358. *The Cumulative Effect of Substituents on the Reaction of NN-Dimethylanilines with Allyl Bromide.*

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The formation of quaternary salts from allyl bromide and substituted dimethylanilines in aqueous acetone has been studied. With monosubstituted amines, *meta-* and *para-*substituents alter the reaction velocity solely by their effects on the activation energy. For all the 3 : 5-disubstituted amines examined, the rates are in close agreement with those calculated, the effects of the two groups being assumed to be additive. In other cases, a strict additivity of group effects is not observed, and with certain *NN*-dimethyl-*o*- and -*p*-anisidine derivatives the observed rate is almost double that calculated, with the activation energy and frequency factor both lower than would be expected.

FOR some reactions of benzene derivatives for which the frequency factor is essentially constant it has been shown that the cumulative effect on the reaction velocity of two nuclear substituents is often additive.[1] In an effort to assess the generality of this principle, the formation of quaternary ammonium salts from disubstituted *NN*-dimethylanilines and allyl bromide has been studied kinetically.

In two previous investigations it was shown that *meta-* and *para-*substituents affect the rate of reaction of *NN*-dimethylaniline with methyl iodide by contributions to the activation energy only. In the first of these, Laidler [2] used nitrobenzene as solvent, but this suffered from the drawback that equilibration occurred. In the second, Evans, Watson, and Williams [3] used methanol (a solvent used in other investigations by later workers [4]) but close examination showed that at 45°, in 0·1M-solution, a slow reaction leading to the formation of iodide ions occurred between methyl iodide and the solvent. This methanolysis, which tended to equilibrium, was sufficient to lead to inaccuracies in rate measurements, particularly with the less reactive bases. Fortunately, Davies and Cox [5] had shown that the reaction between certain *NN*-dimethylanilines and allyl bromide could be followed kinetically in 10% aqueous acetone without complications from the concurrent hydrolysis of the halide, and their results indicated that the tendency towards equilibrium could be avoided by increasing the proportion of water in the solvent. Accordingly, allyl bromide was adopted as halide in preference to methyl iodide, and with 25% aqueous acetone as solvent, rates of the reaction with a wide range of bases could be followed conveniently and be reproduced accurately over the temperature range 0—35°. With an initial concentration of amine twice that of the halide, no tendency towards equilibrium was noted over the range (15—65% completion) of the reaction normally followed, and, in general, the hydrolysis of the halide (k_{20} 1·71 × 10^{-7}; k_{35} 8·52 × 10^{-7} sec.$^{-1}$) could be ignored. However, because of this complication the extremely slow reaction with *NN*-dimethyl-1-naphthylamine could not be determined, and the rates recorded for the very unreactive *m*-nitro- and 3-chloro-2-methoxy-*NN*-dimethylaniline are slightly in error. In view of the operation of several possible factors, no corrections were attempted. As could be expected from the work of Holtzschmidt and Potapoff,[6] a distinct autocatalysis was noted: velocity coefficients calculated in the usual way increased by about 5% during

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[1] (*a*) Bradfield and Brynmor Jones, *J.*, 1928, 1006; Brynmor Jones, *J.*, 1935, 1831; 1942, 418, 676; Sleight and Brynmor Jones, *J.*, 1954, 1775; (*b*) Stubbs and Hinshelwood, *J.*, 1949, S71; (*c*) Branch and Brynmor Jones, *J.*, 1954, 2317; 1955, 2921; (*d*) Brynmor Jones and Robinson, *J.*, 1955, 3845; (*e*) Brynmor Jones and Watkinson, *J.*, 1958, 4064.

[2] Laidler, *J.*, 1938, 1786.

[3] Evans, Watson, and Williams, *J.*, 1939, 1345.

[4] (*a*) Brown and Fried, *J. Amer. Chem. Soc.*, 1943, **65**, 1841; (*b*) Evans, *J.*, 1944, 422; (*c*) Weale, *J.*, 1954, 2959.

[5] Davies and Cox, *J.*, 1937, 614.

[6] Holtzschmidt and Potapoff, *Acta Physicochim. U.R.S.S.*, 1937, **7**, 778; Potapoff and Holtzschmidt, *J. Phys. Chem., U.S.S.R.*, 1941, **15**, 1094.

the reaction, and velocity coefficients were therefore obtained by extrapolation to zero time, the plot being linear within the error of experiment.

The kinetic data obtained are shown in Table 1. The solvent throughout was 25% v/v aqueous acetone, and the initial concentrations at 20° of the allyl bromide and dimethylaniline were 0·1M and 0·2M, respectively. The velocity coefficients recorded are believed be accurate to within 1·5%, and could be duplicated within these limits.

