

Substituent Effects in the Biphenyl Series. Part IV.¹ The Kinetics of Piperidinobromination of 4'-Substituted 3-Bromo-4-nitrobiphenyls

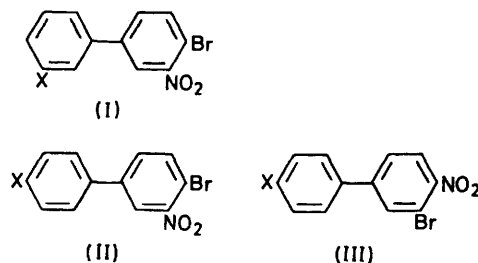
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A series of 4'-substituted 3-bromo-4-nitrobiphenyls have been prepared and the rates of piperidinobromination in methanol at three different temperatures have been measured. The kinetic data are satisfactorily correlated by a modified Hammett relationship ($\rho + 0.35$) using σ_p constants for 4'-halogen and $\sigma_p + 0.32(\sigma^- - \sigma_p)$ for strongly electron-withdrawing 4'-substituents (MeCO, MeSO₂, and NO₂). Comparison with results previously reported for the same reaction on the corresponding 3'- and 4'-substituted 3-nitro-4-bromobiphenyls has been made.

In previous papers on the transmission of substituent effects through biaryl systems (biphenyl^{1,2a} and bi-thienyls^{2b}) we reported the results obtained by a kinetic study of the piperidinobromination in methanol of 2'-,¹ 3'- [(I)],^{2a} and 4'-substituted [(II)]^{2a} 3-nitro-4-bromobiphenyls. In particular we have found that the polar effects of 3'-substituents and 4'-halogen are similar to those exerted by the same substituents in the 5- and 4-positions respectively in piperidinobromination of *o*-nitrobromobenzene. For strongly electron-withdrawing groups in the 4'-position (MeCO, MeSO₂, and NO₂), in contrast to the benzene series, intermediate values³ between σ_p and σ^- , *i.e.* $\sigma_p + 0.32(\sigma^- - \sigma_p)$, were found to be necessary. These results suggested that in nucleophilic substitution at C-4, as well as for electrophilic substitution at the same position,⁴ the biphenyl and benzene systems show more similarities in the transmission of substituent effects than those implied in the Dewar-Grisdale picture.⁵

To investigate whether such similarities could be

extended to nucleophilic reactions occurring at positions of the biphenyl system other than C-4,⁶ we have studied



- a; X = H
- b; X = Cl
- c; X = Br
- d; X = I
- e; X = MeCO
- f; X = MeSO₂
- g; X = NO₂

the kinetics of the reaction of some 4'-substituted 3-bromo-4-nitrobiphenyls (IIIa–g) with piperidine in methanol.

¹ M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

² D. J. Byron, G. W. Gray, and R. C. Wilson, *J. Chem. Soc. (C)*, 1966, 831, 837; V. P. Kreiter, W. A. Bonner, and R. H. Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 5770; E. Berliner and E. A. Blommers, *ibid.*, 1951, **73**, 2479; E. Berliner and L. H. Liu, *ibid.*, 1953, **75**, 2417.

¹ Part III, C. Dell'Erba, G. Guanti, G. Garbarino, and M. Novi, *Gazzetta*, 1972, **102**, 5.

² (a) C. Dell'Erba, G. Guanti, and G. Garbarino, *Tetrahedron*, 1971, **27**, 1807; (b) C. Dell'Erba, D. Spinelli, and G. Garbarino, *Gazzetta*, 1970, **100**, 777.

³ Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 965, 971; M. Yoshioka, H. Hamamoto, and T. Kubota, *ibid.*, 1962, **35**, 1723.

⁴ R. Baker, R. W. Bott, C. Eaborn, and P. M. Greasley, *J. Chem. Soc.*, 1964, 627.

