2,6-Dinitro-4-X-anilino-*N*-methylpropionamides: Reactions with Amines

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2,6-Dinitro-4-X-anilino-*N*-methylpropionamides (where X is an electron-withdrawing group) have been found to react with a number of amines in alcoholic solvents to yield 1-σ (Meisenheimer) complexes *via* attack of alkoxide ion on the 1-position of the aromatic ring. A kinetic study of this reaction for the compounds in which X = NO_2, $MeSO_2$, and CN has been made.

In a preliminary communication [1] we reported that 2,4,6-trinitroanilino-*N*-methylpropionamide (I; X = NO_2), a substituted picramide, reacted with potassium methoxide in methanol to form a 1-σ (Meisenheimer) complex. This type of reaction is typical of picryl ethers [2] but has not been previously observed in a picramide; alkyl picramides have been shown to react with alkoxide ion with the formation of 3-σ complexes and/or loss of the anilino-proton.[3a,b]

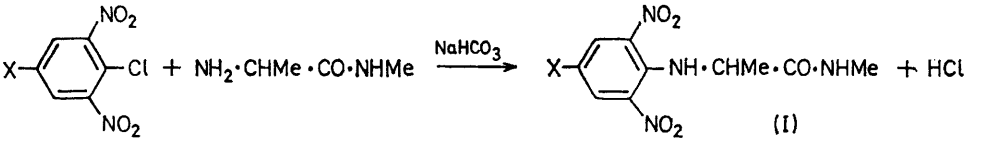
Methyl picryl ether is cleaved by ammonia to give picramide;[4] it was, therefore, of interest to see if compounds of structure (I), which behave like picryl ethers in their reaction with methoxide ion, undergo nucleophilic displacement of the side-chain on treatment with amines.

EXPERIMENTAL

Materials.—Methanol and isopropyl alcohol were heated under reflux over magnesium turnings and fractionally distilled in a nitrogen atmosphere. The purified solvents were stored in nitrogen-blanked burettes.

Amines were heated under reflux over sodium or treated with 4A molecular sieve, and were then fractionally distilled in at atmosphere of nitrogen. Standard solutions of amines in alcoholic solvents were made by weighing the appropriate quantity of amine into a graduated flask and making up to the mark with the alcohol.

Anilinopropionamides were made by warming alcoholic solutions of the appropriate aromatic chlorides with α-alanine *N*-methylamide in the presence of an excess of sodium hydrogen carbonate:

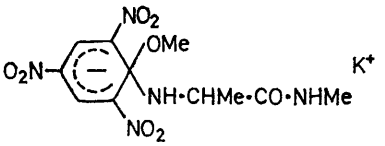


When the reactions were complete, as judged by t.l.c., the solutions were added to a large volume of water and extracted with ether; the ether extracts were dried ($MgSO_4$) and evaporated. The resultant dark solids were chromatographed on silica gel, using methylene chloride–ethanol as eluant. The structures of the pure products were confirmed by elemental analysis and i.r. and n.m.r. spectroscopy. M.p.s were X = NO_2, 172°; X = $MeSO_2$, 223—224°; X = CN, 156°.

Preparation of Solutions for U.v./Visible Spectroscopy and Kinetic Measurements.—Solutions for u.v./visible spectroscopy were made up in a 100-ml two-necked flask. One neck was fitted with a two-way tap for nitrogen ingress, and the other neck could be stoppered when desired. The compound to be investigated was weighed into the vessel, and with passage of nitrogen, an appropriate amount of solvent was added from a burette. After dissolution of the compound the appropriate amount of alcoholic amine solution was added, the contents were mixed, and the solution was quickly transferred to a nitrogen-purged optical cell. The cell was capped and the u.v./visible spectra were measured against a solvent blank using a Unicam SP 800 instrument. Changes in the spectrum in the region 285—667 nm, were recorded at suitable time intervals.

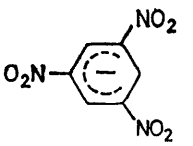
RESULTS AND DISCUSSION

When a solution of 2,4,6-trinitroanilino-*N*-methylpropionamide in methanol ($8{\cdot}6 \times 10^{-4}$ mol l^{-1}; $\lambda_{max.}$ 333 and 400 nm) was treated with a 100-fold excess of piperidine, the spectrum slowly changed to one with maxima at 420 and 500 nm. The final spectrum was identical in appearance to that of the Meisenheimer complex (II) [1] in methanol solution.