TABLE 1. *Reaction of allyl bromide and substituted* NN-*dimethylanilines: velocity coefficients and activation energies.*

Substituent	10^4k (l. mole^{-1} sec.$^{-1}$)				E (cal.)	$\log_{10} PZ$
	0·0°	19·75°	24·9°	35·0°		
p-OEt	7·00	28·3	—	—	11,230	5·85
p-OMe	6·92	28·0	—	—	11,260	5·85
p-Me	3·06	13·2	18·4	35·4	11,710	5·86
m-Me	1·52	6·68	9·60	18·9	12,060	5·83
H	1·18	5·34	7·80	15·0	12,130	5·78
p-F	—	5·24	—	—	—	—
(*NN*-Dimethyl-2-naphthylamine)	0·770	3·63	—	10·4	12,410	5·82
m-OMe	0·845	3·90	5·53	11·1	12,350	5·80
p-Cl	0·315	1·56	2·29	4·66	12,880	5·81
p-Br	0·260	1·29	1·87	3·89	12,980	5·79
p-I	—	1·25	—	—	—	—
m-F	—	0·726	—	2·28	13,470	5·91
m-Cl	—	0·604	—	1·86	13,310	5·73
m-Br	—	0·580	—	1·84	13,540	5·85
m-NO_2	—	0·134	—	—	—	—
(*NN*-Dimethyl-1-naphthylamine)	—	*ca.* 0·02	—	—	—	—
o-OMe	1·96	9·26	13·6	27·0	12,540	6·33
3-Br, 5-Me	—	0·744	—	—	—	—
3-Br, 4-Me	—	1·65	—	—	—	—
4-Br, 3-Me	—	1·82	—	5·40	12,800	5·83
3-Br, 5-OMe	—	0·418	—	—	—	—
3-Cl, 5-Me	—	0·776	—	—	—	—
3-Cl, 4-Me	0·368	1·79	—	5·20	12,650	5·69
4-Cl, 3-Me	—	2·23	—	—	—	—
3-Cl, 5-OMe	—	0·438	—	1·385	13,550	5·74
4-Cl, 3-OMe	—	1·48	—	—	—	—
3-Me, 5-Me	1·92	8·30	—	23·45	11,960	5·85
3-Me, 4-Me	—	16·4	—	—	—	—
3-OMe, 4-OMe	5·94	—	—	—	—	—
3-Me, 5-OMe	—	4·92	—	—	—	—
4-Me, 3-NO_2	—	0·360	—	—	—	—
3-Br, 4-OMe	—	5·90	—	16·05	11,770	5·55
3-Cl, 4-OMe	1·40	5·95	—	16·0	11,650	5·47
3-F, 4-OMe	1·44	5·99	—	—	11,500	5·35
3-I, 4-OMe	—	7·04	—	18·8	11,560	5·48
4-OMe, 3-NO_2	—	1·53	—	4·41	12,460	5·48
4-Cl, 2-OMe	0·706	3·55	—	10·65	12,970	6·23
5-Cl, 2-OMe	—	1·99	—	6·02	13,060	6·04
2-OMe, 5-OMe	1·43	7·00	—	—	12,790	6·39
5-F, 2-OMe	0·510	2·47	—	7·32	12,740	5·90
5-I, 2-OMe	—	2·01	—	6·20	13,260	6·19
5-Me, 2-OMe	2·22	10·9	—	—	12,810	6·59
2-OMe, 5-NO_2	—	0·536	—	1·76	13,990	6·17
3-Cl, 2-OMe	—	0·101	—	—	—	—

Monosubstituted Bases.—Although the non-exponential factor was sensibly constant for the reaction of wide range of *meta*- and *para*-substituted bases with methyl iodide,[2,3] Evans [4b] considered that significant variations in P occurred with alkyl substituted *NN*-dimethylanilines of similar reactivity. Furthermore, for the reaction of allyl bromide with *p*-chloro- and *p*-bromo-*NN*-dimethylaniline in 10% aqueous acetone, remarkably concordant results showing a wide divergence in the non-exponential term had been obtained by two independent groups of workers (see Table 2).

At the outset, therefore, it was thought necessary to check the variation of E and P with 25% aqueous acetone as solvent. For six *meta*- and *para*-substituted bases (including the *p*-chloro- and *p*-bromo-derivatives) rate measurements were carried out at four temperatures. No significant variations in P were observed.

The general order of reactivities for the series of amines is in harmony with previous work and the Hammett equation is obeyed.

NN-Dimethyl-2-naphthylamine gave a slightly lower rate than *NN*-dimethylaniline, the ratio of rates, 0·68, being similar to the ratio of reactivites of 2-naphthylamine and aniline towards benzoyl chloride.[1b] Whereas in the benzoylation 1-naphthylamine was one-fifth as reactive as the 2-isomer, *NN*-dimethyl-1-naphthylamine proved to be so unreactive that the rate could not be determined, probably owing to steric retardation of the reaction by the adjacent *peri*-hydrogen atom.[8]

TABLE 2.