RESULTS

Kinetic runs were followed up to 80–90% completion by a u.v. spectroscopic technique,^{2a} measuring the increase in absorbance at the wavelengths indicated in Table 1,

determining step is probably responsible for this slight difference (for the phenyl group $\sigma^- - \sigma_m$ is positive⁹). (b) The introduction of electron-withdrawing groups in 4'-position of the 3-bromo-4-nitrobiphenyl always pro-

TABLE 1

Physical, analytical, and spectroscopic data for the *N*-(4'-X-4-nitrobiphenyl-3-yl)piperidines

X	Crystallization solvent	M.p. (°C)	Found (%)		Formula	Required (%)		$\lambda_{\max.}^a / \text{nm}$	$\log \epsilon^a$
			N	Hal		N	Hal		
H	Light petroleum ^b	76	9.85		$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	9.95		404	3.22
Cl	Light petroleum ^c	112	8.85	11.3	$\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{O}_2$	8.85	11.2	404	3.22
Br	Methanol	136	7.8	22.2	$\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_2$	7.75	22.15	404	3.22
I	Ligroin	150	6.9		$\text{C}_{17}\text{H}_{17}\text{IN}_2\text{O}_2$	6.85		408	3.24
MeCO	Ligroin	113	8.6		$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$	8.65		412	3.21
MeSO ₂ ^d	Methanol	180	7.8		$\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$	7.8		416	3.17
NO ₂	Ethanol	162	12.85		$\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_4$	12.85		412	3.17

^a In methanol. ^b B.p. 30–60°. ^c B.p. 60–80°. ^d Found: S, 8.85. Required: S, 8.9%.

TABLE 2

Rate constants and activation parameters for the reactions between 4'-X-3-bromo-4-nitrobiphenyls (IIIa–g) and piperidine in methanol^a

Compound	$10^6 k / \text{mol}^{-1} \text{s}^{-1}^b$			$\Delta H^\ddagger / \text{kcal mol}^{-1}^c$	$-\Delta S^\ddagger / \text{cal mol}^{-1} \text{K}^{-1}^d$
	39.86°	49.92°	60.00°		
(IIIa)	1.54	3.77	8.71	17.3	30.0
(IIIb)	1.91	4.84	11.40	17.9	27.8
(IIIc)	1.89	4.69	11.38	17.9	27.6
(IIId)	1.95	4.96	11.50	17.7	28.1
(IIIe)	2.50	6.03	14.45	17.7	27.7
(IIIf)	3.02	7.03	15.64	16.4	31.6
(IIIg)	3.39	7.85	18.28	16.8	30.0

^a [Biphenyl substrate] = $2.5 \times 10^{-3} \text{M}$, [piperidine] = $9.2 \times 10^{-2} \text{M}$. ^b Mean values of three or more independent runs for each temperature. The probable error is ± 3 –4%. ^c At 40°, accurate to $\pm 0.3 \text{kcal mol}^{-1}$. ^d At 40°.

which also reports the absorptions of the substituted *N*-biphenyl-3-ylpiperidines at such wavelengths. All rate determinations were performed with piperidine in large excess over the biphenyl substrate. Quantitative yields for the expected product were indicated by the spectrophotometric data.

Pseudo-first-order rate constants were evaluated graphically,⁷ and divided by the initial piperidine concentration to convert them into second-order rate coefficients (Table 2). The rate constants were determined at different temperatures: they obeyed the Arrhenius equation and the activation parameters were evaluated by standard methods.⁸

DISCUSSION

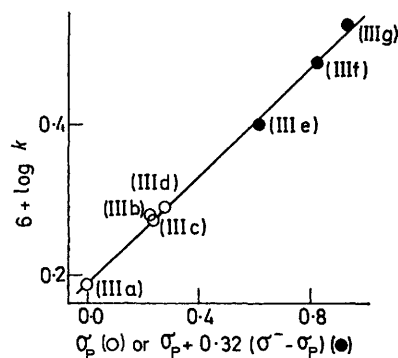
An addition–elimination mechanism, typical of nucleophilic aromatic substitution,^{1,2} with rapid decomposition of the intermediate complex is generally accepted for the reactions studied.

By comparison of the data obtained at 39.86° (Table 2; Figure) with those reported^{2a} for series (I) and (II), and for *o*-nitrobromobenzene the following points emerge. (a) The introduction of a phenyl group at the 4- or 5-position of 1-bromo-2-nitrobenzene increases the piperidinobromination rate by factors of *ca.* 2.3 and *ca.* 2.0 respectively. The greater ability of a *para*-compared with a *meta*-phenyl ring to delocalize the negative charge in the transition state of the rate-

⁷ A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1963, 2nd edn., p. 48.