(II)

The spectrum showed no sign of secondary changes over a period of days. This observation strongly suggests the formation of a compound having the part structure (III). (It is to be noted that the u.v./visible spectra of Meisenheimer complexes are essentially



(III)

[1] E. Bergman, N. R. McFarlane, and J. J. K. Boulton, *Chem. Comm.*, 1970, 511.

[2] For a recent review, see M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211.

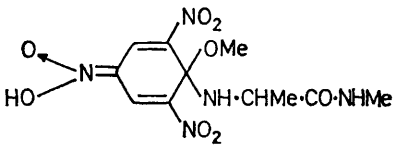
[3] (*a*) M. R. Crampton and V. Gold, *J. Chem. Soc.* (*B*), 1966, 893; (*b*) K. L. Servis, *J. Amer. Chem. Soc.*, 1967, **89**, 1508.

[4] M. R. Crampton, Ph.D. Thesis, University of London.

independent of the nature of the 1-substituents,[5] since the cyclopentadienide structure in which the appropriate electronic transitions occur is insulated from these substituents by a tetrahedral carbon atom.)

Treatment of methanol solutions of the propionamide with morpholine or di-n-propylamine produced similar spectral changes. More significantly, triethylamine reacted with methanolic solutions of the propionamide in a manner similar to the secondary amines; clearly, in this case at least involvement of the solvent (or formation of a zwitterionic Meisenheimer complex) is implicated in the observed reaction.

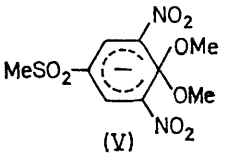
Treatment of the stable products of any of these reactions with methanolic HCl, equivalent to the amine originally used, produced, in all cases, an immediate new spectrum with maxima at 394 and 500 nm. This spectrum decayed in a first-order process ($k = 2{\cdot}65 \times 10^{-4}$ s^{-1} at 25°) to regenerate the spectrum of the propionamide. These observations strongly suggest that the primary product of acid treatment was the neutral Meisenheimer complex (IV).[1]



(IV)

The reactions with amines were, therefore, repeated on a preparative scale, and when reaction was complete, the solutions were cooled to −30° and an equivalent of methanolic HCl was added. Work-up of the resultant solutions as previously described[1] in all cases yielded (IV) as the only product other than the amine hydrochloride. It seems certain that (IV) is produced by simple protonation of the compound arising from the propionamide/methanol/amine reaction; the general reaction with amines may therefore be described by equation (1). The stability of the reaction solutions indicates that displacement of the side-chain is not a significant reaction, and this is confirmed by eventual recovery of the picramide on acidification.

Treatment of methanolic solutions of 4-methylsulphonyl-2,6-dinitroanilino-*N*-methylpropionamide with piperidine produced a spectrum with maxima at 346 and 526 nm, similar in appearance both to the spectrum obtained on treatment of the propionamide with methoxide ion[1] and the spectrum of (V) in methanol.[6]



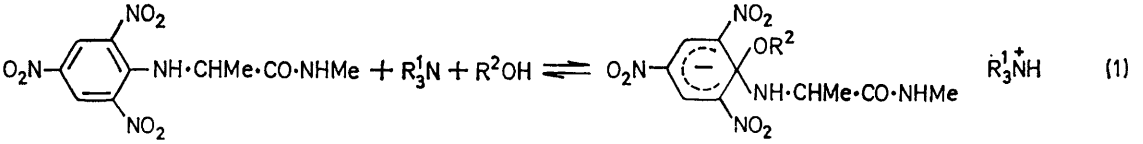
(V)

In a like manner a methanolic solution of 4-cyano-2,6-dinitroanilino-*N*-methylpropionamide gave a spectrum with maxima at 359 and 546 nm on treatment with an excess of piperidine, which was similar to that produced by treating the propionamide with methoxide ion or 4-cyano-2,6-dinitroanisole with methoxide ion.[7]