Amine	Davies and Cox [5] E (cal.)	Davies and Cox [5] $\log_{10} PZ$	Vorob'ev [7] E (cal.)	Vorob'ev [7] $\log_{10} PZ$
p-Chloro-*NN*-dimethylaniline	12,250	5·41	12,250	5·40
p-Bromo-*NN*-dimethylaniline	13,250	4·70	13,260	4·69

Cumulative Effect of Substituents.—In recent investigations,[1b,d] the cumulative effect of nuclear substituents on the reaction at a benzene side-chain has been assessed in terms of the free energy of activation, which reflects changes in the activation energy if the entropy of activation remains constant. Since in the present study the non-exponential term is not always constant, the results are analysed in terms of the velocity coefficients.

For the disubstituted base $C_6H_3XY{\cdot}NMe_2$, if the contributions to the activation energy of the groups X and Y are additive, then

$$k_{XY} = A_{XY}(k_X/A_X)(k_Y/A_Y)(A_U/k_U)$$

which reduces to $k_{XY} = k_Xk_Y/k_U$ on the assumptions that (i) $A_{XY} = A_X$, and (ii) $A_U = A_Y$. This might be expected to apply when X is an *ortho*-substituent (and where $A_X \neq A_U$). When rates calculated according to this equation are compared with the observed values, three distinct groups of results are observed (see Table 3). Within the limits of experimental error (estimated at ±5%), the velocity ratios obtained for all the **3** : 5-disubstituted amines and for 3 : 4-dimethyl-*NN*-dimethylaniline show a strict additivity of group effects. This result is in full accord with earlier work on the hydrolysis of benzoic esters,[1c] with dipole-moment data,[9] and with values of the dissociation constants of disubstituted benzoic acids.[10]

TABLE 3. *Disubstituted bases: comparison of observed and calculated rates.*

Substituents	10^4k_{20} Obs.	10^4k_{20} Calc.	$100k_{obs.}/k_{calc.}$	Substituents	10^4k_{20} Obs.	10^4k_{20} Calc.	$100k_{obs.}/k_{calc.}$
3-Br, 5-Me	0·74	0·726	103	3-Br, 4-OMe ...	5·90	3·04	194
3-Br, 5-OMe ...	0·418	0·424	99	3-Cl, 4-OMe ...	5·95	3·17	188
3-Cl, 5-Me	0·776	0·756	104	3-F, 4-OMe ...	5·99	3·81	157
3-Cl, 5-OMe ...	0·438	0·441	99	3-I, 4-OMe	7·04	3·42	206
3-Me, 5-Me	8·30	8·36	99	3-NO_2, 4-OMe	1·53	0·703	218
3-Me, 5-OMe ...	4·92	4·88	101	5-Cl, 2-OMe ...	1·99	1·05	190
3-Me, 4-Me	16·4	16·5	99	5-F, 2-OMe ...	2·47	1·26	196
3-Br, 4-Me	1·65	1·43	115	5-I, 2-OMe	2·01	1·13	178
4-Br, 3-Me	1·82	1·61	113	5-Me, 2-OMe ...	10·9	11·6	94
3-Cl, 4-Me	1·79	1·49	119	2-OMe, 5-OMe	7·00	6·76	104
4-Cl, 3-Me	2·23	1·97	114	3-Cl, 2-OMe ...	0·101	1·05	9·6
4-Cl, 3-OMe ...	1·48	1·14	130	4-Cl, 2-OMe ...	3·55	2·70	131
4-Me, 3-NO_2 ...	0·360	0·331	109				
3-OMe, 4-OMe (at 0°)	5·94	4·96	120				

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[7] Vorob'ev, *J. Phys. Chem., U.S.S.R.*, 1940, **14**, 686.

[8] Cf. Price, Mertz, and Wilson, *J. Amer. Chem. Soc.*, 1954, **76**, 5131.

[9] Syrkin and Dyatkina, " Structure of Molecules," Butterworths, London, 1950, p. 225.

[10] Shorter and Stubbs, *J.*, 1949, 1180; Dippy, Hughes, and Laxton, *J.*, 1956, 2995.

For the toluidine derivatives and for 3 : 4-dimethoxy- and 4-chloro-3-methoxy-*NN*-dimethyl-aniline, the observed rates are all some 10—30% higher than the predicted values. This could arise from a slight increase in the non-exponential factor (A_{XY}) for the disubstituted base—an increase too small to be detected by experiment. However, a more likely explanation is that group interaction occurs, leading to greater electron-release by the substituents in the 3 : 4-positions, similar perhaps to the slight, but significant, lack of additivity of group dipole moments noted for *ortho*-substituted toluenes.[9] For the above compounds, any reduction of the extent of conjugation of the *para*-substituent with the aromatic ring would reduce the reaction rate, and appreciable steric inhibition of mesomerism by the substituent in the 3-position is clearly absent.

