909. *Aromatic Aminophenylation: a New Substitution Process.*

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On treatment with a solution of tetrafluoroboric acid in tetrahydrothiophen 1,1-dioxide (sulpholane), phenylhydroxylamine condenses with aromatic compounds of moderate reactivity to give substituted 2- and 4-aminobiphenyls and diphenylamines. Yields of the various isomers have been estimated and are discussed in the light of the probable reaction mechanism.

Solutions obtained by dissolving equimolar quantities of boron trifluoride and anhydrous hydrogen fluoride in tetrahydrothiophen 1,1-dioxide (henceforth called "sulpholane") have been described [1] as being of tetrafluoroboric acid in sulpholane. They have obvious vapour pressures of hydrogen fluoride and boron trifluoride and the extent of their dissociation into these compounds is not yet known. Nevertheless, such solutions are strongly acidic and are free from electrophiles capable of forming bonds dissociable with difficulty. These solutions allow the formation of good electrophiles under conditions such that an unsaturated compound, for example, benzene, is the most reactive nucleophile present. It was therefore predicted that treatment of phenylhydroxylamine with tetrafluoroboric acid in a mixture of sulpholane and an aromatic compound would result in the formation, first of the cation $PhNH^+$ (I),[2] and then of the 2- and 4-aminophenyl derivatives, and possibly of the phenylamino-derivative, of the aromatic compound present.[3] This prediction has been realised. In practice it proved necessary to use high concentrations of the aromatic compound to minimise the formation of deeply-coloured polymeric products, which were also formed when no aromatic substrate was added. We worked with a large excess of the substrate and have not investigated techniques for the aminophenylation of scarce aromatic compounds. We have determined isomer distribution patterns (Table 1).

Table 1.

Isomer distribution in aminophenylation products.

Reactant	Method *	*R*	Relative (%)	Isomer distribution (%) ArNHR	4-$H_2N{\cdot}C_6H_4{\cdot}R$	2-$H_2N{\cdot}C_6H_4{\cdot}R$	Total yield (%)	*o*/*p* Ratio
Benzene ...	A	Ph	—	10	67	23	22	0·33
	B	Ph	—	4	77	19	36	0·25
Toluene ...	A	C_6H_4Me †	—	30	60	10	21	0·17
	B	*o*-C_6H_4Me	39	17	51	32	25	0·63
		p-C_6H_4Me	60	32	40	28		0·70
m-Xylene...	A	2,4-$C_6H_3Me_2$	100	11	63	26	33	0·41
Anisole ...	B	*o*-C_6H_4OMe	8	12	4·5	62	52	
		p-C_6H_4OMe	92	10	74	16		0·22
Chloro-	B	*o*-C_6H_4Cl	29	3	84	13	29	0·17
benzene		*p*-C_6H_4Cl	71	3	56	40		0·71
Phenol.....	A	*p*-C_6H_4OH	100	15	85	—	4	

* See Experimental section. † Mixture of isomers.

Total yields were in the range 20—55%, except for phenol (4%), and as the most abundantly-produced isomer, typically the 4′-substituted 4-aminobiphenyl, was often the most readily isolated, we believe that this reaction may be useful preparatively despite the multitude of isomers formed.

Diphenylamine was proved (as expected) to be stable under the conditions of the reaction, being recovered in good yield.

Mixtures were separated chromatographically on alumina, with or without previous

[1] Powell and Whiting, *Proc. Chem. Soc.*, 1960, 412.
[2] Heller, Hughes, and Ingold, *Nature*, 1951, **168**, 909.
[3] Cf. Bamberger, *Annalen*, 1921, **424**, 233, 297; 1925, **441**, 207; Titov and Baryshinkova, *Zhur. obschei. Khim.*, 1953, **23**, 346.

ether–acid partition to segregate the diphenylamine fraction; yields are based on the weights of chromatographic fractions, from which crystalline products were usually obtainable with little loss of material, although occasionally it was necessary to apportion an inseparable mixture on spectrographic evidence. Of the compounds prepared, only 4-amino-2′,4′-dimethylbiphenyl and 2-amino-2′,4′-dimethylbiphenyl were new, and these were readily identified because the acetyl derivative of the former showed the usual strong biphenyl band at *ca.* 2600 Å, whereas in the 2,2′,4′-isomer, as in most 2,2′-disubstituted biphenyls, this was absent through steric hindrance. All structures were checked by the determination of infrared spectra (Table 2).