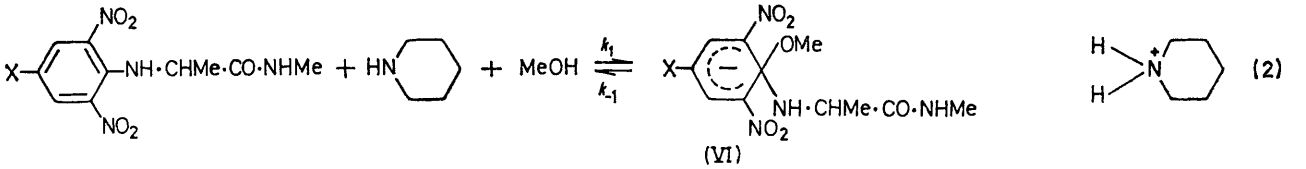
Both the 4-methylsulphonyl- and 4-cyano-anilinopropionamides were regenerated on acidification of the piperidine treated solutions. We assume their reactions with piperidine in methanol to be similar to that of the 4-nitropropionamide.

Kinetic Measurements.—The reaction between the anilinopropionamides and piperidine in methanol may be generalised by equation (2) where X in structures (I) and (VI) may be NO_2, $MeSO_2$, or CN; $k_1 = -\frac{d(I)}{dt}/[I][\text{piperidine}]$ (*i.e.* a pseudo-second-order rate constant); and $k_{-1} = -\frac{d(VI)}{dt}/[(VI)]$.

For all three propionamides, rates of formation of the Meisenheimer complexes (VI) could be followed by mixing methanolic solutions of the propionamides with



(1)



(2)

(VI)

methanolic solutions of piperidine and observing the increase in optical density of the longer wavelength peak of the Meisenheimer complexes. All rate determinations were performed at 25°.

For each compound it was shown that initial rates * of formation of (VI) were first-order, both in piperidine and in propionamide, by holding the concentration of

* Slopes of concn. *vs.* time curves at zero time. Reactions were usually followed to 70—80% conversion.

[5] R. Foster and C. A. Fyfe, *Rev. Pure and Appl. Chem.*, 1966, **16**, 61.

[6] J. J. K. Boulton, unpublished work.

[7] J. E. Dickeson, L. K. Dyall, and V. A. Pickles, *Austral. J. Chem.*, 1968, **21**, 1267.

one reagent constant and varying the concentration of the other.

Typical data, in which the piperidine concentration is held constant and the 4-cyanopropionamide concentration is varied, are shown in Table 1.

Values of k_1 for each compound were then determined from the slopes of initial rate *vs.* [propionamide]^1 [piperidine]^1 plots.

Values of k_{-1} were determined from instantaneous values of d(VI)/dt at various times obtained from extended runs;

$$\left(\frac{d(VI)}{dt}\right)_t = k_1[I]_t\,[\text{piperidine}]_t - (\text{back reaction rate})_t$$

$$(\text{back reaction rate})_t = k_{-1}[VI]_t$$

Values of $[I]_t$, $[\text{piperidine}]_t$, and $[VI]_t$ could all be obtained from the stoicheiometry of the reaction and a knowledge of initial concentrations. Typical data from a single run with the 4-cyanopropionamide are shown in Table 2.

TABLE 1

Variation of initial rate at constant piperidine concentration ($2{\cdot}5 \times 10^{-3}$ mol l^{-1}) *vs.* concentration of 4-cyanopropionamide (25°, methanol)

4-Cyanopropionamide (mol l^{-1} × 10^4)	Initial rate (mol l^{-1} s^{-1} × 10^8)
1·34	2·8
2·54	5·0
3·74	7·2
4·94	9·8
6·7	13·3
7·5	14·0
8·23	15·6

TABLE 2

Analysis of instantaneous rate data * from the reaction of piperidine (initial concentration = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}) and the 4-cyanopropionamide (initial concentration $3{\cdot}74 \times 10^{-4}$ mol l^{-1}) (25°, methanol)

$[VI]_t$ (mol l^{-1} × 10^5)	2	3	4	5
$[I]_t$ (mol l^{-1} × 10^4)	3·54	3·44	3·34	3·24
$[\text{Piperidine}]_t$ (mol l^{-1} × 10^3)	2·48	2·47	2·46	2·45
$k_1[I]_t[\text{piperidine}]_t$ (mol l s^{-1} × 10^8)	6·75	6·54	6·32	6·10
$\left(\frac{d(I)}{dt}\right)_t$ (mol^{-1} l s^{-1} × 10^8)	4·83	3·3	2·16	1·25
Back reaction rate (mol^{-1} l s^{-1} × 10^8)	1·92	3·24	4·16	4·85

* Obtained from measurements of slope of [(VI)] *vs.* time curves at a particular time.