In the case of the five 3-halogeno- or 3-nitro-*NN*-dimethyl-*p*-anisidines examined the additivity principle is seriously violated and a well-defined group-interaction is manifest. Here there can be no question of additivity being masked by variations in A_{XY}—in fact for these compounds the mean experimental value for $\log_{10}PZ$ (5·47) is significantly lower than the value (5·80) found for the monosubstituted bases. In Table 4 these results are compared with those obtained from the hydrolysis of similarly substituted benzoic esters.

TABLE 4. *Velocity ratios of substituted* NN-*dimethyl*-p-*anisidines and ethyl* p-*anisates.*

Substituent	Alkaline hydrolysis (at 25°) 100 $k_{calc.}/k_{obs.}$	Menschutkin (at 20°) 100 $k_{obs.}/k_{calc.}$
3-Bromo-	148	194
3-Chloro-	143	188
3-Nitro-	143	218

(Velocity ratios for the ester hydrolysis have been inverted since this reaction is aided by electron-withdrawal from the reaction centre.) A similar type of interaction leading to an increase in electron density at the reaction centre is present for both series of compounds, but with the esters the effect seems to be far less marked.

This interaction seems to be polar rather than steric in origin. Any steric inhibition of the mesomeric effect of the *p*-methoxy-group by the adjacent halogen would lower the reaction rate. In fact, the velocity ratios increase as the size of the halogen is increased.

With *ortho*- and *para*-disubstituted benzene derivatives the dipole moments due to the individual groups are often not vectorially additive, and there is a close parallelism between the velocity ratios found for 3-substituted *p*-anisidines and the interaction moments of *p*-substituted anisoles given by Leonard and Sutton[11] (Table 5). Since, however, the magnitude of this effect is less with the benzoic esters than in the present case, the dimethylamino-group also seems to be involved in the interaction, and in this context the relatively slight departure from additivity found for 4-chloro-3-methoxy-*NN*-dimethylaniline may have significance.

TABLE 5. *Comparison of the interaction moments of* p-*substituted anisoles and velocity ratios of* 3-*substituted* NN-*dimethyl*-p-*anisidines.*

Substituent	μ (int.)	$100k_{obs.}/k_{calc.}$
Fluoro	−0·06	157
Chloro	0·04	188
Bromo	0·15	194
Iodo	0·16	206
Nitro	0·37	218

The velocity ratios found for the 5-substituted *NN*-dimethyl-*o*-anisidines are very similar to those for the 3-substituted *p*-anisidine derivatives, minor differences perhaps being due to incursion of the *ortho*-effect. Again, large departures from additivity are accompanied by an observed value of $\log_{10}PZ$ appreciably lower than the expected value (that of *NN*-dimethyl-*o*-anisidine), and with the halogeno- and nitro-substituted compounds a similar type of group interaction is indicated. The close correlation between the

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[11] Leonard and Sutton, *J. Amer. Chem. Soc.*, 1948, **70**, 1564.

predicted and the observed rates for 2 : 5-dimethoxy-*NN*-dimethylaniline is comparable with the relatively normal velocity ratio found for the 3 : 4-dimethoxy-compound. Since methoxyl and halogen substituents have similar electronic effects, both results contrast strongly with the abnormal ratios associated with the similarly substituted halogeno-anisidines.

In their study of the benzoylation of disubstituted anilines, Stubbs and Hinshelwood [1b] included five compounds with the same substituents in similar orientation to those used in the present study, and the results are summarised in Table 6. Whereas the toluidine derivatives have given similar results for both reactions, there is no correlation between the ratios obtained for the *o*-anisidine derivatives. It is unfortunate that no 3-halogeno-4-methoxyanilines were studied, for a comparison of results for this series would be free from the complication that no *ortho*-effect is found for the benzoylation reaction.

TABLE 6. *Velocity ratios for disubstituted anilines and dimethylanilines.*

	$100k_{\text{obs.}}/k_{\text{calc.}}$			$100k_{\text{obs.}}/k_{\text{calc.}}$	
Substituents	Benzoylation (at 25°)	Menschutkin (at 20°)	Substituents	Benzoylation (at 25°)	Menschutkin (at 20°)
3-Me, 4-Me	95	99	5-Cl, 2-OMe	89	190
3-Me, 5-Me	92	99	5-NO_2, 2-OMe ...	65	231
3-Cl, 4-Me	113	119			

Finally, the very low rate given by 3-chloro-2-methoxy-*NN*-dimethylaniline exemplifies group interaction of a different character from that found for the preceding compounds. It is well known that the extent of conjugation of a methoxy-group with the benzene ring is much reduced by the presence of two flanking substituents,[12] and with this particular compound it seems that the inductive effect of the methoxy-group is virtually unopposed by the usual mesomeric effect. The steric requirements of the methoxy-group may here also be effectively increased.

