

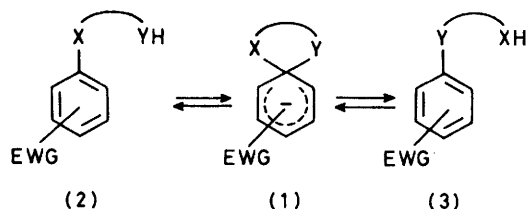
Nucleophilic Displacement and Spiro-complex Formation in *NN'*-Dimethyl-*N*-picrylethylenediamine

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Reaction of the title compound as the hydrochloride salt with Et_3N in dimethyl sulphoxide or dimethylformamide solution gave rise rapidly to the spiro-complex (9), followed by slow formation of (12), the product of intramolecular nitro-displacement. When NaOMe in DMSO-MeOH was used as the base, the overall conversion to (12) was much more sluggish. Reactivities in the two systems are discussed and the more facile reaction with Et_3N is suggested to arise mainly as a result of general acid-catalysed ring-opening of (9) by Et_3NH^+ , thus increasing the concentration of free amine, the reactive species in the displacement process. The results tend to rule out alternative mechanisms of nitro-displacement in which the spiro-complex serves as the reactive species in product formation.

SPIRO-COMPLEXES such as (1), where EWG are electron-withdrawing groups, while of interest structurally, occupy a special place in the area of nitroaromatic base reaction mechanisms. On the one hand, the spiro-complexes represent a model of the species which have been proposed as intermediates in nucleophilic aromatic substitutions¹ and are analogous to various σ -complexes formed by intermolecular nucleophilic attack on activated aromatic systems.² On the other hand, spiro-complexes are models of reaction intermediates in the class of intramolecular transformations grouped under the Smiles rearrangement,³ e.g. (2) \rightleftharpoons (3). The species (4),⁴ (5),⁵ (6),⁶ (7),⁷ (8),⁸ and (9)⁹ have in fact been fully characterized by spectroscopic techniques including n.m.r., having been prepared either as stable compounds or *in situ* by the action of base on the appropriate open-chain derivatives.

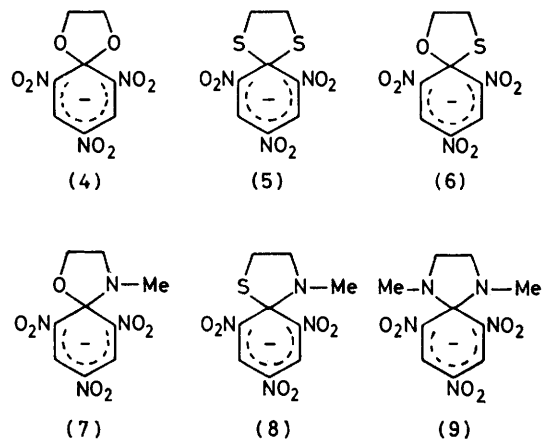
A possible complicating factor in the formation of the



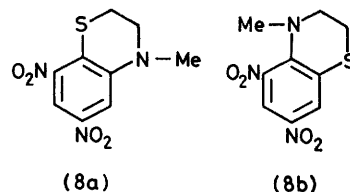
spiro-complexes from their open-chain precursors is competition from displacement of an *ortho*-nitro-substituent by the nucleophilic YH/Y^- (2) or XH/X^- (3) moieties. Literature data on such displacement processes are sparse. In the formation of (4), (5), (6), (7), and (9), substitution of a nitro-group had apparently not occurred. However, *S*-picrylpropane-1,3-dithiol on treatment with base gave the product of nitro-substitution,^{5a} in low yield, while 1-(β -*N*-aminoethylthio)-2,4,6-trinitrobenzene gave rise to the products (8a) and (8b) in variable yields depending on the reaction conditions;⁸ the spiro-complex (8) could also be obtained in this system.⁸

Among the factors determining the feasibility of substitution of a nitro-group in such systems, the nucleophilicities of the O, S, and N moieties will clearly be of

importance. However, the relative concentrations of substrate existing in the complexed (1) and open-chain forms [(2) and (3)] could critically affect the outcome. The studies of Bernasconi¹⁰ and Crampton¹¹ have shown



that kinetic and thermodynamic factors interplay in a complex manner in such processes. Since present knowledge relating to these factors is still fragmentary, it appeared to us desirable to demonstrate that nucleophilic substitution could be effected also in other systems. We now report our results with the title compound, which have shown that depending on the reaction conditions one can obtain either the spiro complex (9)



as a stable species, or the product of nitro-substitution (12) in virtually quantitative yield.

