Formation of 4,6-Dinitro-2-nitrosoaniline by Intramolecular Redox Reaction of Esters and Amides of 2-(2,4,6-Trinitroaniline) Carboxylic Acids

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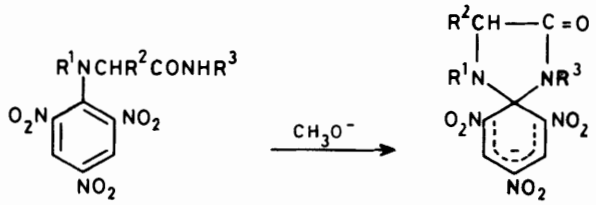
The reaction of methyl and ethyl esters of *N*-(2,4,6-trinitrophenyl)glycine and *N*-(2,4,6-trinitrophenyl)-α-alanine (**3a**—**d**) with methoxide ion in methanol produces 4,6-dinitro-2-nitrosoaniline (**4**). *N*-(2,4,6-Trinitrophenyl)glycine methylamide (**1d**) gives, under the same conditions, the nitroso compound (**4**) in addition to 12% of the spiro adduct (**2d**). A reaction mechanism is suggested, and the influence of the side chain on the reaction kinetics has been studied.

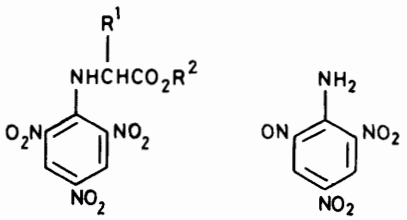
Electron-deficient aromatic compounds with substituents of the type XCR_2CR_2YH (X,Y = O, S, NR) give spiro-Meisenheimer adducts under base catalysis.[1] Amides (**1a**—**c**) react with methoxide ion in methanol to give the spiro adducts (**2a**—**c**).[2,3]



(**1**) (**2**)

a; $R^1 = R^3 = CH_3$; $R^2 = H$
b; $R^1 = CH_3$; $R^2 = R^3 = H$
c; $R^1 = H$; $R^2 = R^3 = CH_3$
d; $R^1 = R^2 = H$; $R^3 = CH_3$

The reaction of the structurally similar amide (**1d**) ($R^1 = R^2 = H$, $R^3 = CH_3$) with methoxide gives only 12% of the corresponding spiro adduct (**2d**). The ^1H n.m.r. spectrum of the main product of this reaction did not contain aliphatic proton absorptions, which means that the reaction involves the splitting off of the $CH_2CONHCH_3$ group. This work is a detailed study of the reaction of the amide (**1d**) with methoxide ion. Also studied were the esters (**3a**—**d**) under these conditions. We presumed that the reaction of the esters (**3**) would lead to the same product as those of amide (**1d**), but that the reaction should not be complicated by the formation of spiro adducts.



(**3**) **a**; $R^1 = H$; $R^2 = CH_3$
b; $R^1 = H$; $R^2 = C_2H_5$
c; $R^1 = CH_3$; $R^2 = CH_3$
d; $R^1 = CH_3$; $R^2 = C_2H_5$

(**4**)

Experimental

The ^1H, ^{13}C, and ^{15}N n.m.r. spectra were measured at 99.602, 25.047, and 10.095 MHz, respectively, on a JNM-FX 100 (JEOL) apparatus. For the measurements the samples were dissolved in hexadeuteriodimethyl sulphoxide or hexadeuteriobenzene. The deuteriated solvents were used as the internal lock. The chemical shifts δ_H are referenced to hexamethyldisiloxane (δ 0.05 in [$^2H_6$]benzene) or to the signal of the solvent (δ 2.55, in [$^2H_6$]Me_2SO). The chemical shifts δ_C are related to the central signal of the multiplet of the solvent (δ 39.6 in [$^2H_6$]Me_2SO, 128.0 in [$^2H_6$]benzene). Chromium(III) trisacetylacetonate (*ca.* 10 mg ml^{-1}) was added to the samples for the measurement of ^{15}N n.m.r. spectra. The chemical shifts, δ_N, are referenced to external nitromethane, negative values denoting an upfield shift.[4]

Mass spectra were measured on a JMS-01 SG-2 (JEOL) spectrometer in the standard way.

