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The Amidomethylation of Some *N,N*-Dialkylanilines (Tscherniac–Einhorn Reaction)

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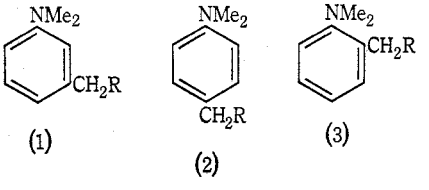
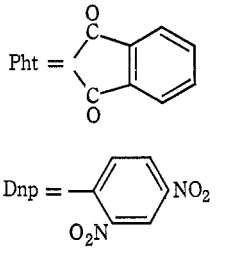
Abstract

The reaction of some representative *N,N*-dialkylanilines with *N*-hydroxymethylphthalimide in concentrated sulphuric acid solution (the Tscherniac–Einhorn reaction) has been studied and the structures of the resultant phthalimide derivatives elucidated (principally by means of p.m.r. spectroscopy). In some instances, when two equivalents of the reagent were used, the incorporation of two phthalimidomethyl groups into the *N,N*-dialkylaniline molecule was achieved. Similar results were obtained when the less reactive *N*-hydroxymethylchloroacetamide was used as the amidomethylating reagent.

In connection with a current research program, we became interested in the reaction of *N,N*-dialkylanilines with typical amidomethylating reagents (for reviews of the amidoalkylation reaction see[1,2]). As far as we could ascertain, only three such reactions, namely those between *N,N*-dimethylaniline and *N*-hydroxymethylphthalimide,[3] -benzamide[4] and -phenylacetamide[4] have been reported. In the present communication, we describe the reaction of several *N,N*-dialkylanilines with *N*-hydroxymethylphthalimide and with *N*-hydroxymethylchloroacetamide in concentrated sulphuric acid solution (the conditions of the Tscherniac–Einhorn reaction, ref.[1], p. 63).



	R
(a)	NPht
(b)	NH_2
(c)	NHDnp
(d)	$NHCOCH_2Cl$

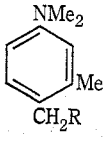


One equivalent of *N*-hydroxymethylphthalimide was found to react with *N,N*-dimethylaniline in concentrated sulphuric acid solution to give a product which appeared to be the same as that described by Tscherniac[3] who assigned to it the *para* structure (2a). However, the p.m.r. spectrum of our product showed it to be a mixture of *two*

[1] Zaugg, H. E., and Martin, W. B., *Org. React.*, 1965, **14**, 53.
[2] Zaugg, H. E., *Synthesis*, 1970, 49.
[3] Tscherniac, J., Ger. Pat. 134,979 (*Chem. Zentralbl.*, 1902, **2**, 1084).
[4] Haworth, R. D., MacGillvray, R., and Peacock, D. H., *J. Chem. Soc.*, 1950, 1493.

phthalimides, the identities of which were established by preparing the isomeric phthalimides (1a), (2a) and (3a) from the parent amines (1b), (2b) and (3b) respectively (see below) and examining appropriate mixtures by means of p.m.r. spectroscopy (unless otherwise stated, the structures of the various amidomethylation products obtained in this investigation were derived from their p.m.r. spectra, which are discussed below). In this way, it was established that our product was a 5 : 1 mixture of the *meta* and *para* phthalimides (1a) and (2a) and that it did not contain the *ortho* phthalimide (3a).* Numerous attempts to separate this mixture into its components either by fractional crystallization or by column chromatography failed. However, acidic hydrolysis gave a mixture of the parent amines (1b) and (2b) which was converted into a mixture of their *N*-(2,4-dinitrophenyl) derivatives (1c) and (2c) from which the pure *meta* derivative (1c) was obtained by fractional crystallization.

The corresponding reaction of one equivalent of *N*-hydroxymethylphthalimide with *N*-methylaniline also gave a mixture, presumably of the *meta* and *para* phthalimides (in the ratio 3 : 1). However, the reaction with *N*,*N*-dimethyl-*m*-toluidine, -*p*-toluidine, -2,6-dimethylaniline and -2,4,6-trimethylaniline, and with julolidine gave, in each case, a single phthalimide (4a)–(8a). No reaction occurred with 4-dimethylaminobenzaldehyde, *N*,*N*-dimethyl-4-nitroaniline or 4-diethylaminosalicyl-



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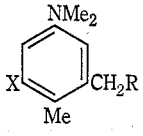

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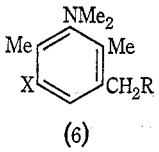

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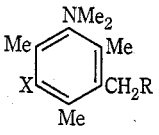

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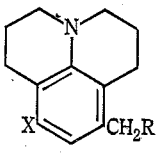


(8)

	R	X		R	X
(a)	NPht	H	(d)	$NHCOCH_2Cl$	H
(b)	NH_2	H	(e)	NPht	CH_2NPht
(c)	NHDnp	H			

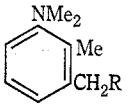
aldehyde. The asymmetric structure assigned to the julolidinylmethylphthalimide (8a)† is based on its p.m.r. spectrum (see below). The assignment of structure (5a) to the phthalimide obtained from *N*,*N*-dimethyl-*p*-toluidine is based (*a*) on its yellow colour (the *meta* and *para* phthalimides (1a) and (2a) are yellow whereas the *ortho* phthalimide (3a) is colourless) and (*b*) on the $\Delta\nu$ value of its *C*-methyl singlet (this spectral parameter is discussed below). Acidic hydrolysis of the phthalimide (4a) obtained from *N*,*N*-dimethyl-*m*-toluidine gave the parent amine (4b) which was prepared by an alternative unequivocal route (see below) (the 2,4-dinitrophenyl derivative (4c) was used for comparison purposes).

* The nitration of *N*,*N*-dimethylaniline in concentrated sulphuric acid solution gives a mixture of the *meta* and *para* nitro derivatives (*meta* derivative predominating) but no *N*,*N*-dimethyl-*o*-nitroaniline.[5]

† Symmetrical substitution of the aromatic nucleus of julolidine is well known.[6] Amidomethylation in concentrated sulphuric acid solution appears to be the first reported example of asymmetrical substitution.