RESULTS AND DISCUSSION

The hydrochloride salt (10) in DMSO solution is quite stable but on addition of Et_3N it reacts instantane-

ously to give the spiro-complex (9). A slow reaction then ensues to give the product of nitro-displacement (12). In the Figure are illustrated the spectra obtained by sampling periodically a reaction solution in DMSO at 70 °C, containing (10) (0.05M) and Et₃N (0.3M) following 100-fold dilution. Scan 1, recorded im-

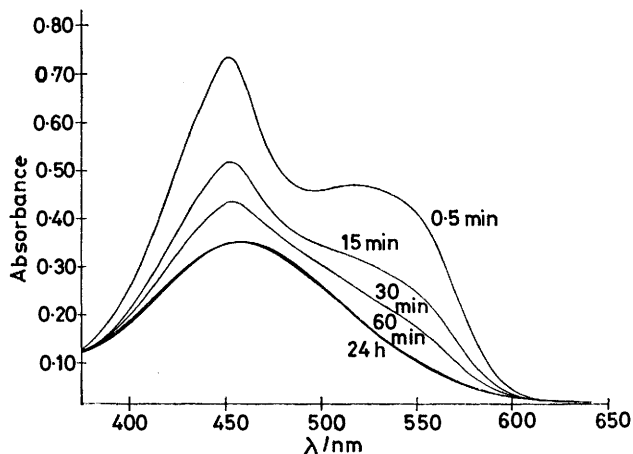


FIGURE 1. Spectral scans showing the disappearance of spiro-complex (9) and formation of product (12) in the overall reaction (10) \rightarrow (12), as induced by Et₃N in DMSO

mediately on mixing the reactants, shows that complete conversion to (9) has occurred.⁹ From the changes with time in the following spectra it is seen that the subsequent slow reaction has reached completion in 1 h. Dilution of the resulting solution with water causes precipitation of a red solid, shown to be (12) (see below). An experiment performed using DMF as solvent while keeping the other variables constant gave quite similar results.

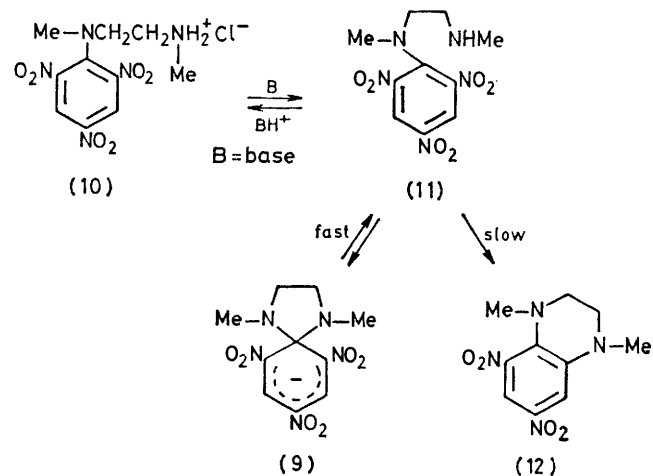
Different behaviour resulted when NaOMe was used as the base. Thus a reaction solution containing (10) (0.037M) and 1.98 equiv. of NaOMe in DMSO-MeOH (95 : 5 v/v) showed no changes in the spectra over a period of 2 h at 80 °C. On raising the bath temperature to 150 °C, a slow reaction ensued and was complete after 90 min, as shown spectrophotometrically. On dilution of the reaction mixture with water an orange precipitate was obtained, in 96% yield based on structure (12). This was recrystallized from CH₂Cl₂-Et₂O to give red crystals of (12), m.p. 188–189 °C (84% yield, see Experimental section for characterization).