TABLE 2.

Infrared absorption bands (in CS_2).

Compound	No. of adjacent ring-hydrogens	C–H deformations (no. of adjacent ring-hydrogens) 1	2	4	5	Other bands
Diphenylamine	5				749s, 689m	
2-Aminobiphenyl	4,5			765s	741s, 700s	726m
4-Aminobiphenyl	2,5		821s		755s, 692s	900w, 710m
2-Methyldiphenylamine	4,5			744s	(744s), 690m	713m
3-Methyldiphenylamine *	1,3,5	860m			749s, 687s	850m
4-Methyldiphenylamine	2,5		830s		741s, 690s	819w, 784w, 728m, 706w
2-Amino-2′-methylbiphenyl	4,4′			761m, 746s		
2-Amino-4′-methylbiphenyl	2,4		811m	742s		778w, 702w
4-Amino-2′-methylbiphenyl	2,4		829s	762s, 732s		
4-Amino-4′-methylbiphenyl	2,2′		828m, 812s			784m, 761m, 731w, 700w
N-*m*-Xylyldiphenylamine	1,2,5	874m	817s		725m, 690s	
2-*m*-Xylylacetanilide	1,2,4′	877w	821s	758s		871m, 710m
4-*m*-Xylylacetanilide	1,2,2′	?	837s, 812s			768m, 662m
2-Methoxydiphenylamine	4,5			767s	744m, 686s	779m
4-Methoxydiphenylamine	2,5		835s, 815m, 800w		750s, 692m	883w, 800w, 775w
2-Amino-2′-methoxybiphenyl	4,4′			744m, 752s		848w, 830w, 707w
2-Acetamido-4′-methoxybiphenyl	2,4		831s, 811m, 800m	755s		800w
4-Acetamido-2′-methoxybiphenyl	2,4		826m, 800m	755s, 739m		800w
4-Amino-4′-methoxybiphenyl	2,2′		837w, 828s, 806m			806w
2-Chlorodiphenylamine	4,5			771s, 742m	762s, 685s	802w
4-Chlorodiphenylamine	2,5		823m, 819m		750s, 694s	702w
2-Amino-2′-chlorobiphenyl	4,4′			749s		827s, 790m, 690s
2-Amino-4′-chlorobiphenyl	2,4		830m	761s, 750vs		680m
4-Amino-2′-chlorobiphenyl	2,4		826s	759s, 750s, 738m		785m, 692m
4-Amino-4′-chlorobiphenyl	2,2′		817s			784w, 758m, 749m, 691w
4-Amino-4′-hydroxybiphenyl †	2,2′		818			

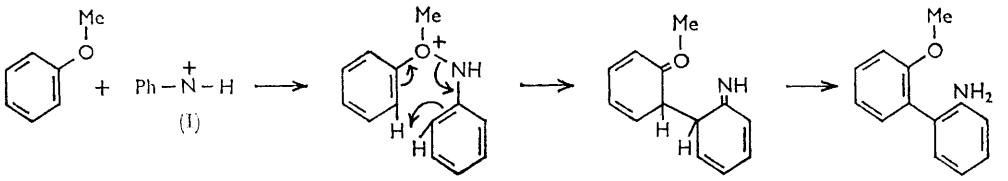
* Bands at 768s and 751s assigned to the 3 adjacent ring-hydrogen atoms. † Nujol mull.

Isomer distribution. As the systems used were often heterogeneous, and as even careful chromatographic separation may lead to incomplete or, occasionally, excessive recovery, we comment on only the most striking features of the Table 1. We know of no precedent for the double orientation phenomena of the present reaction.