EXPERIMENTAL

Kinetic Measurements.—For the reaction with methyl iodide the method of Evans, Watson, and Williams [3] was adopted with minor modifications. 2 c.c. portions of 0·2M-methyl-alcoholic solutions of methyl iodide and *NN*-dimethylaniline, freshly prepared at 45°, were mixed in black-painted, drawn-out test-tubes, which were then sealed and replaced in the thermostat. At intervals, tubes were withdrawn, and the contents analysed for iodide ions. Rate constants obtained, expressed in l. $mole^{-1}$ $sec.^{-1}$, were as follows:

Substituent	H	*m*-Me	*p*-Me	*m*-OMe	*p*-OMe	*m*-Cl	*p*-Cl	*m*-Br	*p*-Br
10^4k (45·0°)	2·71	3·85	6·23	2·15	11·4	0·350	0·774	0·335	0·643

Generally, *k* was sensibly constant throughout the run, but with *p*-bromo-*NN*-dimethylaniline an asymptotic increase with time was noted which was unaltered when both reactants and the solvent were further purified in turn. The extent of solvolysis of 0·1M-solutions of methyl iodide was then found to be appreciable at 45°; 50 or 100 c.c. of solution were taken for each measurement:

Time (hr.)	0·0	6	12	17·5	24	42	72	120
$10^6[I^-]$ (mole/l.)	0	490	943	1345	1640	2650	3420	3810
10^7k_1	—	2·26	2·19	2·15	2·03	1·78	1·34	0·92

For the reaction of allyl bromide with dimethylanilines, 0·3M-solutions were prepared in aqueous acetone at 20°. 10 c.c. of the halide solution and 20 c.c. of the amine solution were introduced into separate arms of an H-shaped reaction vessel [1c] and the solutions were mixed when temperature equilibrium had been attained. At intervals, 2 c.c. samples were removed and added to light petroleum (b. p. 100—120°; 30 c.c.), and the solution was extracted thrice with 10 c.c. portions of distilled water. The combined aqueous extracts were acidified with 5 c.c. of 6N-nitric acid, 5·0 c.c. of 0·04N-silver nitrate solution were added, and the excess of silver nitrate was estimated by titration with 0·01N-ammonium thiocyanate by Volhard's method. The allyl bromide present in the aqueous solution did not affect the estimation.

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[12] Everard and Sutton, *J.*, 1951, 16; Anzillotti and Curran, *J. Amer. Chem. Soc.*, 1943, **65**, 607.

The initial concentrations of the reactants at temperatures other than 20° were calculated from the corresponding density of the solvent:

Temperature	0·0°	19·75°	24·9°	35·0°
Density of solvent (g./c.c.)	0·8966	0·8767	0·8719	0·8617
Initial concentration of halide	0·1023	0·1000	0·09445	0·09830
Initial concentration of base	0·2046	0·2000	0·1989	0·1966

Velocity coefficients calculated from the usual expression $k_2 = [1/t(a - b)] \ln [a(b - x)/b(a - x)]$ increased linearly with time over the range of experiment (15—65% completion), and the observed values were extrapolated to zero time. Typical results are given below:

Reaction of p-*bromo*-NN-*dimethylaniline with allyl bromide in* 25% *v/v aqueous acetone at* 35·0°.

$10t$ (sec.)	269	360	454	634	828	1050	1320	1441	1620
10^5x	1770	2287	2760	3579	4334	5055	5785	6094	6487
10^4k (l. mole^{-1} sec.$^{-1}$)	3·95	4·00	4·00	4·04	4·09	4·11	4·17	4·21	4·25

k (extrapolated) $= 3{\cdot}89 \times 10^{-4}$.

With the exceptions noted below, the precision of the experimental method was satisfactory and results were readily reproducible. In every case the reaction mixture remained homogeneous. On account of its low solubility in aqueous acetone, the initial concentration of *p*-iodo-*NN*-dimethylaniline was 0·1M. The reaction with 3 : 4-dimethoxy-*NN*-dimethylaniline could not be followed at 20° because the end-point of the titration was obscured by an orange colour which developed when the ferric indicator was added.

Solvolysis of the Allyl Bromide.—The extent of hydrolysis of allyl bromide by the reaction medium at 20° and at 35° was determined by periodically analysing aliquot parts (10 or 5 c.c.) of a 0·2M-solution. First-order rate constants, as determined over the early stages of the reaction, were $1{\cdot}71 \times 10^{-7}$ sec.$^{-1}$ at 19·75° and $8{\cdot}52 \times 10^{-7}$ at 35·0°. This solvolysis was normally unimportant, except for the very unreactive bases such as 3-chloro-2-methoxy-*NN*-dimethylaniline.