The overall mechanism which accounts for our results is shown in Scheme 1. Thus the reactive species is considered to be the free amine (11), formed on deprotonation of the hydrochloride salt by the base. There follows the conversion of (11) to (9) in a rapidly attained equilibrium, while (12) is formed in a competing slow irreversible process. The origin of the contrasting behaviour observed in the two basic systems employed is considered further below.

When NaOMe is used as the base, the conversion (10) \rightarrow (11) is essentially quantitative. The equilibrium constant for (11) \rightleftharpoons (9) is expected to be very large in the

medium used, 95% DMSO-5% MeOH.¹² Thus in the overall conversion (10) \rightarrow (9) 2 equiv. base are required, *i.e.* the total MeO⁻ present will have been consumed. Since the displacement reaction (11) \rightarrow (12) also consumes 1 equiv. base, the overall conversion (10) \rightarrow (12) is likewise accompanied by the consumption of 2 equiv. base. Thus the concentration of free base present will be very small. It appears that the dominant factor in this system is the highly favourable conversion in the equilibria (10) \rightleftharpoons (11) \rightleftharpoons (9), resulting in an extremely small equilibrium concentration of the reactive species (11). The overall reaction (10) \rightarrow (12) thus becomes unfavourable, which is in accord with the rather drastic conditions required for product formation.

The use of Et₃N as base will have several contrasting consequences in relation to the NaOMe case discussed above. In the first place, the equilibrium (10) \rightleftharpoons (11) will be relatively unfavourable, since (11) and Et₃N have comparable basicity. The equilibrium constant for (11) \rightleftharpoons (9), though difficult to estimate quantitatively, can be predicted to be fairly high, as based on literature data in related systems.⁹ With Et₃N in large excess, conversion to (9) would hence be largely complete, even though the equilibrium displacement may not be as high as in the NaOMe case. The experimental results indicate that (9) is in fact formed essentially completely in this system. What then is the main



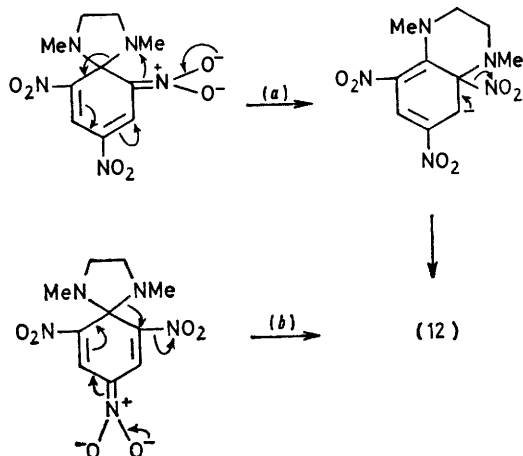
SCHEME 1

reason for the much more facile formation of (12) with Et₃N than when NaOMe is used as base?

We suggest that in the Et₃N system a pertinent factor influencing the overall reactivity is the possibility of general acid catalysis¹³ in the opening of the spiro-complex (9). That the process (9) \rightarrow (11) should be subject to general acid catalysis is indicated from the studies of Bernasconi¹⁰ and of Crampton¹¹ with spiro-complexes (1; X, Y = O, N). The possibility also exists of general acid-catalysed leaving-group expulsion in the conversion (11) \rightarrow (12), by analogy with Bunnett's suggested mechanism for S_NAr processes.^{1b}

While the reaction mechanism considered in the above

discussion is essentially that of nucleophilic displacement, it may be pointed out that the nitro-groups are situated *meta* to the reaction site and hence cannot be activating in the normal sense of S_NAr processes.^{1a} Nevertheless, reaction occurs readily, as noted above. Other possible mechanisms therefore require consideration and the pathways shown in Scheme 2 are of interest. Path (a)



SCHEME 2

depicts an intramolecular rearrangement of the spiro-complex involving nucleophilic substitution on one of the tertiary amino-nitrogens followed by expulsion of an *ortho*-nitro-group and concurrent re-aromatization. In path (b) is shown a one-step intramolecular displacement of NO_2 initiated by the negative charge of the anionic σ -complex. The latter process has analogy in the expulsion of other potential leaving groups from anionic σ -complexes,¹⁴ while nucleophilic displacement on nitrogen has also been described.¹⁵ However, either of these mechanisms would predict that the rate of product formation should be dependent only on the concentration of the spiro-complex reactant. As has been shown, the spiro-complex is formed virtually completely, whether Et_3N or CH_3O^- are used as bases in the reaction. Hence the observed large difference in reactivity in the two basic systems would exclude the pathways shown in Scheme 2.