[5] Brickman, M., Utley, J. H. P., and Ridd, J. H., *J. Chem. Soc.*, 1965, 6851.
[6] Smith, P. A. S., and Yu, T. Y., *J. Org. Chem.*, 1952, **17**, 1281.

It is clear therefore that, with one exception, the amidomethylation of *N,N*-dimethylanilines with *N*-hydroxymethylphthalimide in concentrated sulphuric acid solution occurs *meta* to the dimethylamino group. Clearly in the case of the exception, *N,N*-dimethyl-*m*-toluidine, the *ortho*-activating effect of the *C*-methyl group overrides the *meta*-orienting (but deactivating) effect of the protonated dimethylamino group. On the basis of these findings, we assign the structures (9a) and (10a) to the two phthalimides obtained as an inseparable mixture in the respective ratio 1 : 3 (based on the ratio of the *C*-methyl singlets and on their $\Delta\nu$ values; see below) by the corresponding reaction of *N,N*-dimethyl-*o*-toluidine with *N*-hydroxymethylphthalimide. Substitution *ortho* to the dimethylamino group (and *meta* to the *C*-methyl group) seems unlikely and the possible formation of the phthalimide (11a), which was readily accessible from its parent amine (11b) (see below), was excluded because the singlet due to its methylene protons occurs at a slightly higher field than the corresponding signals of the components of the mixture. Acidic hydrolysis of this phthalimide mixture gave a mixture of amines, (9b) and (10b), from which however a pure *N*-(2,4-dinitrophenyl) derivative could not be obtained.



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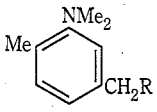

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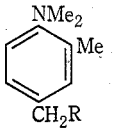


(11)

	R
(a)	NPht
(b)	NH_2
(c)	NHDnp

For comparison purposes, the amines (1b), (2b), (3b), (4b) and (11b) were prepared by reduction of the corresponding oximes with sodium in boiling ethanol,[7]* the corresponding aldehydes, except for *o*-dimethylaminobenzaldehyde, being prepared by literature procedures. This aldehyde was prepared in 73% yield by the reaction of *o*-fluorobenzaldehyde with dimethylamine in ethanolic dimethyl sulphoxide in the presence of anhydrous potassium carbonate (cf.[9]), a procedure which is much superior to the three-step method starting from *o*-nitrobenzaldehyde.[10] In addition, the literature synthesis of *m*-dimethylaminobenzaldehyde[10] was altered in one significant detail (see Experimental section). It is worth noting that acidic hydrolysis of the phthalimides gave substantially higher yields of the parent benzylamines than the route via the oximes and therefore the amidomethylation reaction, provided that it yields a *single* phthalimide, is a better route to these amines which, like benzylamine itself,[11] are somewhat unstable to air (see Experimental). Because of this instability, the amines were characterized as their phthaloyl, *N*-(2,4-dinitrophenyl) and *N*-chloroacetyl derivatives (see Table 1).

* Although giving modest yields, this method, being one-step, was preferred to the possible alternative method (essentially two-step), namely reduction of the corresponding oxime ether with diborane.[8]

[7] Kravtsov, D. N., and Faingor, B. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 289 (*Chem. Abstr.*, 1968, **69**, 66717v).

[8] Feues, H., and Bronstein, D. M., *J. Org. Chem.*, 1969, **34**, 1817.

[9] Gale, D. J., and Wilshire, J. F. K., *Aust. J. Chem.*, 1970, **23**, 1063.

[10] Cocker, W., Harris, J. O., and Loach, J. V., *J. Chem. Soc.*, 1938, 751.

[11] Drefahl, G., and Heublein, G., *J. Prakt. Chem.*, 1963, **20**, 323.

Julolidine and several of the more reactive *N,N*-dimethylanilines reacted with *two* equivalents of *N*-hydroxymethylphthalimide to give the corresponding bis-phthalimidomethyl derivatives, e.g. (5e), (6e), (7e) and (8e). However, in the case of *N,N*-dimethyl-*p*-toluidine, the yellow bis-phthalimide (5e) was accompanied by a significant amount of the mono-phthalimide (5a). No bis-phthalimide was obtained with *N,N*-dimethyl-*o*-toluidine. It is worthy of mention that the bis-phthalimides (5e)–(8e) should provide ready access (by means of acidic hydrolysis) to the parent *m*-bis(aminomethyl) compounds, which may be useful intermediates for the preparation of *basic* polyamides.*

Table 1. Melting points and analytical data

The compounds were recrystallized from hexane–methylene chloride except where stated