⁸ A. Weissberger, 'Technique of Organic Chemistry,' vol. VIII, Part I, Interscience, New York, 1961, pp. 199–204.

duces an increase in the reaction rate with respect to the parent compound. The reactivity increases with the electron-withdrawing power of the substituent and the reactivity order observed agrees with that expected on



Modified Hammett correlation for the reaction of a series of 4'-substituted 3-bromo-4-nitrobiphenyls (IIIa–g) with piperidine in methanol at 39.86°

the basis of polar substituent effects ($\text{NO}_2 > \text{MeSO}_2 > \text{MeCO} > \text{I} > \text{Br} > \text{Cl} > \text{H}$). (c) The spread of the reaction rates is small ($k_{4'-\text{NO}_2}/k_{4'-\text{H}}$ *ca.* 2.2) and it reflects the small changes of both ΔH^\ddagger and ΔS^\ddagger .

In order to clarify the nature of the substituent effect in series (III), we have tentatively compared the

⁹ W. Greizerstein, R. A. Bonelli, and J. A. Brioux, *J. Amer. Chem. Soc.*, 1962, **84**, 1026; A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brioux, *J. Chem. Soc. (B)*, 1966, 963.

piperidinobromination rates with those of series (I) and (II). A plot of $\log k_{(III)}$ against $\log k_{(II)}$ gives a slope of +0.35 while a plot of $\log k_{(III)}$ against $\log k_{(I)}$ gives a slope of +0.52. Data are more satisfactorily correlated in the former case (r 0.9967; s 0.0122) than in the latter (r 0.9424; s 0.0499).¹⁰ Thus, although caution must be exercised on the validity of these correlations owing to the modest substituent effect in series (III), it seems that the effect of a substituent in series (III) is closer to that of the same substituent in series (II) than in (I). Using for series (III) the same substituent constants for series (II), *i.e.* σ_p for 4'-halogen and $\sigma_p + 0.32(\sigma^- - \sigma_p)$ for strongly electron-withdrawing 4'-substituents, a linear correlation with $\rho + 0.35$ (r 0.9978; s 0.0089) was obtained.

On the basis of these results it appears that an electron-withdrawing 4'-substituent is able to delocalize the negative charge developed on C-1 in the rate-determining transition state in both series (II) and (III). Moreover, owing to the peculiar position of the substituted phenyl ring with respect to the reaction centre, this charge is significantly lower in series (III) than in (II) and the effect of the 4'-substituent is thus lower in the former than in the latter.

We can therefore conclude that in nucleophilic substitution on 'ortho'-nitrobromobiphenyl derivatives [series (I)—(III)] the position of a 4'-substituted ring with respect to the reaction centre (C-4 or -3) confines the sensitivity of the reaction rate only to the substituent effect and the substituent effect is essentially dependent on the position of the substituent with respect to the 1,1'-bond.

EXPERIMENTAL

Methanol was dried and distilled as described.¹¹ Piperidine was purified by drying over potassium hydroxide and distillation.

3-Bromo-4-nitrobiphenyl (IIIa).—This compound was obtained by a Sandmeyer reaction from 3-amino-4-nitrobiphenyl,¹² according to the method of Hodgson and Walker,¹³ and had m.p. 48°, b.p. 176° at 5 mmHg (lit.,¹⁴ 252—254° at 7 mmHg) (Found: Br, 29.0; N, 5.0. Calc. for $C_{12}H_8BrNO_2$: Br, 28.8; N, 5.05%).

3-Bromo-4'-halogeno-4-nitrobiphenyls (IIIb—d).—These compounds were prepared by Sandmeyer reactions from the corresponding 3-amino-4'-halogeno-4-nitrobiphenyls following the method¹⁵ described for (IIIa). **3-Bromo-4'-chloro-4-nitrobiphenyl (IIIb)** had m.p. 108° [from ligroin (b.p. 80—100°)] (Found: C, 46.2; H, 2.25; N, 4.5. $C_{12}H_7BrClNO_2$ requires C, 46.1; H, 2.25; N, 4.5%), **3,4'-dibromo-4-nitrobiphenyl (IIIc)** had m.p. 114° (from methanol) (Found: C, 40.5; H, 2.0; N, 4.0. $C_{12}H_7Br_2NO_2$ requires C, 40.35; H, 1.95; N, 3.9%), **3-bromo-4'-iodo-4-nitrobiphenyl (IIIId)** had m.p. 117° (from methanol) (Found: C, 35.75; H, 1.8; N, 3.5. $C_{12}H_7BrINO_2$ requires C, 35.65; H, 1.75; N, 3.45%).

¹⁰ H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

¹¹ D. Spinelli, C. Dell'Erba, and G. Guanti, *Ann. Chim. (Italy)*, 1965, **55**, 1252.

¹² W. Blakey and H. A. Scarborough, *J. Chem. Soc.*, 1927, 3000.

¹³ H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1933, 1620.