With *NN*-dimethyl-1-naphthylamine, after 7 days at 20°, the reaction mixture had a bromide-ion concentration of 0·025 mole/l., corresponding to a rate constant of $2{\cdot}5 \times 10^{-6}$, but the solution had become very dark and solvolysis of the halide would have given a bromide-ion concentration of 0·01 mole/l.

Preparation of Solvents.—Methyl alcohol was purified according to Evans, Watson, and Williams.[3]

Acetone (3 vol.), purified by the method of Conant and Kirner,[13] was diluted with distilled water (1 vol.). The resultant mixture had n_D^{20} 1·3657, corresponding to 29·8% w/w of water. The same batch was used throughout the investigation.

Purification of Alkyl Halides.—Methyl iodide, purified by the method of Evans, Watson, and Williams,[3] had b. p. 42·6°/759 mm., n_D^{20} 1·5300.

Allyl bromide was dried over calcium chloride and twice fractionally distilled, material of b. p. 70·3°/769 mm., n_D^{20} 1·4692, being used for rate-measurements.

Substituted NN-*Dimethylanilines.*—All tertiary bases were treated to remove any primary or secondary amine present. The amine was refluxed with acetic anhydride (4 vol.), weak bases being heated for longer (3 hr.) than more strongly basic ones (½ hr.). The residue left after distillation of the greater part of the anhydride was taken up in ice-cold, dilute hydrochloric acid, and non-basic materials were extracted with ether. The tertiary base was liberated with ammonia, filtered off or extracted with ether, dried, and distilled under reduced pressure. Solids were crystallised several times from alcohol or aqueous alcohol. Liquid bases were further purified by way of the picrates, which were prepared in benzene solution and crystallised to constant m. p. from alcohol or acetic acid. The amine was recovered by decomposing the picrate with warm 10% sodium hydroxide solution, followed by ether-extraction. The ethereal solution was washed with water, dried, and distilled, finally under reduced pressure.

NN-Dimethylaniline, *NN*-dimethyl-*m*- and -*p*-toluidine, *m*-nitro- and *p*-bromo-*NN*-dimethylaniline were purchased. Other substituted dimethylanilines were prepared by methylation of the appropriate aniline with methyl phosphate, the method of Billman *et al.*[14] being

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[13] Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 232.

[14] Billman, Radike, and Mundy, *J. Amer. Chem. Soc.*, 1942, **64**, 2977; Thomas, Billman, and Davis, *ibid.*, 1946, **68**, 895.

followed, with slight modifications. Yields after one distillation, together with the physical properties of the pure amine are given in the annexed Table.

Substituent	M. p. or b. p. (mm.)	M. p. of picrate	Yield (%)	Substituent	M. p. or b. p. (mm.)	M. p. of picrate	Yield (%)
m-Cl	90°/2	144°	70	*p*-OMe	47°	—	70
p-Cl	33°	—	70	5-Cl, 2-OMe [a]	100°/2	190	60
m-Br	126°/14	136	65	2-OMe, 5-OMe [b]	123°/15	186	70
m-F	82°/15	181	45	3-Me, 4-Me	102°/19	165	55
p-F	35°	—	45	*NN*-Dimethyl-1-naphthylamine	136°/12	145	85
m-I	34·5°	148	80	*NN*-Dimethyl-2-naphthylamine	45·5°	—	60
o-OMe	93°/6	145	65				
m-OMe	118°/6	144	60				

[a] Found: C, 58·2; H, 7·1. $C_9H_{12}ONCl$ requires C, 58·6; H, 6·5%. [b] Found: C, 66·4; H, 8·4. $C_{10}H_{15}O_2N$ requires C, 66 3; H, 8 3%.

The physical constants noted are in agreement with literature values, with the exception of the picrates of *m*-bromo-, *m*-chloro-, and *m*-iodo-*NN*-dimethylanilines, for which Hodgson and Nicholson[15] give m. p.s 182°, 179°, and 182°, respectively.

p-Ethoxy-*NN*-dimethylaniline, m. p. 34°, was obtained from *p*-ethoxyphenyltrimethylammonium iodide by treatment with sodium hydroxide in boiling pentyl alcohol. 4-Bromo-3-methyl-*NN*-dimethylaniline, m. p. 53—53·5°, was prepared according to von Braun and Kruber.[16] The nitration of *NN*-dimethyl-*p*-anisidine by the method of Hodgson and Crook[17] gave 4-methoxy-3-nitro-*NN*-dimethylaniline together with much dinitration product, but no detectable dinitro-compound was formed when the fuming nitric acid (*d* 1·5) used in the original procedure was replaced by concentrated nitric acid (*d* 1·4). The pure base had m. p. 45·5°.