Nucleophilic attack on the cation (I) in general followed the order $p > o > N$; conversely, the cation (I), using each of its electrophilic centres, behaved as a typical substituting agent of moderate activity, giving low o/p ratios. There are precedents [3] for a high ratio of *para* to *ortho* attack on the cation (I) in the reactions of the latter with inorganic nucleophiles.

The ratio of products, $RNHC_6H_5/RC_6H_4NH_2$, appears to be higher for more reactive than for less reactive species, RH; and when a weak solution of tetrafluoroboric acid rather than a strong solution is employed. This could be explained by the postulation of two reagents capable of attacking an aromatic nucleus, $Ph{\cdot}NH{\cdot}OH_2^+$ and the ion (I); the former would naturally be the less reactive and would presumably give more diphenylamine. Alternatively a considerable change in the reactivity of cation (I) with solvation could be assumed.

In two of the three cases investigated an *ortho*-substituent in the nucleophile tends to favour attack *para*, rather than *ortho*, to the NH^+ group. In the third, however, that of anisole, a strong preference is observed in the opposite direction; very little attack *ortho* to methoxyl takes place, but most of what does occur gives 2-amino-2′-methoxybiphenyl rather than 4-amino-2′-methoxybiphenyl. This is certainly not due to any thermodynamic advantage, as the former isomer, sterically hindered from a coplanar conformation, is surely the least stable of all the aminomethoxybiphenyls. A special mechanism leading to its formation seems probable, and Norman and Radda's explanation [4] for the high *o*/*p* ratio in the nitration of anisole can very readily be modified to rationalise this, as shown.



In the aminophenylation of toluene an attempt was made to detect the three products expected from attack *meta* to the methyl group, 2- and 3-methyldiphenylamine being prepared by the method of Ullman [5] from the arylanthranilic acids for comparison. Spectrographic examination definitely indicated the presence of the 3-isomer, formed in a yield of about 0·5%, or about 9% of the secondary amine fraction (*m*/*p* ratio about 1 : 8). On the other hand no evidence was obtained, either from infrared spectra or from gas-chromatographic analysis, of 2- or 4-amino-3′-methylbiphenyl; had either compound been present to the extent of 1%, it could hardly have been missed.

Finally, we may note the formal relationship of this reaction to the benzidine rearrangement. This may be considered as an attack of the cation (I) or its analogues either on an aromatic amine (when the reaction is first-order in acid) or on an anilinium cation (when the reaction is second-order in acid). An attempt to induce a reaction between aniline, aniline tetrafluoroborate, and phenylhydroxylamine was unsuccessful, and we are of course aware that much evidence supports the intramolecular character of the benzidine rearrangement. It is nevertheless possible that the transition states in the benzidine rearrangement (at least when first-order in acid) and in the necessarily intermolecular reaction now described are similar or even exactly analogous.

Infrared Spectra. Since the infrared spectra of many compounds of assured structure were obtained under comparable conditions (carbon disulphide solutions) we have tabulated (Table 2) their most useful bands diagnostically, *i.e.*, those C–H out-of-plane modes which reveal the substitution pattern. The correlation is that of Randle and Whiffen; [6] in the substances we examined, the band at *ca.* 690 cm.$^{-1}$ for phenyl groups provides perhaps the most consistent correlation of all (eleven cases had medium or strong bands within the range 685—700 cm.$^{-1}$). Only once could no band be found in the expected region, and that was the relatively weak band at 860—900 cm.$^{-1}$ associated with a single hydrogen atom. In several cases 2—4 bands at 730—770 cm.$^{-1}$ had to be jointly attributed to the

[4] Norman and Radda, *J.*, 1961, 3030.
[5] Ullmann, *Annalen*, 1907, **355**, 324.
[6] Randle and Whiffen, "Molecular Spectroscopy," Inst. of Petroleum, 1955, p. 111.

deformation of four or five adjacent atoms. Most of the bands in the last column, which cannot be assigned to out-of-plane deformations, are weak. The only one described as " strong," and many of those considered " medium," are in chlorine-containing compounds and are probably C–Cl stretching bands.