3-Amino-4'-halogeno-4-nitrobiphenyls.—These compounds were obtained by alkaline hydrolysis¹⁶ of the corresponding 3-acetylamino-derivatives. The **4'-chloro-derivative** had m.p. 179° (from ethanol) (Found: Cl, 14.1; N, 11.35. $C_{12}H_9ClN_2O_2$ requires Cl, 14.3; N, 11.25%), the **4'-bromo-derivative** had m.p. 170° (from ethanol) (Found: Br, 27.45; N, 9.6. $C_{12}H_9BrN_2O_2$ requires Br, 27.3; N, 9.55%), the **4'-iodo-derivative** had m.p. 190° (from ethanol-dioxan) (Found: C, 42.5; H, 2.7; N, 8.35. $C_{12}H_9IN_2O_2$ requires C, 42.35; H, 2.65; N, 8.25%).

3-Acetylamino-4'-halogeno-4-nitrobiphenyls.—These compounds were prepared by nitration of the 3-acetylamino-4'-halogenobiphenyls according to the method reported¹² for the nitration of the 3-acetylamino-4-nitrobiphenyl. The **4'-chloro-compound** had m.p. 180° (from ethanol-dioxan) (Found: Cl, 12.3; N, 9.75. $C_{14}H_{11}ClN_2O_3$ requires Cl, 12.2; N, 9.65%), the **4'-bromo-compound** had m.p. 214° (from ethanol-dioxan) (Found: Br, 24.0; N, 8.45. $C_{14}H_{11}BrN_2O_3$ requires Br, 23.9; N, 8.35%), the **4'-iodo-compound** had m.p. 243° (from ethanol-dioxan) (Found: C, 44.1; H, 2.9; N, 7.4. $C_{14}H_{11}IN_2O_3$ requires C, 44.0; H, 2.9; N, 7.35%).

3-Acetylamino-4'-halogenobiphenyls.—**3-Acetylamino-4'-chloro-**, m.p. 184° (lit.,¹² 184°), and **3-acetylamino-4'-bromo-biphenyl**, m.p. 194° (lit.,¹² 193°) were prepared as reported. **3-Acetylamino-4'-iodobiphenyl**, m.p. 193° (from benzene) (Found: C, 49.75; H, 3.6; N, 4.2. $C_{14}H_{12}INO$ requires C, 49.85; H, 3.55; N, 4.15%), was obtained by acetylation with acetic anhydride in benzene of the 3-amino-derivative. **3-Amino-4'-iodobiphenyl**, m.p. 130° (from methanol) (Found: C, 48.9; H, 3.35; N, 4.8. $C_{12}H_{10}IN$ requires C, 48.8; H, 3.4; N, 4.15%), was prepared by reduction of 4'-iodo-3-nitrobiphenyl¹⁶ with tin and ethanolic hydrochloric acid.

4'-Acetyl-3-bromo-4-nitrobiphenyl (IIIe).—Anhydrous aluminium chloride (0.1 mol) and (IIIa) (0.08 mol) were dissolved in dry nitrobenzene (85 ml). Acetyl chloride (0.1 mol) was added and the solution was stirred at room temperature for 12 h and for a further 6 h at 50°. The solution was poured into a mixture of ice, water, and hydrochloric acid. The organic layer was separated and the nitrobenzene removed by steam distillation. The residue was cooled and the precipitate was filtered and purified by column chromatography (silica gel-benzene). After the initial fractions [containing unchanged (IIIa)] the **ketone (IIIe)** was obtained, m.p. 154—155° (from ethanol) (Found: Br, 25.15; N, 4.45. $C_{14}H_{10}BrNO_3$ requires Br, 25.0; N, 4.35%).

3'-Bromo-4'-nitrobiphenyl-4-yl Methyl Sulphone (IIIIf).—**3'-Bromo-4'-aminobiphenyl-4-yl methyl sulphone** (0.053 mol) was dissolved in concentrated sulphuric acid (50 ml) and added to a solution of sodium nitrite (0.14 mol) in the same acid (50 ml). The mixture obtained was dropped with stirring onto acetic acid (200 ml), the temperature being maintained below 20 °C. Ether (700 ml) was added and the mixture stirred at 0° for 1 h. The diazonium salt was separated by filtration, washed with ether and ethanol, dissolved in cold water (100 ml), and the aqueous solution was dropped with stirring onto a mixture of sodium nitrite

¹⁴ F. H. Case and H. A. Sloviter, *J. Amer. Chem. Soc.*, 1937, **59**, 2381.

