-establishment of the aromatic system. The highly endothermic addition of ammonia in step (a) and the loss of halogen (b or b′) would thus both be required to be rapid equilibria.[4]

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(1) Supported in part by the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is hereby made to the Donors of this Fund.

(2) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, THIS JOURNAL, **78**, 601 (1956).

(3) R. B. Sandin and M. Liskear, *ibid.*, **57**, 1304 (1935).

(4) A variant of the above mechanism (A. A. Morton, *J. Org. Chem.*, **21**, 593 (1956)) involves, as already has been pointed out,[2] a most unfavorable intermediate. This mechanism appears, moreover, to be inconsistent with the lack of rearrangement found in the amination of substances like *m*-bromoanisole.

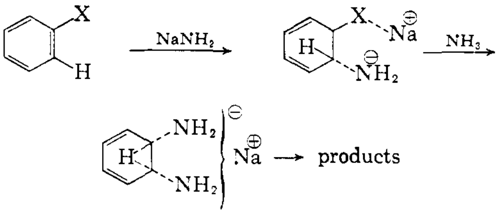


TABLE I

RADIOACTIVITY ANALYSES OF DEGRADATION PRODUCTS

		Cyclohexanone	CO_2 (aniline-1-^{14}C)	1,5-Diaminopentane (aniline-2-^{14}C)
Iodobenzene-1-^{14}C-2,4,6-$^2H_3$	Meas. act.[a]	0.1195 ± 0.0020	0.0566 ± 0.005	0.0632 ± 0.0010
	Total act., %	(100)	47.4 ± 0.9	52.8 ± 1.2
Iodobenzene-1-^{14}C	Total act., %	(100)	46.4 ± 0.1[b]	53.0 ± 0.2[b]

[a] Activities in microcuries per millimole. [b] Data from ref. 2.

In the present research, we have concentrated our attention on determining whether or not any direct halogen displacement occurs, either by an SN2-like reaction or through the path of eq. 2, in amination reactions which have been postulated to involve benzyne intermediates. First, we shall consider the possibility that competing direct and rearranging displacements occur in the amination of iodobenzene and, second, we shall consider the mechanism of the non-rearranging amination of 3-substituted halides and, in particular, *m*-bromoanisole.

Results and Discussion

Information as to direct halogen displacement was sought through an investigation of the extent of rearrangement in the amination of iodobenzene-1-^{14}C-2,4,6-$^2H_3$. The substituted iodobenzene, rather than the corresponding chloro or bromo compound, was chosen for study since, in the apparently analogous hydrolysis of halotoluenes,[5] iodotoluene showed the greater tendency for direct substitution.

Iodobenzene-1-^{14}C-2,4,6-$^2H_3$ was prepared from commercially available aniline-1-^{14}C which had been deuterated by repeated equilibrations with 99% deuterium oxide. The calculated deuterium purity of the iodobenzene-1-^{14}C-2,4,6-$^2H_3$ used was 98.5%. Carbon–hydrogen absorption peaks at 10.03, 13.70 and 14.65μ in the infrared spectrum of normal iodobenzene were not present in the spectrum of the deuterated iodobenzene. The amination was carried out with potassium amide in anhydrous liquid ammonia and the aniline formed degraded by methods described previously.[2]

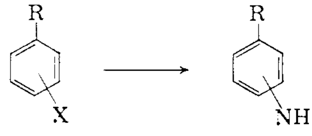
The extent of rearrangement observed (Table I) in the amination of iodobenzene-1-^{14}C-2,4,6-$^2H_3$ is nearly identical to that found in the amination of iodobenzene-1-^{14}C. If the amination had occurred by a combination of direct and rearranging substitutions, the presence of the *o*-deuterium atoms must, as a result of the kinetic isotope effect, slow down the rearranging reaction by a factor of 8–12 relative to the non-rearranging substitution. Similarly, if the formulation of eq. 2 were correct, the final step (c) would proceed preferentially with the loss of hydrogen, rather than deuterium, thus increasing the proportion of unrearranged product. In either case, the product mixture resulting from the amination of iodobenzene-1-^{14}C-2,4,6-$^2H_3$ would have a higher ratio of aniline-1-^{14}C to aniline-2-^{14}C than found for the amination of iodobenzene-1-^{14}C.