Experimental

The purification of sulpholane and the preparation of solutions of tetrafluoroboric acid in solution were as described in the preceding Paper. " Light petroleum " is the fraction, b. p. 40—60°.

Aminophenylation with Dilute (1 : 3·5) *Tetrafluoroboric Acid* (*Method A*).—A mixture of the aromatic compound (benzene, toluene, or *m*-xylene) (50 g.) and sulpholane–tetrafluoroboric acid (41·7 g.) was cooled to −15°, when solid separated (benzene), or a mixture of two liquid phases (toluene and *m*-xylene) was obtained. Phenylhydroxylamine (5·45 g.) in sulpholane (10 g.) was added during 5 min., and the mixture was allowed to warm during 30 min., the highest temperature reached being 40° (benzene); in the other two cases the mixture was stirred at −15° for 30 min., then at 20° for 3 hr. Water was added, the aromatic layer was separated, and washed with water, then basic and neutral fractions were separated using hydrochloric acid. Isolation methods were as follows.

Benzene. Chromatography of the neutral fraction on alumina (350 g.) gave, successively, diphenylamine (177 mg.), m. p. 54°, 2-aminobiphenyl (63 mg.), m. p. 49°, and sulpholane (2 g.) (this compound is surprisingly hard to elute). Similar chromatography of the basic fraction on alumina (450 g.) separated the aminobiphenyls (eluted with ether) from sulpholane (1·1 g.; eluted with methanol); the former were rechromatographed in benzene giving the *ortho*- (433 mg.), m. p. 49°, and the *para*-isomer (1230 mg.), m. p. 51—52·5°, undepressed on admixture with authentic specimens prepared from *o*- and *p*-nitrobiphenyl, respectively.

m-*Xylene.* The non-basic fraction (40 g.) was evaporated at 20 mm. to 7·6 g. to remove the excess of xylene and chromatographed on alumina (200 g.); the ether eluate was evaporated and the residue (466 mg.) was rechromatographed on alumina (50 g.) giving a fraction (358 mg.) believed (infrared spectroscopy) to be essentially *N*-(2,4-dimethylphenyl)aniline. Acetylation in pyridine, chromatography, and trituration with light petroleum gave *N*-(2,4-dimethylphenyl)acetanilide (121 mg.), m. p. 113—114° (lit.,[7] 114—115°).

The basic fraction (7·87 g.) was chromatographed on alumina (300 g.), giving amines (3·07 g.) eluted with ether and sulpholane (3·32 g.). Rechromatography on alumina (300 g.) gave a fraction (868 mg.), eluted with ether–light petroleum (1 : 1; 700 c.c.), which was converted into 2-*acetamido*-2′,4′-*dimethylbiphenyl* (856 mg.), m. p. 93—94° (Found: C, 79·7; H, 7·0; N, 6·1. $C_{16}H_{17}NO$ requires C, 80·3; H, 7·15; N, 5·85%). Elution with ether (800 c.c.) gave a fraction (2062 mg.) converted into 4-*acetamido*-2′,4′-*dimethylbiphenyl* (1925 mg.), m. p. 164—165° (Found: C, 79·6; H, 7·1; N, 6·2%).

Toluene. In this case the separation of isomers was complicated and incomplete. The neutral fraction was chromatographed on alumina (260 g., then 100 g.), giving crude secondary amine (870 mg.), which yielded 4-methyldiphenylamine (610 mg.), m. p. 89° (lit.,[5] 89°).