¹⁵ C. Dell'Erba, G. Garbarino, and G. Guanti, *Tetrahedron*, 1971, **27**, 113.

¹⁶ H. O. Wirth, R. Mueller, and W. Kern, *Makromol. Chem.*, 1964, **77**, 90.

(1.45 mol), Cu_2SO_4 [prepared from CuSO_4 (50 g) and sodium sulphite (50 g) in water], and water (400 ml). The stirring was continued overnight and the precipitate filtered, washed with water, and extracted with chloroform. The solvent was evaporated *in vacuo* and the residue chromatographed on a silica gel column using chloroform as eluant. After the initial fractions [containing 3'-bromobiphenyl-4-yl methyl sulphone (4.5 g), m.p. 130° (from methanol) (Found: Br, 25.8; S, 10.3. $\text{C}_{13}\text{H}_{11}\text{BrO}_2\text{S}$ requires Br, 25.7; S, 10.3%)], the sulphone (III_f) was obtained, m.p. 177° (from ethanol) (Found: Br, 22.4; N, 3.9; S, 8.95. $\text{C}_{13}\text{H}_{10}\text{BrNO}_4\text{S}$ requires Br, 22.45; N, 3.95; S, 9.0%).

3'-Bromo-4'-aminobiphenyl-4-yl Methyl Sulphone.—This compound was obtained by alkaline hydrolysis¹⁵ of the corresponding acetylamino-derivative and had m.p. 187° (from ethanol) (Found: Br, 24.6; N, 4.3; S, 9.85. $\text{C}_{13}\text{H}_{12}\text{BrNO}_2\text{S}$ requires Br, 24.55; N, 4.3; S, 9.8%).

3'-Bromo-4'-acetylamino-biphenyl-4-yl Methyl Sulphone.—This was prepared by bromination of 4'-acetylamino-biphenyl-4-yl methyl sulphone. A solution of bromine (5 ml) in acetic acid (20 ml) was added at 40° to the sulphone (3 g) dissolved in acetic acid (20 ml). The solution was slowly warmed at 70°, cooled, and poured into water. The precipitate product was filtered and crystallized from ethanol, m.p. 206° (Found: Br, 21.85; N, 3.85; S, 8.7. $\text{C}_{15}\text{H}_{14}\text{BrNO}_3\text{S}$ requires Br, 21.75; N, 3.8; S, 8.7%).

¹⁷ D. J. Byron, G. W. Gray, and R. C. Wilson, *J. Chem. Soc. (C)*, 1966, 840.

4'-Acetylamino-biphenyl-4-yl Methyl Sulphone.—This was synthesized by acetylation with acetic anhydride in benzene of 4'-aminobiphenyl-4-yl methyl sulphone and had m.p. 268° (from ethanol-dioxan) (Found: N, 4.8; S, 11.2. $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{S}$ requires N, 4.8; S, 11.05%).

4'-Aminobiphenyl-4-yl Methyl Sulphone.—This amine was prepared by Beckmann rearrangement¹⁷ from the oxime of the 4'-acetylbiphenyl-4-yl methyl sulphone and had m.p. 212° (from ethanol-dioxan) (Found: N, 5.7; S, 12.9. $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{S}$ requires N, 5.65; S, 12.95%).

4'-Acetylbiphenyl-4-yl Methyl Sulphone.—This derivative was obtained by acetylation of biphenyl-4-yl methyl sulphone¹⁸ according to the method reported for (III_e), using 0.2 mol of aluminium chloride for 0.08 mol of sulphone. The ketone had m.p. 197° after crystallization from ethanol-dioxan (Found: S, 11.7. $\text{C}_{15}\text{H}_{14}\text{O}_3\text{S}$ requires S, 11.7%). The oxime had m.p. 243° (from ethanol-dioxan) (Found: N, 4.85; S, 11.1. $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{S}$ requires N, 4.85; S, 11.05%).

3-Bromo-4,4'-dinitrobiphenyl (III_g).—This was prepared according to the literature, m.p. 206° (lit.,¹⁹ 205–206°).

Substituted N-Biphenyl-3-ylpiperidines.—These were prepared according to the method previously reported¹ for the substituted N-biphenyl-4-ylpiperidines. Further data are given in Table I.

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¹⁸ E. E. Gilbert, *J. Org. Chem.*, 1963, 28, 1945.

¹⁹ F. H. Case, *J. Amer. Chem. Soc.*, 1945, 67, 116.