Compound	M.p. (°C)	Molecular formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
			Phthalimides							
(1a)	113–115[A]	$C_{17}H_{16}N_2O_2$	72·7	5·8	10·0		72·9	5·8	10·0	
(2a)	175–176[A]	$C_{17}H_{16}N_2O_2$	72·9	6·0	10·0					
(3a)	154–156	$C_{17}H_{16}N_2O_2$	72·7	5·8	9·9					
(4a)	153–155[A]	$C_{18}H_{18}N_2O_2$	73·7	6·2	9·6		73·5	6·2	9·5	
(5a)	135–136[A]	$C_{18}H_{18}N_2O_2$	73·7	6·2	9·4					
(6a)	111–113[A]	$C_{19}H_{20}N_2O_2$	74·0	6·6	8·9		74·0	6·5	9·1	
(7a)	104–106[B]	$C_{20}H_{22}N_2O_2$	74·7	6·9	8·6		74·5	6·9	8·7	
(8a)	189–191[A]	$C_{21}H_{20}N_2O_2$	76·0	6·2	8·0		75·9	6·0	8·4	
(11a)	87–89	$C_{18}H_{18}N_2O_2$	73·7	6·4	9·0		73·5	6·2	9·5	
			N-(2,4-Dinitrophenyl) derivatives							
(1c)	172–174	$C_{15}H_{16}N_4O_4$			17·6				17·7	
(2c)	149–152	$C_{15}H_{16}N_4O_4$			17·8					
(3c)	126–128	$C_{15}H_{16}N_4O_4$			18·1					
(4c)	196–198	$C_{16}H_{18}N_4O_4$			17·3				17·0	
(11c)	97–99[A]	$C_{16}H_{18}N_4O_4$			17·1					
			N-Chloroacetyl derivatives							
(1d)	94–96	$C_{11}H_{15}ClN_2O$			12·1	16·0			12·4	15·6
(2d)	113–115	$C_{11}H_{15}ClN_2O$			12·2	15·8				
(3d)	74–76[B]	$C_{11}H_{15}ClN_2O$			12·5	16·0				
(4d)	134–136	$C_{12}H_{17}ClN_2O$			11·3	15·0			11·6	14·7
(6d)	101–102[C]	$C_{13}H_{19}ClN_2O$			10·9	14·2			11·0	13·9
(8d)	150–152[D]	$C_{15}H_{19}ClN_2O$	65·0	7·2	10·0		64·6	6·9	10·1	
(12)	220–222[A]	$C_{16}H_{23}Cl_2N_3O_2$			11·9	19·7			11·7	19·7
			Bis-phthalimides							
(5e)	237–239[E]	$C_{27}H_{23}N_3O_4$	71·1	4·9	9·2		71·5	5·1	9·3	
(6e)	219–220[E]	$C_{28}H_{25}N_3O_4$	71·9	5·3	8·9		71·9	5·4	9·0	
(7e)	228–231[E]	$C_{29}H_{27}N_3O_4$	72·2	5·7	8·5		72·3	5·4	8·7	
(8e)	272 (dec.)[E]	$C_{30}H_{25}N_3O_4$	72·9	5·2	8·7		73·3	5·1	8·6	

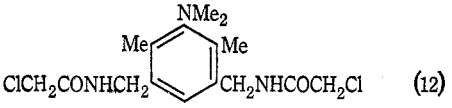
[A] From ethanol. [B] From pentane. [C] From hexane. [D] From aqueous alcohol. [E] From acetic acid.

The corresponding reaction of *N*-hydroxymethylchloroacetamide with several *N,N*-dimethylanilines in concentrated sulphuric acid solution was also briefly

* The parent diamine, *m*-xylylenediamine, has been used for the preparation of polyamides (e.g. with adipic acid[12]).

[12] Carlston, E. F., and Lum, F. G., *Ind. Eng. Chem.*, 1957, **49**, 1239.

investigated. This reagent proved to be less reactive than *N*-hydroxymethylphthalimide since no reaction occurred with *N,N*-dimethylaniline at room temperature.



(12)

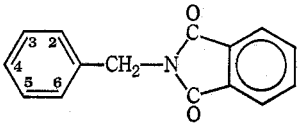
However, *N,N*-dimethyl-*m*-toluidine and julolidine gave the expected chloroacetamides (4d) and (8d) respectively. The structure of (4d) was verified by its synthesis (by the chloroacetylation of the parent amine (4b)). *N,N*,2,6-Tetramethylaniline reacted with two equivalents of *N*-hydroxymethylchloroacetamide to give a mixture of the monosubstituted (6d) and disubstituted (12) chloroacetamides.

Proton Magnetic Resonance Spectra

The assignment of structures to the amidomethylation and other products obtained in this investigation is based largely on an examination of their p.m.r. spectra (the

Table 2. P.m.r. spectral data for some *N*-benzylphthalimides

Chemical shifts in δ ex $SiMe_4$ for 0·2M solutions in $CDCl_3$. Unless otherwise stated, all signals quoted are singlets; bs, broad singlet; q, quartet. Phthalimido residue: AA′BB′ pattern centred at δ 7·78



Substituent(s)	$ArCH_3$[A]	$N(CH_3)_2$[A]	CH_2[B]	Aromatic CH
Unsubstituted			4·88 (5·00)	
2-Dimethylamino (3a)		2·75 (−12)	5·07 (5·17)	
3-Dimethylamino (1a)		2·93 (−1)	4·82 (5·10)	
4-Dimethylamino (2a)		2·92 (−2)	4·77 (5·10)	AA′BB′ q[C]
4-Dimethylamino-2-methyl (4a)	2·50 (11)	2·92 (1)	4·83	
4-Dimethylamino-3-methyl (11a)	2·30 (−1)	2·65 (−1)	4·78	
5-Dimethylamino-2-methyl (5a)	2·42 (10)	2·87 (0)	4·85	
3-Dimethylamino-2,4-dimethyl (6a)	2·25 (−1) 2·40 (8)	2·82 (−1)	4·85	6·97 bs[D]
3-Dimethylamino-2,4,6-trimethyl (7a)	2·25 (−1) 2·37 (5) 2·42 (9)	2·80 (0)	4·90	6·88 bs
Julolidine derivative (8a)			4·78	AB q[E] (*J* c. 8 Hz)

[A] Numbers in brackets are $\Delta\nu$ values [shifts (in Hz) downfield with respect to the corresponding signal (in $CDCl_3$ solution) of the parent *N,N*-dialkylaniline (i.e. lacking the *N*-phthalimidomethyl group)].

[B] Figures in brackets are chemical shifts in trifluoroacetic acid solution. Signals are doublets (*J* c. 5 Hz).

[C] Branches centred at 6·68 and 7·38.

[D] AB quartet (*J* c. 8 Hz); branches centred at 6·87 and 7·06 [in $C_6D_6/CDCl_3$ (1 : 1) solution].