In conclusion, the much greater efficiency of Et_3NH^+ acting as a general acid catalyst, relative to MeOH , is believed to be the factor chiefly responsible for the facile formation of substitution product in the Et_3N system, as compared to the use of NaOMe as base.

EXPERIMENTAL

NN'-Dimethyl-*N*-picrylethylenediamine hydrochloride (10) was prepared by a modification of the procedure given by Bernasconi and Gehriger,⁹ which resulted in an improved yield. A solution of picryl chloride (2.5 g, 0.01 mol) in benzene (20 ml) was added dropwise during 20 min to a stirred mixture of *NN'*-dimethylethylenediamine (1.32 g, 0.012 mol) in benzene (15 ml) and 1*N* NaOH solution (20 ml). After 1 h the benzene layer was separated and the residue acidified with dilute HCl until 1*N*. The aqueous solution after heating with carbon, filtering, and

cooling, yielded 1.9 g (57%) of product which was recrystallized from 1*N* HCl . Use of the two-phase system, as above, minimizes the formation of dicationic product, which led to the rather low yield (25%) when EtOH was used as the reaction medium.⁹

The reaction of (10) with Et_3N in DMSO was carried out as follows. A solution of (10) (35 mg, 0.10 mmol) and Et_3N (41 μl , 0.57 mmol) in DMSO (2.0 ml) was heated at 70 °C. Aliquots of 20 μl were removed periodically, diluted to 2 ml with DMSO and the u.v.–visible spectrum recorded in a 1-mm cuvette using a Beckman Mark IV spectrophotometer. Reaction of (10) with Et_3N in DMF was performed similarly. In both cases, when the spectra indicated complete reaction, the solution was added to water and the precipitate collected and recrystallized from CH_2Cl_2 – Et_2O , to yield red crystals of (12), m.p. 188–189 °C.

Reaction of (10) with NaOMe in DMSO – MeOH was carried out on a larger scale for characterization of the product. A solution of (10) (247 mg, 0.736 mmol) in DMSO (20 ml) was treated with 1.46*N* NaOMe – MeOH (1.0 ml) and monitored spectrophotometrically as described above while heating first at 80 °C (2 h) and subsequently at 150 °C (1.5 h). The reaction mixture was then added to water (50 ml), and the precipitated orange solid collected (179 mg) and recrystallized from CH_2Cl_2 – Et_2O to yield ruby-red crystals of (12) (157 mg), m.p. 188–189 °C (Found: C, 47.60; H, 4.98; N, 21.97. Calc. for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_4$: C, 47.62; H, 4.80; N, 22.21%); λ_{max} 279 (ϵ 13 100), 330 (8 500), and 448 nm (11 400).

The n.m.r. spectrum of (12) was obtained on a Brücker 60-MHz HFX-60 instrument. The δ values, referenced to tetramethylsilane as internal standard in $[\text{D}_6]\text{DMSO}$, are 8.04 (1 H, d, J 2.7 Hz), 7.18 (1 H, d, J 2.7 Hz), 3.76 (2 H, t, J 5.0 Hz), 3.35 (2 H, t, J 5.0 Hz), 2.95 (3 H, s), and 2.82 (3 H, s). The δ 8.04 signal can be assigned to the proton flanked by the NO_2 groups, while the δ 7.18 signal is then assignable to the other aromatic proton. The δ 3.76 and 2.95 resonances are assigned, respectively, to the NCH_2 and NMe groups situated *para* to the NO_2 group since these protons are expected to be deshielded as a result of conjugation between the amino-nitrogen and the *para*- NO_2 . The δ 3.35 and 2.82 resonances can then be assigned, respectively, to the remaining NCH_2 and NMe protons.