4-Methyl-3-nitro-*NN*-dimethylaniline, m. p. 35·5°, was prepared by the nitration, under similar conditions, of *NN*-dimethyl-*p*-toluidine. The nitration of *NN*-dimethyl-*o*-anisidine, following the same procedure, gave a crude product from which a more volatile isomer was removed by steam-distillation and small amounts of dinitro-derivatives were removed by virtue of their insolubility in dilute hydrochloric acid. The required 2-methoxy-5-nitro-*NN*-dimethylaniline had m. p. 37·5°. *p*-Iodo-*NN*-dimethylaniline, m. p. 79°, was readily prepared by direct iodination of dimethylaniline in methyl alcohol with iodine and yellow mercuric oxide.

Several halogeno-substituted bases were prepared from commercial samples of the appropriate nitroanilines by conversion into the halogenonitrobenzene by the Sandmeyer reaction followed by reduction ($SnCl_2$) and *N*-methylation of the resulting aniline with methyl phosphate:

Substituents	M. p.	Found (%)	Required (%)
4-Cl, 3-Me	40°	N, 8·2; Cl, 21·3	N, 8·2; Cl, 20·9
3-Cl, 4-Me	33	N, 8·1; Cl, 21·1	N, 8·2; Cl, 20·9
4-Cl, 3-OMe	49	C, 58·7; H, 6·5	C, 58·6; H, 6·5
3-Cl, 4-OMe	63·5	C, 58·5; H, 6·5	C, 58·6; H, 6·5
3-Br, 4-OMe	66·5	N, 6·15; B, 34·6	N, 6·1; Br, 34·7
3-Br, 4-Me	33	N, 6·3; Br, 36·8	N, 6·5; Br, 37·3

Other disubstituted bases were obtained by successive reduction and *N*-methylation of the corresponding nitrobenzenes which were synthesised as outlined below. The properties of the purified dimethylanilines are listed in the following table.

Substituents	M. p. or b. p. (mm.)	M. p. of picrate	Found (%)	Required (%)
3-F, 4-OMe	28°	145°	C, 63·3; H, 7·2	C, 63·9; H, 7·2
5-F, 2-OMe	98°/13	164	C, 63·7; H, 7·4	C, 63·9; H, 7·2
3-Cl, 2-OMe	110°/13	133	C, 58·9; H, 6·6	C, 58·6; H, 6·5
2-OMe, 5-Me	120°/23	194	C, 72·4; H, 9·2	C, 72·7; H, 9·2
3-OMe, 4-OMe	41·5°	—	C, 66·5; H, 8·3	C, 66·3; H, 8·3
5-I, 2-OMe	34·5°	191	N, 4·8; I, 45·3	N, 5·0; I, 45·8
3-I, 4-OMe	54°	—	N, 4·8; I, 45·0	N, 5·0; I, 45·8
3-Me, 5-Me	98°/14	186	—	—
3-Cl, 5-Me	124°/14	174	C, 63·9; H, 7·2	C, 63·7; H, 7·1
3-Br, 5-Me	140°/15	182	N, 6·8; Br, 36·8	N, 6·5; Br, 37·3
3-Cl, 5-OMe	29°	—	C, 58·3; H, 6·5	C, 58·6; H, 6·5 [a]
3-Br, 5-OMe	30°	—	N, 6·1; Br, 34·7	N, 6·1; Br, 34·7
3-OMe, 5-Me	116°/6	—	C, 73·0; H, 9·2	C, 72·7; H, 9·2

[a] Calculated values (*i.e.*, not a new compound).

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[15] Hodgson and Nicholson, *J.*, 1941, 766.

[16] von Braun and Kruber, *Ber.*, 1913, **46**, 3468.

[17] Hodgson and Crook, *J.*, 1932, 1812.

5-Fluoro-2-methoxy-1-nitrobenzene, m. p. 61°, and 3-fluoro-4-methoxy-1-nitrobenzene, m. p. 104°, were prepared by the nitration of *p*-fluoroanisole and *o*-fluoroanisole respectively (method of Elderfield *et al.*[18]). The similar nitration of *o*-chloroanisole gave a crude product from which the required 3-chloro-2-methoxynitrobenzene was concentrated by steam-distillation from less volatile isomers. Fractionation under reduced pressure followed by crystallisations from alcohol gave the pure nitro-compound, m. p. 56°.

2-Methoxy-5-methyl-1-nitrobenzene was obtained from *o*-cresol by nitration with dilute nitric acid and subsequent methylation with an excess of methyl sulphate and 10% aqueous potassium hydroxide. 3 : 4-Dimethoxynitrobenzene was readily prepared by nitration of veratrole with diluted nitric acid (1 : 1); in this case, sodium sulphide [19] was a convenient reducing agent for the subsequent preparation of the aniline. The direct iodination of *o*- and of *p*-nitroanisole [2] by overnight stirring with a suspension of iodine in concentrated nitric acid at 15° furnished 5-iodo-2-methoxy-1-nitrobenzene, m. p. 96·5°, and 3-iodo-4-methoxy-1-nitrobenzene, m. p. 94°, in almost the theoretical yield.