Derivatives of 2-(2,4,6-Trinitrophenylamino)carboxylic Acids.—Procedure A. 1-Chloro-2,4,6-trinitrobenzene (2.4 g, 9.7 mmol), $NaHCO_3$ (3 g, 36 mmol), and the hydrochloride of glycine methyl ester or methyl amide or alanine ethyl ester (10 mmol) were stirred in methanol (20 ml) at room temperature for 5 h. The separated solid was collected by suction, mixed with 0.2M-HCl (100 ml), again collected by suction, and washed with water.

Procedure B. Hydrochlorides of glycine ethyl ester or alanine methyl ester (44 mmol) were treated with 1M-sodium methoxide (40 ml; 40 mmol) and shaken 5 min, whereupon the suspension was filtered into a stirred solution of 1-chloro-2,4,6-trinitrobenzene (5 g, 20 mmol) in methanol (20 ml). After 5 min the suspension was cooled in a refrigerator, and the separated solid was collected by suction and washed with water.

N-(2,4,6-*Trinitrophenyl*)*glycine methylamide* (**1d**): procedure A (2.3 g, 79%), m.p. 196—199 °C (decomp.) (from ethyl acetate) (Found: C, 36.0; H, 3.2; N, 23.6. $C_9H_9N_5O_7$ requires C, 36.1; H, 3.0; N, 23.4%); δ_H([$^2H_6$]Me_2SO) 9.81 (br, NH), 9.02 (s, Ar), 8.30 (br q, NH), 3.76 (s, CH_2), and 2.70 (d, CH_3); δ_C([$^2H_6$]Me_2SO) 166.7 (CO), 141.9 (C-1), 136.4 (C-2), 127.2 (C-3), 133.2 (C-4), 47.1 (CH_2), and 25.8 (CH_3).

N-(2,4,6-*Trinitrophenyl*)*glycine methyl ester* (**3a**): procedure A, (2.1 g, 72%), m.p. 127—129 °C (from benzene) (Found: C, 36.1; H, 2.5; N, 18.6. $C_9H_8N_4O_8$ requires C, 36.0; H, 2.7; N, 18.7%); δ_H([$^2H_6$]Me_2SO) 9.40 (br t, NH), 9.03 (s, Ar), 4.05 (d, CH_2), and 3.77 (s, CH_3); δ_C([$^2H_6$]Me_2SO) 169.1 (CO), 142.0 (C-1), 136.7 (C-2), 127.2 (C-3), 133.8 (C-4), 52.8 (CH_3), and 46.8 (CH_2).

N-(2,4,6-*Trinitrophenyl*)*glycine ethyl ester* (**3b**): procedure B,

(4.2 g, 66%), m.p. 90—91 °C (from benzene–cyclohexane) (Found: C, 38.4; H, 3.3; N, 17.6. $C_{10}H_{10}N_4O_8$ requires C, 38.2; H, 3.2; N, 17.8%); $\delta_H([^2H_6]Me_2SO)$ 9.40 (br, NH), 9.03 (s, Ar), 4.24 (q, OCH_2), 4.04 (d, CH_2), and 1.27 (t, CH_3); $\delta_C([^2H_6]Me_2SO)$ 168.4 (CO), 141.9 (C-1), 136.7 (C-2), 127.0 (C-3), 133.9 (C-4), 61.8 (OCH_2), 46.8 (NCH_2), and 13.9 (CH_3).