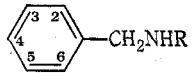
[E] Branches centred at 6·52 and 6·77.

relevant chemical shift data are shown in Tables 2–4). The asymmetrical structures assigned to the julolidine derivatives (8a) and (8d) follow from the appearance of an

aromatic AB quartet (*J c.* 8 Hz) in their spectra and, although the two aromatic protons of amide (6a) were revealed as a broad singlet in deuterochloroform, the addition of benzene[D_6] to the solution produced the expected AB quartet. In addition, the asymmetrical structures assigned to the amides (6a) and (6d) follow from the appearance of *two* *C*-methyl singlets whereas the symmetrical structure assigned to the bis-phthalimide (6e) is based on the appearance of only one *C*-methyl singlet (integrating for six protons). The symmetrical structure (8e) assigned to the julolidine bis-phthalimide does not follow unequivocally from its p.m.r. spectrum but is based on the reasonable expectation that the second phthalimidomethyl group will enter the remaining position *meta* to the nitrogen atom.

Table 3. P.m.r. spectral data for some benzylamines and their *N*-substituted derivatives

Chemical shifts in δ ex $SiMe_4$ for 0·2M solutions in $CDCl_3$. Unless otherwise stated, all signals quoted are singlets; d, doublet (*J c.* 6 Hz)



Substituent(s)	NH_2	CH_3[A]	$N(CH_3)_2$[A]	CH_2NH	CH_2Cl
Benzylamine (R = H)					
Unsubstituted	1·55			3·88	
2-Dimethylamino (3b)	1·93		2·68	3·92	
3-Dimethylamino (1b)	1·72		2·92	3·80	
4-Dimethylamino (2b)	1·75		2·90	3·75	
4-Dimethylamino-2-methyl (4b)	1·77	2·33	2·90	3·78	
4-Dimethylamino-3-methyl (11b)	1·57	2·32	2·67	3·78	
R = 2,4-Dinitrophenyl					
Unsubstituted				d 4·67	
2-Dimethylamino (3c)			2·77	d 4·72	
3-Dimethylamino (1c)			2·97	d 4·60	
4-Dimethylamino (2c)			2·97	d 4·52	
4-Dimethylamino-2-methyl (4c)		2·37	2·97	d 4·52	
4-Dimethylamino-3-methyl (11c)		2·33	2·72	d 4·55	
R = $COCH_2Cl$					
Unsubstituted				d 4·52	4·12
2-Dimethylamino (3d)			2·73 (−13)	d 4·63	4·08
3-Dimethylamino (1d)			2·93 (−1)	d 4·47	4·10
4-Dimethylamino (2d)			2·93 (−1)	d 4·38	4·05
4-Dimethylamino-2-methyl (4d)		2·32 (0)	2·93 (+2)	d 4·40	4·02
3-Dimethylamino-2,4-dimethyl (6d)[B]		2·27 (0) 2·32 (3)	2·85 (+3)	d 4·43	4·10
Julolidine derivative (8d)[C]				d 4·38	4·07

[A] Numbers in brackets are $\Delta\nu$ values (see Table 2) in Hz.
[B] Aromatic protons: s 7·00.
[C] Aromatic protons: AB quartet (*J c.* 8 Hz); branches centred at 6·52 and 6·85.

A useful adjunct to the structural determination of the phthalimides proved to be the parameter $\Delta\nu$ (in Hz), which is derived by comparing the chemical shifts of their *C*-methyl and *N*,*N*-dimethylamino groups with those of the corresponding groups of the parent *N*,*N*-dimethylanilines. It will be seen (Table 2) that a *C*-methyl

substituent situated *ortho* to a phthalimidomethyl group is deshielded significantly (by 8–11 Hz) whereas an *ortho*-situated dimethylamino substituent is shielded (presumably because it is twisted out of the plane of the aromatic ring). Application of this parameter to (*a*) the phthalimide (5a) and bis-phthalimide (5e) (see Table 4) obtained from *N*,*N*-dimethyl-*p*-toluidine supports the assigned structures and (*b*) to the mixture of phthalimides (9a) and (10a) obtained from *N*,*N*-dimethyl-*o*-toluidine indicates that the minor component almost certainly has the structure (9a). However, the chloroacetamidomethyl group has a negligible deshielding effect on an adjacent *C*-methyl group (cf. the $\Delta\nu$ values associated with each amidomethyl substituent (Tables 2 and 3)). Presumably the deshielding effect of the phthalimidomethyl group is associated with the anisotropic effect of the rigid phthaloyl residue. However, the large *shielding* effect on the dimethylamino group is approximately the same for each substituent (cf. the relevant $\Delta\nu$ values for the amides (3a) and (3d)). We conclude therefore that the dimethylamino group of both amides is twisted out of the plane of the aromatic ring.

Table 4. P.m.r. spectral data for some bis-amides

Chemical shifts in δ (p.p.m.) ex $SiMe_4$ for 0·2M solutions in $CDCl_3$. All signals quoted are singlets unless otherwise stated

Compound	$ArCH_3$[A]	$N(CH_3)_2$[A]	CH_2	Aromatic CH
(5e)	2·42 (16)	2·70 (5)	4·87	6·80
(6e)	2·33 (4)	2·70 (0)	4·78	7·05
(7e)	2·37 (7) 2·48 (14)	2·70 (0)	4·93	—
(8e)[B]			4·57	not visible
(12)[C]	2·25 (−1)	2·73 (2)	4·10 d 4·47[D]	6·98

[A] Numbers in brackets are $\Delta\nu$ values (see Table 2). [B] In $(CD)_3SO$.
[C] Saturated solution. [D] *J c.* 6 Hz.

It is worthy of note that the singlet due to the methylene protons of *N*-(2-dimethylaminobenzyl)phthalimide (3a) occurs at a significantly lower field than do the corresponding singlets not only of the isomeric *meta* and *para* phthalimides (1a) and (2a) but also of the unsubstituted analogue (*N*-benzylphthalimide) (see Table 2). Since this deshielding effect occurs to a very much lesser extent in trifluoroacetic acid solution (see Table 2) in which the dimethylamino group of all three phthalimides (1a)–(3a) is protonated (the relevant signal is a doublet, *J c.* 5 Hz), it seems certain that the dimethylamino nitrogen lone pair is involved. It is probable that the phenomenon has its origin in the fact that the dimethylamino group of the *ortho* phthalimide (3a) is rotated out of the plane of the aromatic ring (p.m.r. evidence for which is the appearance of its dimethylamino signal at unusually high field). In the resultant conformation, the adjacent methylene protons are located in the deshielding zone of the dimethylamino nitrogen lone pair. The same deshielding phenomenon was observed but to a lesser extent (see Table 3) for the methylene protons of the corresponding *ortho*-substituted benzylamine (3b), its 2,4-dinitrophenyl derivative (3c) and its *N*-chloroacetyl derivative (3d).