3-Bromo- and 3-chloro-5-methoxy-1-nitrobenzene were prepared from 3 : 5-dinitroanisole: Partial reduction of the latter compound with sodium polysulphide gave 3-amino-5-methoxy-1-nitrobenzene in high yield, from which the halogeno-compounds were prepared by the Sandmeyer reaction. Sodium polysulphide was a convenient reagent for the reduction of these compounds to the 3 : 5-disubstituted anilines.

3 : 5-Dimethyl-1-nitrobenzene was prepared from 2 : 4-dimethylaniline by the method of Haller and Adams.[21] However, on addition of a solution of the diazotised 2-amino-3 : 5-dimethyl-1-nitrobenzene to a stirred suspension of cuprous oxide in ice-cold absolute alcohol deamination occurred more cleanly and in higher yield than by the published procedure.

4-Methyl-2-nitroaniline was converted into 3-bromo- and 3-chloro-5-nitrotoluene following the general method of Brynmor Jones and Robinson.[1d]

3-Methoxy-5-nitrotoluene was prepared according to Haworth and Lapworth's instructions [22] from 3-amino-5-nitrotoluene, but several modifications were introduced into published methods for the preparation of the latter compound from *p*-toluidine. Thus the well-known nitration of acetyl-*p*-toluidine with fuming nitric acid gave low yields of the required dinitro-derivative (cf. Brady, Day, and Rolt [23]), and acetyl nitrate was preferred as nitrating agent: the acetyl compound (100 g.) was added gradually to a stirred solution of fuming nitric acid (*d* 1·5; 1 l.) in acetic anhydride (240 c.c.) at 0—10°. The mixture was allowed to reach room temperature, then diluted with water (5 l.), and the solid was removed and washed free from acid. The crude product was hydrolysed by stirring with 50% v/v sulphuric acid at 100° for 30 min. Dilution of the resultant suspension with water (1·5 l.) precipitated most of the 4-amino-3 : 5-dinitrotoluene (90 g., 67%), m. p. 168°, unaltered by crystallisation from alcohol. The dinitrotoluidine (63 g.) was dissolved with cooling in a solution of sodium nitrite (23 g.) in concentrated sulphuric acid (160 c.c.). Glacial acetic acid (160 c.c.) was then added below 15° and the resultant solution of diazonium sulphate was added gradually to a suspension of cuprous oxide (15 g.) in ice-cold absolute alcohol (1 l.). When the reaction was complete, half of the alcohol was distilled off and dilution of the concentrated solution with water (2 l.) then precipitated 3 : 5-dinitrotoluene (41 g., 70%), m. p. 90—90·5°. Partial reduction of the latter compound with the calculated amount of sodium polysulphide gave 3-amino-5-nitrotoluene, m. p. 98°, in 88—92% yield.

4-*Chloro*-2-*methoxy*-NN-*dimethylaniline* (Found: C, 58·6; H, 6·6. $C_9H_{12}ONCl$ requires C, 58·6; H, 6·5%), b. p. 124°/12 mm. (picrate, m. p. 131°), was obtained by methylation of the corresponding aniline, which in turn was prepared, in 53% overall yield, from 2-amino-5-nitroanisole. The latter amine (50 g.) was acetylated and then reduced overnight by a refluxing mixture of iron pin-dust (60 g.), concentrated hydrochloric acid (1·5 c.c.), alcohol (200 c.c.), and water (30 c.c.), which had been boiled for 30 min. before addition of the nitro-compound. Most of the alcohol was distilled from the resultant suspension, dilute hydrochloric acid (1 : 1 by volume; 200 c.c.) was added, and the solution was filtered. The acid solution was diazotised

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[18] Elderfield, Gensler, Williamson, Griffing, Kupchan, Maynard, Kreysa, and Wright, *J. Amer. Chem. Soc.*, 1946, **68**, 1584.

[19] Fargher, *J.*, 1920, **117**, 865.

[20] Robinson, *J.*, 1916, **109**, 1078.

[21] Haller and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 1840.

[22] Haworth and Lapworth, *J.*, 1923, **123**, 2982.

[23] Brady, Day, and Rolt, *J.*, 1922, **121**, 526.

and then treated with a solution of cuprous chloride in concentrated hydrochloric acid at 30° until no diazonium chloride remained, and finally at the b. p. for 30 min. 4-Chloro-2-methoxyaniline (25 g.) was recovered from the neutralised solution by steam-distillation. Distillation under reduced pressure followed by crystallisation from alcohol gave the amine as needles, m. p. 57°.

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