Addition of *NN*-Dimethylaniline Oxides to Nitrilium Salts and to Dimethyl Acetylenedicarboxylate. Direct Alkylamination of *NN*-Dimethylanilines

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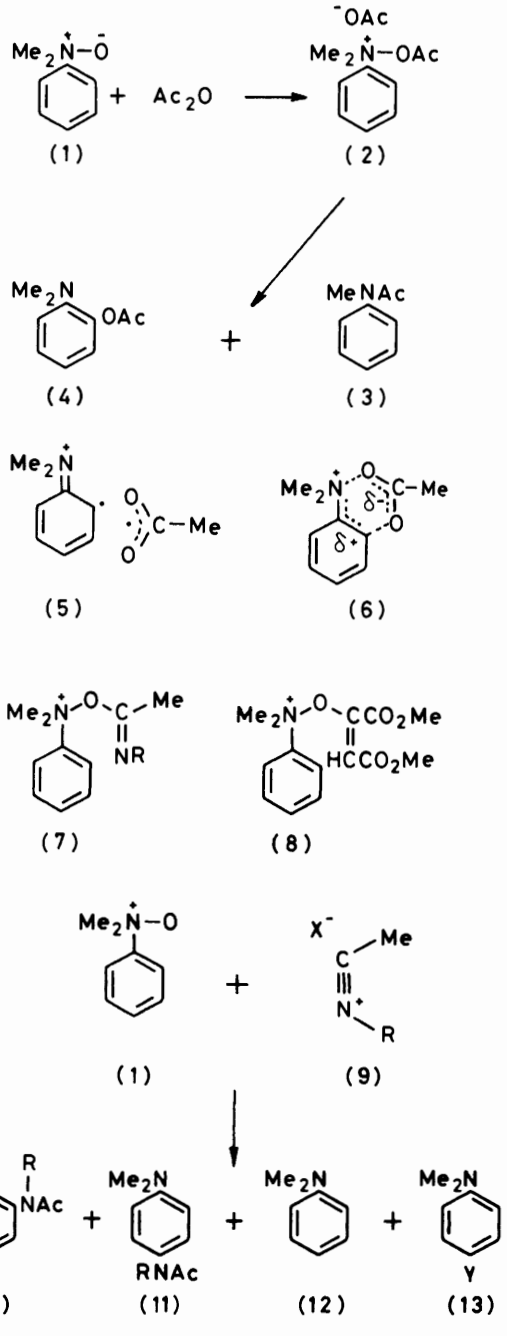
NN-Dimethylaniline oxide (1) and its ring-substituted derivatives react with *N*-alkylacetonitrilium salts to give the corresponding 2- and 4-(*N*-alkylacetamido)dimethylanilines. The mechanism, which involves migration of an amide group from the aniline nitrogen onto the ring, is discussed. Addition of the oxide (1) to dimethyl acetylenedicarboxylate leads either to demethylation of the aniline (main path in dichloromethane) or to a rearrangement, which involves migration of the succinyl moiety onto the *ortho*-carbon (in ethanol).

The reaction of *NN*-dimethylaniline oxide (1) with acetic anhydride has been reported [1] to yield two main products, *N*-methylacetanilide (3) (the Polonovski product) [2] and 2-acetoxy-*NN*-dimethylaniline (4). The mechanism of the rearrangement of the initially formed intermediate (2) to (4) has been investigated twice by Oae *et al.* with the use of ^{18}O-labelling techniques. In their first study [3] (in 1962) they concluded that it proceeds *via* homolytic cleavage of the N–O bond in the intermediate (2), followed by radical recombination (5). Their more recent study [4] (in 1979) led to a revision and to the proposal that the major pathway involves the polarized 6-membered cyclic transition state (6). The latter mechanism is also in better agreement with the substituent and solvent effects observed.[1,3]

We have now studied the possibility of also introducing nitrogen and carbon substituents to the *ortho*-position of *NN*-dimethylaniline *via* suitable *N*-oxide derivatives (7) and (8), which would rearrange through analogous mechanisms. The chosen route to system (7) was the nucleophilic addition of the oxide (1) to the nitrilium salts (9). The salts (9) are easily prepared by reaction of nitriles with powerful alkylating agents, or with alkyl halides in the presence of Lewis acids.[5] The reaction of the oxide (1) with a series of *N*-alkylacetonitrilium salts was carried out in acetonitrile at room temperature, and afforded mixtures of products which were separated by chromatography. The results are summarized in the Table. Structural assignments are based mainly on high resolution (300 MHz) n.m.r. spectroscopy. In the aromatic region compounds (10) showed two doublets and two triplets, all with further small *m*-splitting, while compounds (11) showed two 2 H doublets. The N–Me_2 peak appeared at δ 2.8 in the spectra of compounds (10) and at δ 3.0 in those of compounds (11). In the i.r. spectra compounds (10) exhibited a strong peak at 760—770 cm^{-1} and compounds (11) at 820 cm^{-1}.