Experimental

(*a*) General

All melting points are uncorrected. The elementary analyses were carried out by the Australian Microanalytical Service, Melbourne. Merck alumina (activity II–III) was used for the column chromatography. Light petroleum refers to a grade of b.p. 40–60°. Infrared spectra (1% solutions in chloroform) were recorded on a Perkin–Elmer 257 instrument and p.m.r. spectra (for 0·2M solutions in deuterochloroform unless otherwise stated) were obtained on a Varian A60D spectrometer operating at 60 MHz (tetramethylsilane as internal standard) and at 37°.

N-Hydroxymethylphthalimide, m.p. 145–147° (lit.[1] 148·5–149°), was prepared and purified (by crystallization from pyridine) as described in the literature (ref.[1], p. 130). Its p.m.r. spectrum (in $(CD_3)_2SO$) exhibited signals at δ 7·95 (bs, aromatic protons), 6·38 (t, *J c.* 6 Hz, OH) and 5·03 (d, *J c.* 6 Hz, CH_2). The addition of deuterium oxide caused the triplet to disappear and the doublet to become a singlet. The presence of unchanged starting material (phthalimide) can be detected by (i) the presence of a sharp singlet at 7·90 and (ii) a broadening of the OH triplet and of the CH_2 doublet.

N-Hydroxymethylchloroacetamide, m.p. 102–104° (lit.[13] 102°), was obtained by the literature procedure.[13] Its p.m.r. spectrum (in $(CD_3)_2SO$) exhibited signals at δ 10·43 (vb, NH), 5·68 (t, *J c.* 6 Hz, OH) and 4·57 (quintet, $J(CH_2OH)$ *c.* 6 Hz, $J(CH_2NH)$ *c.* 3 Hz; CH_2). The addition of deuterium oxide caused the triplet to disappear and the quintet to become a triplet (*J c.* 3 Hz).

N,N-Dimethyl-*p*-toluidine,[14] -2,6-dimethylaniline[15] and -2,4,6-trimethylaniline[15] were prepared by methylation of the corresponding anilines as described in the literature. The other *N,N*-dimethylanilines (Fluka) and julolidine (Aldrich) were commercial samples.

The melting points and analytical data of most of the compounds prepared in this investigation are collected in Table 1.

(*b*) Reactions of *N*-Hydroxymethylphthalimide

Unless otherwise stated, reactions involving 1 equiv. of *N*-hydroxymethylphthalimide were carried out with stirring (magnetic) at room temperature for 5 h; reactions involving 2 equiv. of reagent lasted for 20 h. In the reaction of 1 equiv. with *N,N*-dimethylaniline (cf. (i)), several experimental variations were investigated (see below). However, the relative proportions of the phthalimides (1a) and (2a) formed remained unchanged. Different workup procedures were found to be necessary. During the workup (*procedure A*) described below for the reaction with *N,N*-dimethylaniline (cf. (i)), occasionally a small amount of a solid or a gummy precipitate was obtained when the reaction mixture was poured onto ice-water. This impurity was removed by filtration (usually with Celite) before the next step (basification). In *procedure B*, the product obtained on basification was only sparingly soluble in ether. However, the ether-soluble and -insoluble fractions were identical and were therefore combined. In *procedure C*, a portion of the product was insoluble in dilute acid (i.e. when the reaction mixture was poured onto ice-water) and was therefore removed by filtration prior to the basification step. The product obtained on basification was only sparingly soluble in ether. As the acid-insoluble, ether-insoluble and -soluble fractions all proved to be identical, they were combined. In *procedure D*, the product (bis-phthalimide) appeared to be insoluble in dilute acid and practically no further product was obtained in the subsequent basification step.

Several reactions are described in detail (unless otherwise stated, only 1 equiv. of *N*-hydroxymethyl compound was used). The workup procedures used and the results obtained for the remainder of the reactions investigated are summarized in Table 5. The reaction of *N,N*-dimethyl-*p*-toluidine with 2 equiv. of reagent gave a mixture of the mono- and bis-phthalimides (5a) and (5e) (see Table 5), which was readily separated into its components because (5e), unlike (5a), is insoluble in ether.

(i) *Reaction with* N,N-*Dimethylaniline*

Powdered *N*-hydroxymethylphthalimide (3·54 g; 20 mmol) was added portionwise over a period of 20 min to a stirred solution of *N,N*-dimethylaniline (2·42 g; 20 mmol) in concentrated sulphuric

[13] Einhorn, A., and Mauermayer, T., *Justus Liebigs Ann. Chem.*, 1905, **343**, 282.
[14] Hodgson, H. H., and Kershaw, A., *J. Chem. Soc.*, 1930, 278.
[15] Borkowski, W. L., and Wagner, E. C., *J. Org. Chem.*, 1952, **17**, 1128.

acid (20 ml) at room temperature. When the hydroxymethyl compound had dissolved, the solution was heated at 50° for 3 h before being poured onto ice-water. Basification with dilute ammonia gave an oily yellow solid which was isolated by extraction with ether. Trituration of the product with pentane gave a yellow solid (3·46 g; 62% yield), m.p. 98–104°, which was filtered, washed with light petroleum and then dried. The filtrate, which contained (p.m.r. spectrum) unchanged *N,N*-dimethylaniline in addition to a further quantity of the phthalimide mixture, was not investigated further. Recrystallization of the main product from ethanol gave a solid, m.p. 104–106° (in some preparations, some material remained unmelted until 176°) (lit.[2] 104–105°) (Found: C, 72·7; H, 5·8; N, 9·7. Calc. for $C_{17}H_{16}N_2O_2$: C, 72·9; H, 5·8; N, 10·0%). The p.m.r. spectrum exhibited two singlets at δ 2·92 and 2·93 in the $N(CH_3)_2$ region and two singlets (at 4·77 and 4·82) in the CH_2 region in the respective ratio 1 : 5 (as measured by integration of the methylene singlets). Neither crystallization from a variety of solvents nor column chromatography on alumina effected a separation of the two components (1a) and (2a).