The 1:1 ratio of ^{14}C-labeled anilines obtained in the amination of iodobenzene-1-^{14}C-2,4,6-$^2H_3$ is consistent only with an elimination–addition mechanism; the *o*-deuterium is removed during the formation of benzyne and has no influence on the manner of addition of ammonia to the reactive benzyne bond. If one considers the most adverse limits of error and accepts the value of 53.0 ± 0.2% of activity in the 2-position (*i.e.*, aniline-2-^{14}C formed) as a measure of the ^{12}C–^{14}C isotope effect, it is possible to calculate an upper limit to the extent of direct substitution accompanying the amination of iodobenzene-1-^{14}C of about 0.2%.

The second point investigated regarded the non-rearranging aminations of certain 3-substituted halobenzenes (data relevant to the extent of the rearrangement as a function of the nature and position of substituent groups[6] are summarized in Table II). In spite of the lack of rearrangement which typifies aminations of compounds like *m*-bromoanisole, they may well involve the benzyne mechanism found with most other non-activated halobenzenes. The important point is that lack of rearrangement may reflect a high degree of orientating power exerted by the substituent on addition of ammonia and not incursion of a direct substitution mechanism. Indeed, the observed orientations in aminations of *o*- and *m*-substituted halobenzenes have been explained successfully through consideration of the relative inductive effects of the substituents.[6]

TABLE II

ORIENTATIONS IN AMINATIONS OF SUBSTITUTED HALOBENZENES (Data from ref. 6)



R	X	*Ortho*, %	*Meta*, %	*Para*, %
o-OCH_3	Br	....	100	....
m-OCH_3	Br	....	100	....
p-OCH_3	Br	....	49 ± 1	51 ± 1
o-CF_3	Cl	....	100	....
m-CF_3	Cl	....	100	....
p-CF_3	Cl	....	50 ± 5	50 ± 5
o-CH_3	Cl	45 ± 4	55 ± 4	....
m-CH_3	Cl	40 ± 4	52 ± 4	8 ± 4
p-CH_3	Cl	....	62 ± 4	38 ± 4

Despite the coherency of the explanation offered for the lack of rearrangement in aminations of *m*-haloanisoles, there is no evidence which rules out the possibility that *m*-haloanisoles react with amide ion in liquid ammonia by a direct substitution mechanism, rather than by an elimination–addition mechanism. Substituents which do not lead to rearrangement when in the *m*-position (*e.g.*, $-OCH_3$, $-CF_3$) are inductively electron-attracting

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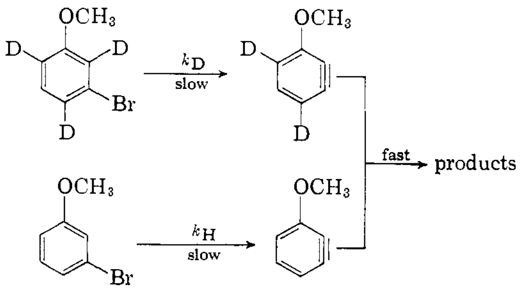
(5) A. T. Bottini and J. D. Roberts, THIS JOURNAL, **79**, 1458 (1957).

(6) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *ibid.*, **78**, 611 (1956).

and might activate a *m*-halogen toward direct nucleophilic substitution. It is conceivable that such activation could alter the course of the amination reaction.

In order to determine the mechanisms by which 3-bromoanisole reacts with potassium amide in liquid ammonia and with lithium diethylamide in ether, aminations were carried out with mixtures of 3-bromoanisole and 3-bromoanisole-2,4,6-$^2H_3$. If 3-bromoanisole is aminated by an elimination–addition mechanism, the presence of the *o*-deuterium atom should result in a kinetic isotope effect and the undeuterated compound should react faster than the deuterated. The experimental isotope effects, k_H/k_D summarized in Table III, are calculated on the assumption that the *o*-hydrogen is removed in the rate-determining step (eq. 4). That k_H/k_D is much larger than unity confirms participation of the *o*-hydrogen and, hence, offers strong evidence for the intermediacy of 3-methoxybenzyne.