The basic fraction gave secondary amine (7 mg.), a series of fractions eluted with ether–light petroleum (1 : 1) (402 mg.) containing 2-aminobiphenyl derivatives, a more polar fraction (659 mg.) containing 4-aminobiphenyl derivatives, and sulpholane. The second fraction was rechromatographed and, on the basis of spectra, one group of fractions (70 mg.) was converted into 2-amino-2′-methylbiphenyl hydrochloride (35 mg.), m. p. 127° (from water) (lit.,[8] 128°) and another (23 mg.) was benzoylated, giving 2-benzamido-4′-methylbiphenyl (11 mg.), m. p. 119—120° (lit.,[9] 121°), depressed by benzoic acid. The total weight of these incompletely resolved fractions was 235 mg. The more polar 4-aminobiphenyl fractions gave 4-amino-4′-methylbiphenyl (669 mg.), m. p. 98—99° (lit.,[10] 99°), whilst a set of non-crystalline subfractions (502 mg.) gave, on acetylation, a low yield of 4-acetamido-2′-methylbiphenyl, m. p. 146—147·5° (lit.,[11] 147°; cf. also ref. 10).

[7] Borsche and Hahn, *Chem. Ber.*, 1949, **82**, 262.
[8] Mascarelli and Gatti, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1932, **15**, 89.
[9] von Braun and Wallach, *Chem. Zentr.*, 1909, **2**, 1993.
[10] Kliegel and Hüber, *Ber.*, 1920, **53**, 1646.
[11] Bamberger, *Ber.*, 1895, **28**, 405.

Aminophenylation with Concentrated (~1 : 1) *Tetrafluoroboric Acid* (Method B, normally preferable).—Phenylhydroxylamine (5·45 g.) was dissolved in benzene (50 g.) or toluene, anisole, or chlorobenzene (60 g.) and added, during 2 min., to a stirred, ice-cooled solution of tetrafluoroboric acid (41·6% w/w; 22·5 g.) in sulpholane. The mixture was stirred for 15 min. with cooling and 60 min. without; it consisted of a liquid and a solid phase (benzene), or of two liquid phases (toluene), or a single phase. After neutralisation with solid sodium carbonate it was made alkaline (pH > 12) with aqueous sodium hydroxide and extracted with ether, the products being isolated as follows.

Benzene. Separation into acidic and basic components was only partly successful, but systematic chromatography gave the following fractions, selected on spectroscopic grounds, (*a*) (159 mg.) gave diphenylamine (125 mg.), m. p. 51—52°; (*b*) (613 mg.) gave 2-aminobiphenyl (573 mg.), m. p. 49—49·5°; (*c*) (2457 mg.) gave 4-aminobiphenyl (2001 mg.), m. p. 53·5—54°.

Toluene. The total product was chromatographed giving, successively, toluene, azoxybenzene (76 mg.), a mixture of secondary amines (682 mg.) from which 4-methyldiphenylamine (358 mg.) was isolated by crystallisation, a mixture of primary amines, and finally a glass which was shown by infrared spectroscopy to contain primary amino-groups and probably consisted of bisaminophenylated products.

The secondary-amine fraction was examined in the infrared region (in CS_2) to measure approximately the ratio of 2′-, 3′-, and 4′-methyldiphenylamines present. The primary-amine fraction was first separated into the 2-aminobiphenyl fraction (685 mg.), eluted from deactivated alumina with light petroleum–ether (1 : 1), and the 4-aminobiphenyl fraction (706 mg.), eluted with ether. The latter partly crystallised, giving 4-amino-4′-methylbiphenyl (334 mg.), m. p. 98—99°.