Table 5. Reaction of *N*-hydroxymethyl-phthalimide and -chloroacetamide with some *N,N*-dialkylanilines

Reactions (5 h at room temperature) with 1 equiv. of reagent are denoted by *1*; those (20 h at room temperature) with 2 equiv. by *2*

N,N-Dialkylaniline	Procedure[A]	Scale (mmol)	Product	Yield (%)
With *N*-hydroxymethylphthalimide				
N,N-Dimethyl-*m*-toluidine, *1*	B	20	(4a)	68
N,N-Dimethyl-*p*-toluidine, *1*	A	5	(5a)	95
N,N-Dimethyl-*p*-toluidine, *2*	C	2·5	(5a)	35
			(5e)[B]	46
N,N-Dimethyl-2,6-dimethylaniline, *1*	A	14	(6a)	96
N,N-Dimethyl-2,6-dimethylaniline, *2*	C	5	(6e)[B]	86
N,N-Dimethyl-2,4,6-trimethylaniline, *2*	D	5	(7e)[B]	90
Julolidine, *1*	C	10	(8a)	89
Julolidine, *2*	D	5	(8e)[B]	93
With *N*-hydroxymethylchloroacetamide				
N,N-Dimethyl-*m*-toluidine, *1*	A	20	(4d)	28[C]
Julolidine, *1*	A	5	(8d)	93
N,N-Dimethyl-2,6-dimethylaniline, *2*[D]	B	5	(6d)	82
			(12)[B]	13

[A] See text. [B] Bis-amide. [C] Reaction at 50° for 3 h gave 56% yield. [D] Reaction for 60 h.

When the reaction was carried out at room temperature for 4 h after the addition of the hydroxymethylphthalimide, the yield (24%) was lower but was raised to 50% after 18 h. The use of oleum instead of concentrated sulphuric acid for 3 h at room temperature also produced a higher yield (45%). When the order of addition was reversed, i.e. when *N,N*-dimethylaniline (1·2 g) was added dropwise over a period of 15 min to a stirred solution of *N*-hydroxymethylphthalimide (1·8 g) in concentrated sulphuric acid (15 ml) at 50° and the solution allowed to stand at 50° for 3 h, the yield of product was 37%.

The mixture of phthalimides (1a) and (2a) (10·1 g) was converted into a mixture of the parent amines (1b) and (2b) by boiling its solution in concentrated hydrochloric acid (50 ml) under reflux for 8 h. On cooling, the precipitate (phthalic acid) (4·8 g; m.p. 207–209°) was filtered off and the filtrate basified with ammonia. After the addition of salt, the mixture was extracted with ether and the ether layer washed three times with saturated salt solution before being dried (anhydrous sodium sulphate). After removal of the solvent, the residual oil was fractionated in a vacuum to give a mixture of the amines (1b) and (2b), b.p. 106–108°/0·5 mm, as a colourless liquid (2·3 g; 43% yield) which exhibited singlets at δ 2·93 and 2·95 ($N(CH_3)_2$), 3·77 and 3·83 (CH_2), and 1·42 (bs, NH_2). A portion (0·50 g) was converted into a mixture of the corresponding *N*-(2,4-dinitrophenyl) derivatives by stirring its solution in dimethyl sulphoxide (10 ml) with 1-fluoro-2,4-dinitrobenzene (0·62 g) in the presence of triethylamine (0·95 ml; 2 equiv.) at room temperature for 2 h. The mixture was then poured onto ice-water to give a red solid which was sparingly soluble in ether. The ether-soluble and the sparingly soluble and insoluble solids were combined (0·98 g; m.p. 166–172°)

and crystallized from hexane/methylene chloride and then from methanol to give dark red needles, m.p. 172–174° (0·46 g). This product was identical (m.p., m.m.p., and i.r. spectrum) with the 2,4-dinitrophenyl derivative (1c) of *m-N,N*-dimethylaminobenzylamine (1b) (see below).

(ii) *Reaction with* N,N-*Dimethyl-o-toluidine*

The reaction was carried out on a 80-mmol scale at room temperature for 5 h. Workup as described in (i) followed by trituration of the semi-solid product with pentane gave a mixture of two phthalimides, (9a) and (10a), as a colourless solid, m.p. 95–114°, in 69% yield (Found: C, 73·4; H, 6·2; N, 9·8. Calc. for $C_{18}H_{18}N_2O_2$: C, 73·5; H, 6·2; N, 9·5%). The filtrate, which contained unchanged *N,N*-dimethyl-*o*-toluidine together with a further quantity of the phthalimide mixture, was not investigated further. The mixture, m.p. 95–114°, showed singlets at δ 2·28 and 2·47 ($ArCH_3$) ($\Delta\nu$ values: −2 and +9 Hz respectively), 2·68 and 2·65 ($N(CH_3)_2$), and 4·83 and 4·92 (CH_2) in the respective ratio 3 : 1. Attempts to isolate the pure components by crystallization from a variety of solvents were unsuccessful.