TABLE 3

Values of k_1, k_{-1}, and k_1/k_{-1} for the reactions of the anilinopropionamides with piperidine (25°, methanol)

X in structure (I)	k_1 (mol^{-1} l s^{-1} × 10^2)	k_{-1} (s^{-1} × 10^4)	k_1/k_{-1} (l mol^{-1} × 10^{-1})
NO_2	38·5	4	96·3
C≡N	7·7	10·1	7·63
CH_3SO_2	5·4	9·3	5·8

From the data of Table 2, and that obtained from other runs in a like manner, a plot of (back reaction rate) *vs.* $[VI]_t$ was constructed (Figure); it is a straight line passing through the origin, with slope equal to k_{-1}.

Values of k_1, k_{-1}, and k_1/k_{-1} for the three propionamides are shown in Table 3.

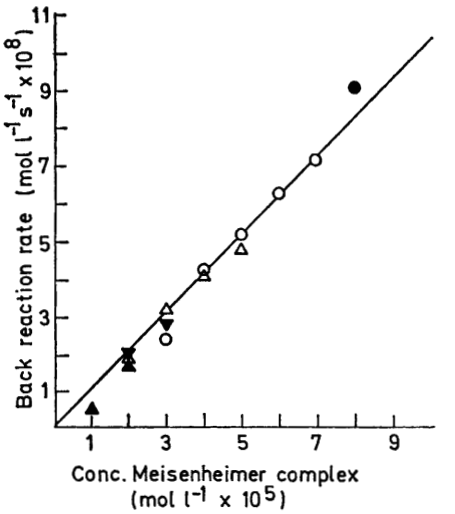
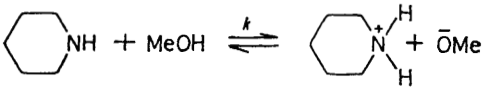
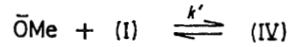


FIGURE Back reaction rate *vs.* $[(VI)]_t$. Data taken from runs for which initial concentrations of reagents are as follows: ○, cyanopropionamide = $4{\cdot}94 \times 10^{-4}$ mol l^{-1}, piperidine = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}; △, cyanopropionamide = $3{\cdot}74 \times 10^{-4}$ mol l^{-1}, piperidine = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}; ▲, cyanopropionamide = $1{\cdot}34 \times 10^{-4}$ mol l^{-1}, piperidine = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}; ●, cyanopropionamide = $6{\cdot}7 \times 10^{-4}$ mol l^{-1}, piperidine = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}; ▼, cyanopropionamide = $2{\cdot}54 \times 10^{-4}$ mol l^{-1}, piperidine = $2{\cdot}5 \times 10^{-3}$ mol l^{-1}

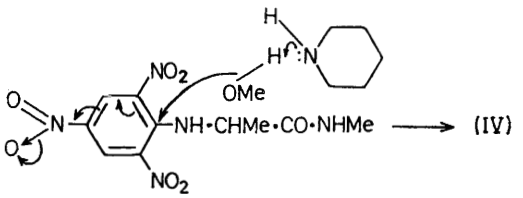
Mechanistically, it seems likely that the observed reactions proceed by one of two schemes shown below:

(i)





(ii) A concerted reaction of the type



It will be observed that the rate of the forward reaction is considerably more sensitive to changes in the *para*-substituent than is the back reaction rate; the transition state for these reactions therefore lies closer to the product than to the initial states. This is in contrast with attack of potassium methoxide on the propionamides [8] and attack of sodium methoxide on 2,6-dinitro-4-X-anisoles,[9] where the transition state lies closer to the initial states than to the product.

If mechanism (i) above obtains, differences in rates

[8] J. J. K. Boulton, P. J. Jewess, and N. R. MacFarlane, *J. Chem. Soc.* (*B*), following paper.

[9] J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, 1969, **34**, 689.

between the anilinopropionamides will be reflections of differences in the rate of the second step of that mechanism. We feel it to be unlikely that the position of the transition state along the reaction co-ordinate will be profoundly affected by the gegenion (piperidinium ion *vs.* alkali metal) and hence prefer mechanism (ii).

[0/1563 *Received, August 10th,* 1970]