N-(2,4,6-*Trinitrophenyl*)-α-*alanine methyl ester* (**3c**): procedure B, (4.1 g, 64%), m.p. 54—56 °C (from benzene–cyclohexane) (Found: C, 38.4; H, 3.3; N, 17.6. $C_{10}H_{10}N_4O_8$ requires C, 38.2; H, 3.2; N, 17.8%); $\delta_H([^2H_6]Me_2SO)$ 9.14 (br d, NH), 9.02 (s, Ar), 4.11 (m, CH), 3.76 (s, OCH_3), and 1.49 (d, CH_3); $\delta_C([^2H_6]Me_2SO)$ 171.4 (CO), 141.2 (C-1), 137.4 (C-2), 127.0 (C-3), 134.4 (C-4), 54.2 (CH), 52.9 (OCH_3), and 18.2 (CH_3).

N-(2,4,6-*Trinitrophenyl*)-α-*alanine ethyl ester* (**3d**): procedure A, (2.0 g, 63%), m.p. 91—92 °C (from benzene–cyclohexane) (Found: C, 40.4; H, 3.8; N, 17.3. $C_{11}H_{12}N_4O_8$ requires C, 40.3; H, 3.7; N, 17.1%); $\delta_H([^2H_6]Me_2SO)$ 9.02 (s, Ar), 8.99 (br d, NH), 4.18 (q, OCH_2), 4.09 (m, CH), 1.48 (d, CH_3), and 1.24 (t, CH_3); $\delta_C([^2H_6]Me_2SO)$ 170.8 (CO), 141.2 (C-1), 137.4 (C-2), 127.0 (C-3), 134.4 (C-4), 61.9 (CH_2), 54.2 (CH), 18.2 ($CHCH_3$), and 13.8 (CH_2CH_3).

4,6-*Dinitro*-2-*nitrosoaniline* (**4**).—A solution of *N*-(2,4,6-trinitrophenyl)glycine ethyl ester (6.3 g, 20 mmol) in methanol (200 ml) was stirred, and 1M-sodium methoxide (21 ml; 21 mmol) was added within 15 s. After 30 s, the dark solution was acidified with acetic acid (1.5 ml; *ca.* 26 mmol), and after 30 min, ethyl acetate (200 ml) and water (300 ml) were added. The aqueous layer was extracted twice with ethyl acetate (2 × 150 ml), and the combined extracts were extracted with water (about 100 ml) and dried (Na_2SO_4). The solvent was evaporated to dryness under reduced pressure. Chromatography on silica gel with ethyl acetate–chloroform (3:1) as the eluant yielded the title product (3.2 g, 75%), m.p. 157—163 °C (decomp.) (Found: C, 34.1; H, 2.2; N, 26.7. $C_6H_4N_4O_5$ requires C, 34.0; H, 1.9; N, 26.4%); $\delta_H([^2H_6]Me_2SO)$ 10.53 and 8.97 (br, NH), 9.13 (d, *J* 2.9 Hz, 5-H), and 8.23 (d, 3-H); $\delta_C([^2H_6]Me_2SO)$ 154.5 (C-4), 143.9 (C-1), 135.3 and 133.8 (C-2 and/or C-6), 128.9 (C-5), and 121.8 (C-3); $\delta_N([^2H_6]Me_2SO)$ 473.9 (NO), −14.4 and −14.9 (2 × NO_2), and −293.9 (NH_2) p.p.m.; *m/z* 212 (M^+).

Methyl glyoxylate dimethyl acetal was prepared by the reaction of methyl dichloroacetate with sodium methoxide in methanol:[5] $\delta_H([^2H_6]$benzene) 4.64 (s, CH), 3.42 (s, CO_2CH_3), and 3.18 (s, OCH_3); $\delta_C([^2H_6]$benzene) 167.5 (CO_2CH_3), 99.1 (CH), 53.5 (OCH_3), and 51.7 p.p.m. (CO_2CH_3).