Hydrolysis of the phthalimide mixture (12 g) by concentrated hydrochloric acid (80 ml; 6 h reflux) gave phthalic acid (6 g) and a basic oil, which was fractionated in a vacuum to give a colourless liquid (3·4 g; 51% yield), b.p. 106–109°/1·2 mm. This liquid, which was a mixture of amines (probably (9b) and (10b) showed singlets at δ 2·33 and 2·35 ($ArCH_3$), 2·70 and 2·73 ($N(CH_3)_2$), 3·85 and 3·88 (CH_2), and at 1·47 (NH_2). A portion (1·64 g) was converted into a mixture of the corresponding 2,4-dinitrophenyl derivatives (2·8 g; m.p. 108–113°) as described in (i). However, numerous attempts (fractional crystallization) to obtain the pure components failed.

(iii) *Reaction with* N-*Methylaniline*

Reaction on a 6-mmol scale for 24 h at room temperature gave (procedure A) a semi-solid product. Trituration with pentane removed unchanged *N*-methylaniline to give a pale yellow solid (64% yield), m.p. 119–124°. The p.m.r. spectrum of this product exhibited singlets at δ 2·83 (CH_3), at 4·78 and 4·82 (CH_2) (ratio of CH_2 singlets 1 : 3). This ratio was not altered by crystallization from aqueous ethanol although the melting point was raised to 121–125°.

(iv) *Reaction with* N,N-*Dimethyl-2,4,6-trimethylaniline*

When the reaction mixture (10-mmol scale) was poured onto ice-water, a colourless ether-insoluble solid was obtained which was dissolved in aqueous ethanol. Basification of the resultant solution with ammonia gave a solid which was isolated by ether extraction. The original filtrate (from the ether-insoluble solid) was also basified and the resultant precipitate isolated by ether extraction. The solids, m.p. 97–(137–140°), from both extractions were combined and extracted with boiling hexane in order to remove an insoluble amorphous by-product (0·27 g; m.p. 172–179°) which was not investigated further. The hexane-soluble solid was chromatographed on alumina (50 g) (benzene/light petroleum 1 : 4) to give phthalimide (7a), m.p. 104–106°, in 63% yield (2·08 g).

(c) Reactions of *N*-Hydroxymethylchloroacetamide

The general comments expressed above regarding the reactions involving *N*-hydroxymethylphthalimide apply also to this reagent. Experimental details are shown in Table 5. In the reaction with *N,N*-dimethyl-*m*-toluidine at room temperature (5 h), the yield was low (28%) and the basic product was contaminated with starting material. The yield was raised to 50% when the reaction was carried out at 50° for 3 h. The reaction of 2 equiv. of reagent with *N,N*,2,6-tetramethylaniline gave a mixture of the mono- and bis-chloroacetamides (6d) and (12) (see Table 5) which were separated from one another by virtue of the fact that (6d) is easily soluble in ether whereas (12) is insoluble.

(*d*) Preparation of *N,N*-Dimethylaminobenzylamines (1b)–(4b) and (11b)

(i) *Preparation of* N,N-*Dimethylaminobenzaldehydes and their Oximes*

The oximes were obtained by a standard method (i.e. via aldehyde, hydroxylamine hydrochloride and sodium acetate in boiling 80% aqueous ethanol). *p*-Dimethylaminobenzaldehyde (oxime, m.p. 145–147°; lit.[16] 144°) was a commercial (B.D.H.) product.

[16] Duff, J. C., *J. Chem. Soc.*, 1945, 276.

(A) *Preparation of* o-*dimethylaminobenzaldehyde.*—A mixture of *o*-fluorobenzaldehyde (12·4 g; 0·1 mol), dimethylamine (33% w/w solution in ethanol) (24 ml; 0·4 mol) in dimethyl sulphoxide (100 ml) was stirred with anhydrous potassium carbonate (27·6 g; 0·2 mol) on a steam bath for 3 h. A further quantity of dimethylamine solution (12 ml) followed by dimethyl sulphoxide (20 ml) was then added and stirring continued on the steam bath for a further 3 h. The mixture was then cooled and poured onto ice; the resultant yellow oil was isolated by ether extraction. The oily product was fractionated in a vacuum to give *o*-dimethylaminobenzaldehyde, b.p. 110–113°/4·5 mm (lit.[10] 132°/25 mm), in 73% yield (10·9 g). Its p.m.r. spectrum (CCl_4 solution) showed the following signals: δ 2·90 (s, $N(CH_3)_2$) and 10·28 (d, J 0·6 Hz, CHO). In addition, the pattern (AMXY) due to its aromatic protons, which exhibited a strong resemblance to that found for the corresponding protons of *o*-nitroaniline and its *N*-methyl derivative,[17] showed four groups of signals which were amenable to first-order analysis. The following tentative assignments were made: δ 7·04 (m, H 3), 7·43 (m, H 4), 6·97 (m, H 5) and 7·77 (m, H 6). The oxime had m.p. 86–88° (lit.[18] 87°). Its p.m.r. spectrum ($CDCl_3$ solution) showed the following signals: δ 2·77 (s, $N(CH_3)_2$) and 8·53 (s, CH=NOH).

(B) *Preparation of* m-*dimethylaminobenzaldehyde.*—This aldehyde was prepared from *m*-nitrobenzaldehyde by the three-step method described in the literature.[10] However, a significant alteration in the final step was required before the desired aldehyde could be obtained. The oily intermediates, *m*-nitrobenzaldehyde dimethyl acetal [δ 3·32 (6H, s, $(OCH_3)_2$) and 5·43 (1H, s, CH)] and *m*-aminobenzaldehyde dimethyl acetal [δ 3·25 (6H, s, $(OCH_3)_2$) and 5·25 (1H, s, CH)], were readily obtained. Methylation of the latter compound (65 g) in ether (250 ml) was carried out as described[10] by stirring with a total of 220 g (added in four lots) of dimethyl sulphate in the presence of 7% sodium carbonate (1200 ml; added in four lots) over a period of 4 days. The crude *m*-dimethylaminobenzaldehyde dimethyl acetal [δ 2·88 (s, $N(CH_3)_2$)] was recovered from the ether layer and treated with 5% sulphuric (500 ml) for 1 h on a steam bath (in our hands, the alkaline treatment described by Cocker *et al.*[10] effected little or no hydrolysis). The cooled solution was basified with dilute ammonia and the oily aldehyde isolated by ether extraction. The resultant oil was fractionated in a vacuum to give *m*-dimethylaminobenzaldehyde (30 g), b.p. 130–133°/5 mm, which contained a small amount (*c.* 10%) of an aldehydic impurity (an extra CHO singlet at δ 9·92 was observed in addition to the main CHO singlet at 9·97). This impurity (possibly the mono *N*-methylated aldehyde) persisted (as its oxime) when the product was converted into the oxime (m.p. 70–75°; lit.[10] 75–76°). No attempt was made to remove this oxime impurity as the subsequent reduction of the crude oxime gave a pure sample of 3-dimethylaminobenzylamine (1b) (see below).