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REFERENCES

- (a) J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1; (b) J. A. Orvick and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1970, **92**, 2417; (c) S. D. Ross, *Prog. Phys. Org. Chem.*, 1963, **1**, 31; (d) F. Pietra, *Quart. Rev.*, 1969, **23**, 504; (e) J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, New York, 1968; (f) E. Bunce, A. R. Norris, and K. E. Russell, *Quart. Rev.*, 1968, **22**, 123; (g) C. F. Bernasconi, *M.T.P. Internat. Rev. Sci., Org. Chem. Ser. One*, 1973, **3**, 33.
- (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem. (Australia)*, 1966, **16**, 16; (b) M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; (c) M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667; (d) J. H. Fendler, W. L. Hinze, and L. J. Liu, *J.C.S. Perkin II*, 1975, 1768; (e) L. H. Gan and A. R. Norris, *Canad. J. Chem.*, 1974, **52**, 1; (f) E. Bunce and W. Eggimann, *J.C.S. Perkin II*, 1978, 673; (g) F. Terrier, F. Millot, and W. P. Norris, *J. Amer. Chem. Soc.*, 1976, **98**, 5885.
- (a) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1935, 181; (b) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 275;

- (c) W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. Reactions*, 1970, **18**, 99; (d) E. Buncel, N. Chuaqui-Offermans, B. K. Hunter, and A. R. Norris, *Canad. J. Chem.*, 1977, **55**, 2852.
- ⁴ (a) R. Foster, C. A. Fyfe, and J. W. Morris, *Rec. Trav. chim.*, 1965, **84**, 516; (b) J. Murto, *Suomen Kem.*, 1965, **B38**, 255; (c) R. Foster, C. A. Fyfe, P. H. Elmslie, and M. I. Foreman, *Tetrahedron*, 1967, **23**, 227; (d) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, 1968, **33**, 4141.
- ⁵ (a) E. Farina, C. A. Veracini, and F. Pietra, *J.C.S. Chem. Comm.*, 1974, 672; (b) V. N. Knyazev, A. A. Klimov, N. G. Yarishev, and V. N. Drozd, *Zhur. org. Khim.*, 1974, **10**, 2587.
- ⁶ V. N. Knyazev, A. A. Klymov, and V. N. Drozd, *Zhur. org. Khim.*, 1975, **11**, 1440.
- ⁷ S. Sekiguchi and T. Shiojima, *Bull. Chem. Soc. Japan*, 1973, **46**, 693.
- ⁸ V. N. Knyazev, V. N. Drozd, and V. M. Minov, *Tetrahedron Letters*, 1976, 4825.
- ⁹ C. F. Bernasconi and C. L. Gehrig, *J. Amer. Chem. Soc.*, 1974, **96**, 1092.
- ¹⁰ (a) C. F. Bernasconi, R. H. DeRossi, and C. L. Gehrig, *J. Org. Chem.*, 1973, **38**, 2838; (b) C. F. Bernasconi and F. Terrier, *J. Amer. Chem. Soc.*, 1975, **97**, 7458; (c) C. F. Bernasconi, *Accounts Chem. Res.*, 1978, **11**, 147.
- ¹¹ (a) M. R. Crampton, *J.C.S. Perkin II*, 1973, 2157; (b) M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 1974, 1681, 1686; (c) M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 1976, 901.
- ¹² E. Buncel and H. Wilson, *Adv. Phys. Org. Chem.*, 1977, **14**, 133.
- ¹³ E. Buncel, J. G. K. Webb, and J. F. Wiltshire, *J. Amer. Chem. Soc.*, 1977, **99**, 4429.
- ¹⁴ E. Buncel, N. Chuaqui-Offermans, R. Y. Moir, and A. R. Norris, *Canad. J. Chem.*, 1979, **57**, 494.
- ¹⁵ P. A. S. Smith, 'Open-Chain Nitrogen Compounds,' Benjamin, New York, 1965.