(4)

TABLE III

DEUTERIUM KINETIC ISOTOPE EFFECTS

Reagent	Solvent	Mole % deuterated haloanisole At start	Mole % deuterated haloanisole At finish	Formation of halide ion at finish, %	k_H/k_D (apparent)
KNH_2	NH_3	28.5 ± 2	38.5 ± 2	54.3 ± 0.3	1.9 ± 0.1
$LiN(Et)_2$	Ether	27.0 ± 2	71.0 ± 2	84.1 ± 0.4	3.1 ± 0.1

The "apparent" isotope effects are considerably lower than those expected [~5.7][7] if the *o*-hydrogen were removed in a concerted elimination (eq. 4) as is assumed in the calculations. The low isotopes effect may imply that considerable exchange of hydrogen for deuterium is taking place prior to the loss of the bromine to form 3-methoxybenzyne. This conclusion is suggested by the relatively high rate constant for the exchange of deuterium *ortho* to a methoxy group.[8]

The isotope effect of 3.1 found for the reaction of 3-bromoanisole-2,4,6-$^2H_3$ with lithium diethylamide in ether probably represents the actual isotope effect for the reaction. This low value compared to those found for chloro- and bromobenzenes-2-$^2H_2$ could conceivably result from competing elimination–addition and direct-substitution reactions. However, it seems more reasonable that the isotope effect is smaller because of a decrease in the zero-point energy change of the *o*-hydrogen between ground and transition states resulting from the strong inductive effect of the methoxy group. This explanation is consistent with evidence from similar reactions, *e.g.*, the known dependence of the magnitude of the isotope effect on electron density at the reactive center.[9] It also agrees with the observed 250- to 400-fold greater rate of reaction of 3-bromoanisole over 2- and 4-bromoanisole with lithium piperidide and piperidine.[10]

Experimental

Iodobenzene-1-^{14}C-2,4,6-$^2H_3$.—Aniline-1-^{14}C hydrochloride[11] (68.0 mg., 0.163 mc.) was diluted with 18.15 g. of aniline hydrochloride (0.14 mole). The mixture was equilibrated five times with 15 ml. (0.64 mole) of 99.5% deuterium oxide.[12] The calculated isotope purity of the deuterated material was 98.5%. Aniline-1-^{14}C-2,4,6-$^2H_3$ was converted to iodobenzene-1-^{14}C-2,4,6-$^2H_3$ by diazotization and addition of potassium iodide.[13]

Amination and degradation of the labeled iodobenzene and the aniline formed therefrom were carried out as described previously for iodobenzene-1-^{14}C.[1] The ^{14}C-activities of the derivatives were determined by the vibrating-reed electrometer method.[14]

3-Bromoanisole-2,4,6-$^2H_3$.—*m*-Anisidine-2,4,6-$^2H_3$ was prepared by repeated equilibrations of *m*-anisidine hydrochloride with deuterium oxide.[11] The isotopic purity, calculated on the basis of complete equilibration, was 95% and was confirmed by the infrared spectrum.

The deuterated *m*-anisidine was converted to 3-bromoanisole-2,4,6-$^2H_3$ by the Sandmeyer reaction.[15] The material used in the aminations gave only one peak on analysis by vapor-phase chromatography.

3-Bromoanisole-2,4,6-$^2H_3$ with Potassium Amide in Liquid Ammonia.—The method was similar to that described previously.[2] 3-Bromoanisole-2,4,6-$^2H_3$ (3.1616 g.) was diluted with normal 3-bromoanisole (8.3288 g.), and 9.9388 g. (0.0528 mole) of the mixture was dissolved in 300 ml. of anhydrous liquid ammonia. A mixture of potassium amide (0.0883 mole) prepared from 3.4 g. of potassium metal and 80 ml. of anhydrous liquid ammonia was added to the 3-bromoanisole over a period of 30 seconds. The reaction was allowed to run for 5 minutes and was then quenched by the addition of 22 g. of ammonium nitrate. Anhydrous ether (100 ml.) was added and the ammonia allowed to evaporate. The residue was extracted several times with water. The water washings (400 ml. total) were combined, boiled to remove excess ether and ammonia and then diluted quantitatively to 500 ml. Bromide ion was determined by the Volhard method with a precision of 0.3%.

The ethereal solution, containing the unreacted 3-bromoanisole, was washed with 250 ml. of 3 *M* hydrochloric acid to remove anisidine and the 3-bromoanisole distilled through a 20-cm. semi-micro column.[16] The recovered bromoanisole (b.p. 89°, 8 mm.), showed only one peak on analysis by vapor-phase chromatography.