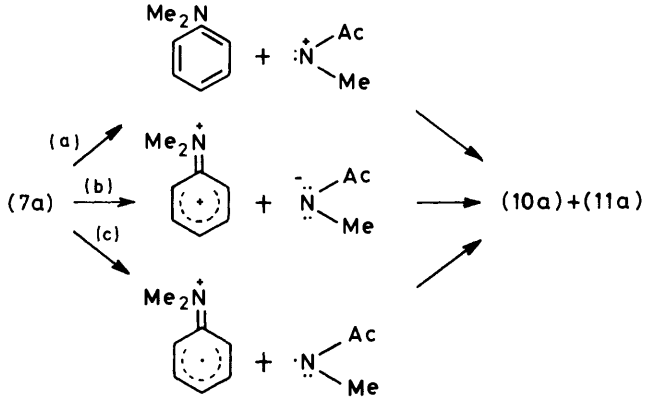
These results imply that the intermediate (7) is formed and undergoes the expected rearrangement, but unlike that in the case of the intermediate (2), the migrating group took up both the *o*- and *p*-positions and the ratio was dependent on the steric effect of the substituent R. This rearrangement could not have occurred through a cyclic mechanism, and a real dissociation must have taken place. Three modes of dissociation–recombination can be considered, involving the following highly energetic and unlikely species: (a) dimethylaniline and an acetylnitrenium cation; (b) a dimethylaniline dication and an amide anion; and (c) a dimethylaniline cation-radical and an amide radical (see Scheme).

Pathway (b) is supported by the formation of the halogeno-derivatives (13b) and (13c). The source of the halide ion which attacked the positively charged ring, is probably some decomposition of the anion X. Mechanism (b) is also the one most

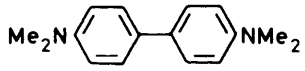


Table

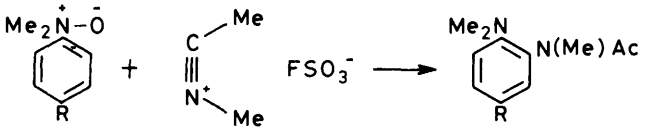
Nitrilium salt	R	X	Yield (%) (10)	(11)	(12)	(13)
(9a)	Me	SO_3F	45	17	10	—
(9b)	Et	BF_4	34	22	3	4 (Y = F)
(9c)	Pr^i	$SbCl_6$	—	15	5	21 (Y = Cl)



Scheme



(14)



(15) (16)

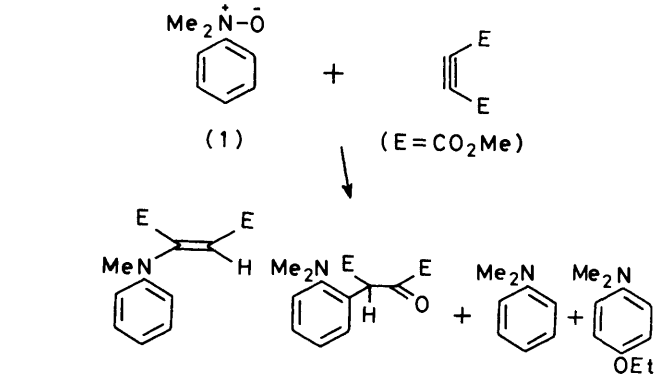
(a) R = Me

(b) R = OMe

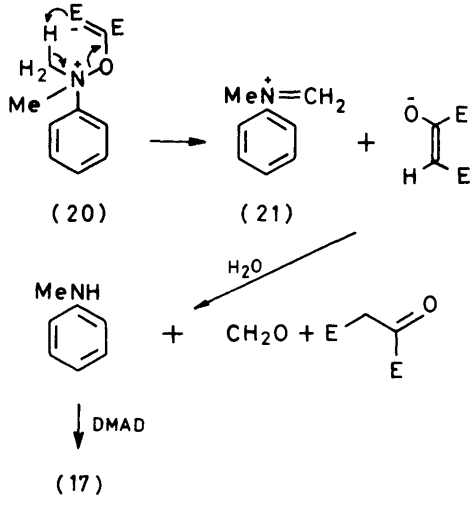
similar to that suggested for the rearrangement of compound (2);[2] however, the *N*-alkyl groups interfere sterically with the formation of the cyclic transition state. It is also most probable that, as has been shown[6] in the case of compound (2), the dimethylaniline formed results from homolytic cleavage of the N–O bond in the *N*-oxide (7). Indeed, in the reaction of compound (1) with the nitrilium salt (9b) we have isolated a small amount (2%) of *NN*-tetramethylbenzidine (14), formed by radical coupling.