Anisole. The total product was chromatographed, giving firstly (light petroleum–ether) an oil (248 mg.), b. p. 125—130°/0·06 mm. (Found: C, 74·25; H, 5·5; N, 12·6. Calc. for $C_{12}H_{10}N_2O$: C, 72·7; H, 5·05; N, 14·1. Calc. for $C_{13}H_{13}NO$: C, 78·4; H, 6·5; N, 7·0%), which for analytical and spectroscopic reasons is believed to have been a mixture of azoxybenzene and 2-methoxydiphenylamine (3 : 1). There followed four fractions (531 mg.) which were crystallised from light petroleum–ether giving 4-methoxydiphenylamine (491 mg.), m. p. 104·5—105° (lit.,[12] 105°); then a group (1157 mg.) which after rechromatography gave more pure 4-methoxydiphenylamine (251 mg.) and oils (903 mg.) which were acetylated in aqueous acetic acid to give 2-*acetamido*-4′-*methoxybiphenyl* (908 mg.), m. p. 130—130·5° (Found: C, 74·1; H, 6·3; N, 5·9. $C_{15}H_{15}NO_2$ requires C, 74·65; H, 6·25; N, 5·8%). The next group (749 mg.) gave 2-amino-2′-methoxybiphenyl (352 mg.), m. p. 77—78° (lit.,[13] 80—81°). A large group of fractions (3760 mg.) now crystallised readily, yielding 4-amino-4′-methoxybiphenyl (3502 mg.), m. p. 144—145·5° (lit.,[14] 146·5—147·5°).

Chlorobenzene. After removal of the excess of substrate at 20 mm. the total product was chromatographed on deactivated alumina (700 g.) and the fractions were grouped as follows. The first (light petroleum–ether; 3 : 1) was distilled at 0·5 mm. giving an oil (29 mg.), probably mainly 2-chlorodiphenylamine. The next group (74 mg.) was recrystallised from light petroleum giving 4-chlorodiphenylamine (69 mg.), m. p. 69—70° (lit.,[15] 74°). Fractions (131 mg.), distilled at 0·5 mm., gave 2-amino-2′-chlorobiphenyl (113 mg.), m. p. 50—51° (from light petroleum) (lit.,[16] 54°). Fractions (987 mg.) eluted with light petroleum–ether (1 : 1) were recrystallised fram light petroleum giving 2-amino-4′-chlorobiphenyl (858 mg.), m. p. 43—43·5° (lit.,[17] 42—44°). The next group (980 mg.) was acetylated in aqueous acetic acid; recrystallisation from light petroleum gave 4-acetamido-2′-chlorobiphenyl (873 mg.), m. p. 160—161·5° (lit.,[18] 162°). Finally, ether eluted fractions (1370 mg.) which gave 4-amino-4′-chlorobiphenyl (1210 mg.), m. p. 133° (from benzene) (lit.,[19] 134°).

Aminophenylation of Phenol.—Essentially method A was used, with phenol (60 g.) replacing benzene, but the reaction period was 30 min. at 20°, after warming to homogenise the mixture.

[12] Willstätter and Kubli, *Ber.*, 1909, **42**, 4138.
[13] Mascarelli and Gatti, *Atti Congr. Naz. Chim. Pura Appl.* 4° (1932), 1933, 503.
[14] Ivanov and Panaistov, *Doklady Akad. Nauk S.S.S.R.*, 1953, **93**, 1041.
[15] Ullmann, *Annalen*, 1907, **355**, 399.
[16] Sandin and Hay, *J. Amer. Chem. Soc.*, 1952, **74**, 275.
[17] Bradsher and Wissow, *J. Amer. Chem. Soc.*, 1946, **68**, 405.
[18] Harris, U.S.P. 2,126,009.
[19] Gelme, *Ber.*, 1906, **39**, 4181.

After the addition of sodium carbonate the mixture was steam-distilled to remove most of the phenol, then extracted with ether. When the extract was evaporated to 50 c.c. crystals separated, and recrystallisation gave 4-amino-4′-hydroxybiphenyl (173 mg.), m. p. 269—271° (lit.,[20] 273°). The mother-liquors were evaporated and treated with an excess of diazomethane; the excess was destroyed with acetic acid and the excess of the latter was washed out (Na_2CO_3). Chromatography of the resultant tar gave, as the only recognisable products, a suspected 4 : 1 mixture of azoxybenzene and 2-methoxydiphenylamine (87 mg.), and fractions (40 mg.) which gave 4-methoxydiphenylamine (30 mg.), m. p. 104° (from light petroleum).

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[20] Täuber, *Ber.*, 1894, **27**, 2629.