3-Bromoanisole-2,4,6-$^2H_3$ with Lithium Diethylamide in Ether.—Lithium diethylamide was prepared from diethylamine (4.52 g., 0.062 mole) and freshly prepared methyllithium in ether (70 ml., 0.90 *N*, 0.055 mole). A mixture of 3-bromoanisole-2,4,6-$^2H_3$ and 3-bromoanisole (10.7039 g., 0.0554 mole) was added over a period of 2 minutes. The initially strongly exothermic reaction subsided within 5 min-

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(7) The isotope effect resulting from the reactions of halobenzenes with lithium diethylamide in ether is 5.5–5.8. In these reactions, exchange is not important.[2] The value of 5.7 may, therefore, be considered the actual value of k_H/k_D, as distinct from the "apparent" value which is lowered by exchange. The k_H/k_D ratio of 5.7 is close to 6–7 range reported for concerted E2 dehydrobrominations (V. J. Shiner, THIS JOURNAL, **74**, 5285 (1952)).

(8) G. E. Hall, R. Piccolini and J. D. Roberts, *ibid.*, **77**, 4540 (1955).

(9) V. J. Shiner, Jr., *ibid.*, **78**, 2653 (1956); V. J. Shiner, Jr., and M. L. Smith, *ibid.*, **80**, 4095 (1958).

(10) R. Huisgen, "Kekulé Symposium on Theoretical Organic Chemistry," Butterworths Scientific Publications, London, September, 1958, p. 166.

(11) Obtained from Tracerlab, Inc.

(12) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 239 (1946).

(13) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 351.

(14) O. K. Neville, THIS JOURNAL, **70**, 3499 (1948).

(15) *Org. Syntheses*, **24**, 22 (1944).

(16) C. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

utes. The reaction mixture was stirred for 3 hours and then quenched by the addition of 20 ml. of water. The ether layer was extracted with 400 ml. of water; the water extract was boiled to remove excess ether and diluted to 500 ml. The Volhard method was used for the analysis for bromide ion. Iodide (from the methyl iodide used in the preparation of methyllithium) was removed by oxidation with 0.05 *N* nitrous acid.[17] Analyses were precise to 0.4%. The ether layer, which contained the unreacted bromoanisole, was washed with 400 ml. of 3 *N* hydrochloric acid to remove amines. The bromoanisole was distilled and then purified for analysis by vapor-phase chromatography.

Analysis of Mixtures of 3-Bromoanisole-2,4,6-$^2H_3$ and 3-Bromoanisole.—Mixtures were analyzed for deuterium by the "base-line" method at 11.061 μ[18] with a Perkin–Elmer (model 21) infrared spectrophotometer.

Transmittances of undiluted mixtures were measured in a 0.05-mm. cell. The 0.05-mm. cell in the reference beam was filled with pure protonated 3-bromoanisole. In this manner, the deuterium absorption peak was made sufficiently large for the desired accuracy without interference from adjacent hydrogen absorption. A calibration graph was prepared from several standard mixtures. The plots were linear to within 1% over the concentrations calibrated. Duplicate analyses agreed to within 1%.

Calculation of Kinetic Isotope Effects.—"Apparent" kinetic deuterium isotope effects were calculated on the basis of a concerted dehydrohalogenation mechanism (eq. 2). The following assumptions were made in formulating the kinetic expression below: only the 2-hydrogen of 3-bromoanisole is involved in the amination, the reactions of benzyne are not rate-determining nor reversible, and the initial elimination reaction is first order with respect to 3-bromoanisole. The rate of disappearance of 3-bromoanisole-2,4,6-$^2H_3$(D) and 3-bromoanisole (H), respectively, are

$$-\,\mathrm{d}[\mathrm{D}]/\mathrm{d}t = k_{\mathrm{D}}[\mathrm{D}][\mathrm{NR_2}'\ominus]^n \qquad (5)$$

and

$$-\,\mathrm{d}[\mathrm{H}]/\mathrm{d}t = k_{\mathrm{H}}[\mathrm{H}][\mathrm{NR_2}'\ominus]^n \qquad (6)$$

Division of (6) by (5) and integration yields

$$\frac{k_{\mathrm{H}}}{k_{\mathrm{D}}} = \frac{\ln([\mathrm{D}_t]/[\mathrm{D}_0])}{\ln([\mathrm{H}_t]/[\mathrm{H}_0])} \qquad (7)$$

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[17] W. W. Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 190.