The addition of the oxides of *NN*-dimethyl-*p*-toluidine (15a) and *NN*-dimethyl-*p*-anisidine (15b) to the nitrilium salt (9a) gave less complex mixtures. The 2-methylamino-derivatives (16a) and (16b) were isolated in good yields.

The addition of compound (1) to dimethyl acetylenedicarboxylate (DMAD) was expected to give the *N*-oxide (8) or its rearrangement products. Surprisingly, the reaction in dichloromethane yielded only dimethyl (*N*-methylanilino)-maleate (17), in addition to *NN*-dimethylaniline. The structure (17) was established by its identity to the addition product of *N*-methylaniline to DMAD.[7]



Yield (%)	(17)	(18)	(12)	(19)
In CH_2Cl_2	35	–	41	–
In EtOH	8	30	6	38



The formation of compound (17) involves demethylation and thus parallels the Polonovski reaction. It probably proceeds through initial formation of the zwitterion (20), proton transfer from a methyl group, and dissociation at the N–O bond. This is followed by the facile hydrolysis of the iminium ion (21) and addition of the resulting *N*-methylaniline to a second molecule of DMAD.

It would be expected that this pathway would be inhibited, at the proton transfer step, in protic solvents. On running the reaction in ethanol the yield of compound (17) decreased considerably, with the appearance of compounds (18) and (19). The assignment of compound (18) as the *o*-rearrangement product follows from its spectral properties (see Experimental section). The formation of a large amount of *NN*-dimethylphenetidine (19) indicates that here, as in the case of the rearrangement of compound (7), positively charged, highly electrophilic aromatic species are involved.

Experimental

I.r. spectra were recorded for Nujol mulls (solids) or films (liquids) on a Perkin-Elmer 157 spectrometer, and n.m.r. spectra for $CDCl_3$ solutions on a Bruker WH-300 instrument. Distillations were carried out on a Büchi GKR-50 instrument;

oven temperatures are given. Column chromatography was carried out on silica gel 60 (Merck) 70—230 mesh.

Materials.—Oxidations of *NN*-dimethylaniline, *NN*-dimethyl-*p*-toluidine and *NN*-dimethyl-*p*-anisidine to the oxides (1), (15a), and (15b), respectively, and the work-up, were carried out according to the procedure of Craig and Purushutman [8] in nearly quantitative yields. *N*-Methylacetonitrilium fluorosulphonate (9a) was prepared from acetonitrile and methyl fluorosulphonate.[9] *N*-Ethylacetonitrilium fluoroborate (9b) was prepared from acetonitrile and triethyloxonium fluoroborate.[5] *N*-Isopropylacetonitrilium hexachloroantimonate (9c) was prepared from acetonitrile, isopropyl chloride, and antimony pentachloride.[5]

Reaction of the Oxide (1) *with the Nitrilium Salt* (9a).—A solution of *N*-methylacetonitrilium fluorosulphonate (9a) (0.01 mol) in acetonitrile (2 ml) was added by injection to a cooled (0 °C), stirred (under a nitrogen atmosphere) solution of *NN*-dimethylaniline oxide (1) (1.37 g, 0.01 mol) in dry acetonitrile (20 ml). After 3 h at room temperature the solution was evaporated; the residue was then dissolved in water, neutralized (NaOH), and extracted twice with ether. The extract was dried and evaporated to yield a dark brown oil which was chromatographed on silica gel (50 g). Elution with chloroform–ethyl acetate (1 : 1) gave in the first fraction *NN*-dimethylaniline (0.14 g). Further elution gave 2-(N-*methylacetamido*)-NN-*dimethylaniline* (10a) as a light yellow oil (0.86 g, 45%), b.p. 110 °C at 0.2 mmHg; $\nu_{max.}$ 1 655 and 780 cm^{-1}; δ 1.93 (3 H, s), 2.80 (6 H, s), 3.23 (3 H, s), 6.90 (1 H, t, *J* 7.3 Hz), 6.96 (1 H, d), 7.01 (1 H, d), and 7.20 (1 H, t) (Found: C, 68.5; H, 8.35; N, 14.3. $C_{11}H_{16}N_2O$ requires C, 68.7; H, 8.4; N, 14.6%).