(C) *Preparation of 4-dimethylamino-3-methylbenzaldehyde.*—This aldehyde, b.p. 130–134°/3 mm and δ 2·37 (s, CH_3), 2·83 (s, $N(CH_3)_2$) and 9·88 (s, CHO), was prepared in 43% yield by the formylation of *N,N*-dimethyl-*o*-toluidine according to the paraformaldehyde–hexamine method* described in the literature.[20] Its *oxime*, m.p. 97–98° (from aqueous ethanol), exhibited singlets at δ 2·33 (CH_3), 2·73 ($N(CH_3)_2$) and 8·12 (CH=NOH) (Found: N, 16·1. $C_{10}H_{14}N_2O$ requires N, 15·7%).

(D) *Preparation of 4-dimethylamino-2-methylbenzaldehyde.*—This aldehyde was obtained in 87% crude yield (m.p. 55–60°) by the phosphorus oxychloride–dimethylformamide formylation (cf. the formylation of julolidine[21]) of *N,N*-dimethyl-*m*-toluidine. A pure sample, m.p. 66–68° (from hexane/methylene chloride) (lit.[16] 67°), exhibited singlets at δ 2·63 (CH_3), 3·07 ($N(CH_3)_2$) and 10·07 (CHO). Its *oxime* (obtained from the crude aldehyde), m.p. 107–109° (from aqueous ethanol), exhibited singlets at δ 2·42 (CH_3), 2·98 ($N(CH_3)_2$) and 8·38 (CH=NOH) (Found: N, 15·9. $C_{10}H_{14}N_2O$ requires N, 15·7%).

(ii) *Preparation of Substituted* N,N-*Dimethylaminobenzylamines*

The preparation of 4-dimethylamino-2-methylbenzylamine (4b) is typical. A solution of 4-dimethylamino-2-methylbenzaldehyde oxime (10·7 g) in anhydrous ethanol (200 ml) was heated

* A by-product obtained in 3% yield from the non-distillable portion of this reaction proved to be 3-methyl-4-methylaminobenzaldehyde, m.p. 114–116° (lit.[19] 115°); δ 2·58 (s, CH_3), 2·98 (d, J *c.* 5 Hz, $NHCH_3$), 4·33 (vb, NH) and 9·82 (s, CHO).

[17] Gale, D. J., and Wilshire, J. F. K., *Aust. J. Chem.*, 1972, **25**, 2145.
[18] Bamberger, E., *Ber. Deut. Chem. Ges.*, 1904, **37**, 978.
[19] Ullmann, F., and Frey, B., *Ber. Deut. Chem. Ges.*, 1904, **37**, 863.
[20] Berres, C., and Mueller, W., Fr. Pat. 1,377,226 (Bayer 1964) (*Chem. Abstr.*, 1965, **62**, P7691f).
[21] Benington, F., Morin, R. D., and Clark, L. C., *J. Org. Chem.*, 1956, **21**, 1470.

to boiling and freshly cut sodium metal (12 g) added at such a rate that the solution continued to boil gently. After all the sodium had been added, the mixture was boiled gently under reflux for 30 min. Most of the ethanol was then removed in a vacuum at 60° and the resultant slush diluted with water. After the addition of salt, the mixture was extracted with ether and the ether layer washed three times with saturated salt solution before being dried over anhydrous sodium sulphate. Removal of the solvent gave a yellow oil which was fractionated in a vacuum (4 mm) to give two main fractions of b.p. 142–146° and 146–150°, each of which proved (p.m.r. spectrum; see Table 3) to be the desired amine (4b). The total yield was 2·87 g (30%). A higher-boiling fraction contained (p.m.r. spectrum) unchanged oxime.

The following substituted benzylamines (b.p.; yield (%)) were prepared in a similar fashion: 2-dimethylamino- (3b) (112–116°/4 mm; 27), 3-dimethylamino- (1b) (129–133°/3 mm; 17), 4-dimethylamino- (2b) (137–140°/3 mm; 21) and 4-dimethylamino-3-methyl- (11b) (106–108°/1 mm; 29). When pure, these benzylamines were colourless liquids which exhibited the expected p.m.r. spectra (see Table 3). However, they showed a marked tendency to deposit crystals which appeared to be salts (carbonates?). In addition, their solutions in carbon tetrachloride and methylene chloride rapidly deposited crystals (presumably containing the corresponding hydrochloride; cf. the corresponding reaction with benzylamine[11]); this decomposition was considerably slower in deuterochloroform solution.

The 2,4-dinitrophenyl derivatives were prepared in high yield (85–95%) (cf. the reaction of 1-fluoro-2,4-dinitrobenzene with the mixture of amines (1b) and (2b) (see above)). The phthaloyl derivatives were obtained by boiling a solution of equimolar amounts of amine and phthalic anhydride in acetic acid for 1 h. On cooling, the mixture was basified with dilute ammonia to give the required derivative which was isolated either by filtration or by ether extraction. The chloroacetyl derivatives were prepared by the reaction in benzene solution of 1 equiv. of amine with 2 equiv. of chloroacetyl chloride as described elsewhere.[22] Occasionally, especially for low-melting derivatives of each of the three classes of derivative, Florisil chromatography was used to obtain the pure derivatives.

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