[18] J. J. Heigel, M. F. Bell and J. U. White, *Anal. Chem.*, **19**, 293 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Polyethers. IX. Poly-(2,6-dimethyl-1,4-phenylene Oxide)

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The reaction of 4-bromo-2,6-dimethylphenolate ion with a number of oxidizing agents, such as ferricyanide ion, lead dioxide, iodine and oxygen and light, leads to the ready conversion at room temperature to polymer. The soluble polymer had molecular weights in the range 2000–10,000. Analysis indicates one bromine atom and one phenol group per chain. Efforts to polymerize 4-bromo-2,6-di-*t*-butylphenol, bromodurenol and pentabromophenol under the same conditions failed. A mechanism involving propagation by displacement of bromide ion by phenoxy radical is proposed.

In a series of papers, Hunter[2] reported on the polymerization of trihalophenols under a variety of conditions. Solid polymers with molecular weights around 2000 were reported. Hunter established that iodine was displaced somewhat more readily than bromine, which in turn was more reactive than chlorine, and that *p*-halogen reacted more readily than *ortho*.[3] Furthermore, only halogen in a ring with a free ionizable phenol group could be displaced.

Efforts on our part to prepare poly-(1,4-phenylene oxide) by a variety of methods either gave low yields of intractable, high melting, insoluble material or very low molecular weight product. Because of the potential thermal stability of a polymer system built on this backbone, we have investigated the polymerization of 4-bromo-2,6-dimethylphenol by procedures analogous to those of Hunter.

Experimental

2,4,6-Tribromophenol, m.p. 93.5°, was converted to the red silver salt,[4] which was polymerized by treatment with iodine in refluxing chloroform suspension. Precipitation with methanol after 12 hours gave 60% yield of amorphous polymer, softening about 235° and having a molecular weight of 3700 (cryoscopically in ethylene dibromide).

Silver *p*-bromophenoxide under similar conditions gave an amorphous solid, softening at 140–145°, with a reduced viscosity of 0.048.

Efforts to prepare **silver 4-bromo-2,6-dimethylphenoxide** were unsuccessful, yielding only black precipitates (evidently silver).

4-Bromo-2,6-dimethylphenol (0.8 g., m.p. 78°[5]) was dissolved in 10 ml. of Claisen alkali and 50 ml. of benzene and stirred in the dark for 22 hours. No polymer was formed. A similar reaction mixture exposed to a Hanovia ultraviolet lamp turned yellow. The benzene layer was washed and then added to ten volumes of methanol. The precipitated polymer was freeze-dried from benzene to yield 0.135 g. (27.6% conversion), softening at 212–218°.

Treatment of a similar reaction mixture with iodine (1–2 %) with stirring for 24 hours gave 87.5% recovery of starting phenol and 12.5% of amorphous polymer, softening at 205–210°, $[\eta]$ 0.23 (benzene, 25°).

When one equivalent of the phenol in Claisen alkali was shaken with one equivalent of iodine, the purple color faded to yellow almost immediately. After 5 minutes, the benzene layer yielded 70%[6] of polymer, softening at 218–222°.

Anal. Found: C, 77.65; H, 6.92; Br, 5.30.

Poly-(2,6-dimethyl-1,4-phenylene oxide) was prepared for fractionation by stirring a solution of 94.6 g. of 2,6-dimethyl-4-bromophenol in 2.3 l. of benzene with 26.4 g. of potassium hydroxide in 2.3 l. of water and adding 1.13 g. (1 mole %) of lead dioxide. After stirring for 45 hours at room temperature an aliquot from the aqueous layer was titrated for bromide ion, indicating 77% reaction. The benzene layer was separated, washed, concentrated to 500 ml.

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[1] Supported in part by Contract No. DA-19-129-QM-1265, U. S. Army Quartermaster Corps.

[2] See W. H. Hunter and M. A. Dahlen, *J. Am. Chem. Soc.*, **84**, 2459 (1932).

[3] W. H. Hunter and F. E. Joyce, *ibid.*, **39**, 2640 (1917).

[4] (a) A. Hantzsch, *Ber.*, **40**, 4875 (1907). (b) H. A. Torrey and W. H. Hunter, THIS JOURNAL, **33**, 194 (1911).

[5] T. C. Bruice, N. Kharasch and R. J. Wizzler, *J. Org. Chem.*, **18**, 83 (1953).

[6] W. H. Hunter and L. M. Seyfried, THIS JOURNAL, **43**, 151 (1921), reported yields of poly-(dichlorophenylene oxide) increasing sharply with the amount of iodine used.