The next fraction solidified and was crystallized from cyclohexane to give 4-(N-*methylacetamido*)-NN-*dimethylaniline* (11a) (0.33 g, 17%), m.p. 87 °C; $\nu_{max.}$ 1 655 and 820 cm^{-1}; δ 1.88 (3 H, s), 2.99 (6 H, s), 3.22 (3 H, s), 6.67 (2 H, d, *J* 8.8 Hz), and 7.00 (2 H, d) (Found: C, 68.4; H, 8.6; N, 14.2. $C_{11}H_{16}N_2O$ requires C, 68.7; H, 8.4; N, 14.6%).

Reaction of the Oxide (1) *with the Nitrilium Salt* (9b).—As described above for the reaction with compound (9a). The first fractions yielded *NN*-dimethylaniline (0.1 g) and *p*-fluorodimethylaniline (0.1 g). Further elution gave a mixture of compounds (10b) and (11b) (1.15 g) in the ratio of 1 : 1.6 (determined through the n.m.r. peaks at δ 2.76 and 2.97, respectively). Repeated chromatography of this fraction did not give a complete separation; however, a pure sample of 4-(N-*ethylacetamido*)-NN-*dimethylaniline* (11b) was obtained, b.p. 110 °C at 0.2 mmHg; $\nu_{max.}$ 1 650 and 820 cm^{-1}; δ 1.15 (3 H, t, *J* 8 Hz), 1.90 (3 H, s), 2.97 (6 H, s), 3.62 (2 H, q), 6.70 (2 H, d, *J* 7.5 Hz), and 7.03 (2 H, d) (Found: C, 70.15; H, 8.9; N, 13.3. $C_{12}H_{18}N_2O$ requires C, 69.9; H, 8.8; N, 13.6%).

2-(N-*Methylacetamido*)-NN-*dimethyl*-p-*toluidine* (16a).—The reaction of *NN*-dimethyl-*p*-toluidine oxide (1.51 g, 0.1 mol) with the nitrilium salt (9a) (0.1 mole) was carried out as above. Elution with chloroform gave first *NN*-dimethyl-*p*-toluidine (0.15 g) and then the product (16a), (1.11 g, 54%), b.p. 135 °C at 0.2 mmHg; $\nu_{max.}$ 1 650 and 825 cm^{-1}; δ 1.93 (3 H, s), 2.30 (3 H, s), 2.90 (6 H, s), 3.24 (3 H, s), 6.88 (1 H, d, *J* 1.6 Hz), 6.91 (1 H, d, *J* 8.1 Hz), and 7.06 (1 H, dd) (Found: C, 69.7; H, 9.0; N, 13.4. $C_{12}H_{18}N_2O$ requires C, 69.9; H, 8.8; N, 13.6%).

2-(N-*Methylacetamido*)-NN-*dimethyl*-p-*anisidine* (16b).—As above from *NN*-dimethyl-*p*-anisidine oxide (1.67 g, 0.1 mol) and the nitrilium salt (9a) (0.1 mol). After chromatography compound (16b) (1.27 g, 57%) was obtained as an oil, b.p. 120—130 °C at 0.2 mmHg; $\nu_{max.}$ 1 655 and 820 cm^{-1}; δ 1.95 (3 H, s), 2.92 (6 H, s), 3.29 (3 H, s), 3.77 (3 H, s), and 6.6—7.0 (4 H, m) (Found: C, 64.5; H, 8.2; N, 12.7. $C_{12}H_{18}N_2O_2$ requires C, 64.8; H, 8.2; N, 12.6%).

Reaction of the Oxide (1) *with Dimethyl Acetylenedicarboxylate.*—(a) *In dichloromethane.* A solution containing *NN*-dimethylaniline oxide (1) (1.37 g, 0.01 mole) and DMAD (2.84 g, 0.02 mol) in dichloromethane (30 ml) was stirred at room temperature for 3 h and evaporated. Chromatography on silica gel (elution with dichloromethane) yielded *NN*-dimethylaniline (0.5 g) and dimethyl (*N*-methylanilino)maleate (17) (0.77 g, 35%), m.p. 82 °C (lit.,[7] 80—82 °C) identical with an authentic sample.[7]

(*b*) *In ethanol.* The reaction was run as above in ethanol (30 ml). Chromatography gave *NN*-dimethyl-*p*-phenetidine (0.57 g) and then *dimethyl 2-oxo*-3-[2-(NN-*dimethylamino*)*phenyl*]-*succinate* (18) (0.84 g, 30%); $\nu_{max.}$ 1 740, 1 730, and 760 cm^{-1}; δ 2.62 (6 H, s), 3.64 (3 H, s), 3.78 (3 H, s), 4.35 (1 H, s), and 6.90—7.35 (4 H, m) (Found: C, 59.9; H, 6.3; N, 5.0. $C_{14}H_{17}NO_3$ requires C, 60.2; H, 6.1; N, 5.0%). The third fraction yielded compound (17) (0.2 g, 8%), m.p. 82 °C.

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