Identification of Methylglyoxylate Hemiacetal.—To a solution of (**3b**) (3.14 g, 10 mmol) in methanol (100 ml) was added 1M-sodium methoxide (10.5 ml; 10.5 mmol) during 15 s. After 30 s, the solution was acidified with acetic acid (0.75 ml; *ca.* 13 mmol), concentrated under reduced pressure to a volume of *ca.* 10 ml, and the separated solid was collected by suction. The filtrate was diluted with benzene (20 ml), and the volume was reduced to about 2 ml under reduced pressure. After the addition of hexadeuteriobenzene, the n.m.r. spectra were measured: $\delta_H([^2H_6]$benzene) 4.96 (s, CH) and 3.83 and 3.52 (2 × s, OCH_3); $\delta_C([^2H_6]$benzene) 170.1 (CO_2CH_3), 93.9 (CH), 54.7 (CH_3OCH), and 52.2 p.p.m. (CO_2CH_3).

Kinetics of the Re-esterification (**3d**) ⟶ (**3c**).—A freshly prepared solution of (**3d**) (50 mg, 0.15 mmol) in methanol (10 ml) was stirred at 25 °C, and 1M-sodium methoxide (0.25 ml; 0.25 mmol) was added thereto. After a time interval Δt (Δt = 10—70 s) the reaction was stopped by the addition of methanolic HCl (0.15 ml; 0.45 mmol). The solution was transferred into a small separating funnel, diluted with water (20 ml), shaken with $NaHCO_3$ (*ca.* 100 mg), and the esters were extracted with benzene (20 ml). The solution was dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in [^{2}H]-chloroform and its ^{1}H n.m.r. spectrum was measured. The ratio of the esters (**3d**) and (**3c**) was determined by integration of the spectrum in the region δ 3.5—5.0. The rate of esterification was determined from the slope of the dependence of log [(**3d**)] on Δt.

Determination of the Amount of the Spiro Adduct (**2d**) *formed in the Reaction of* (**1d**) with CH_3O^-.—A solution of (**1d**) in methanol (*c*, 10^{-4}M; 2 ml) placed in a cell of the spectrophotometer was treated with 0.1M-sodium methoxide (40 μl) and, after 40 min, the spectrum 1 was measured in the region λ 300—600 nm [corresponding to the sum of the spectra of the anion of nitroso compound (**4**) and spiro adduct (**2d**)]. The solution was acidified with methanolic 1M-HCl (20 μl) and, after 40 min, the spectrum 2 of the pure nitroso compound (**4**) was measured (the absorbance at λ 435 nm is A_1 = 0.635). The solution was treated with methanolic 1M-sodium acetate (20 μl), and the spectrum 3 [which corresponds to the sum of the spectra of neutral nitroso compound (**4**) and spiro adduct (**2d**)] was measured. Subtraction of spectrum 2 from 3 gave the spectrum of the spiro adduct with the absorbance A_2 = 0.300 at λ 422 nm. The amounts of the spiro adduct (**2d**) and nitroso compound (**4**) formed in the raction of (**1d**) were calculated from the absorbance coefficients of the pure nitroso compound (**4**) at 435 nm and of the spiro adduct[2] (**2c**) at 422 nm (a = 7.45 × 10^3 and 2.57 × 10^4 l mol^{-1} cm^{-1} respectively).

The reaction kinetics of compounds (**1d**) and (**3a—d**) with methoxide was studied in methanol at 25 °C by means of a Specord UV-VIS spectrophotometer with 1 cm cells. (*a*) A solution of 4-bromophenolate buffer (2 ml; [4-BrC_6H_4ONa] = 0.04M; [4-BrC_6H_4OH]/[4-BrC_6H_4ONa] = 5.5 and 3.0) was placed in the cell of the spectrophotometer, and a solution of (**3a**) or (**3b**) (40 μl; c = 2 × 10^{-3}M) was added, whereupon the absorbance increase was measured at 400 nm.

(*b*) A solution of sodium methoxide (2 ml; c = 1.6 × 10^{-3}—1M) was placed in the cell of the spectrophotometer, and a solution of (**1d**), (**3c**), or (**3d**) was added, whereupon the absorbance increase was measured at 488 or 400 nm, respectively {for (**3c**) and (**3d**) at [CH_3O^-] < 0.02M}.

Estimation of the Equilibrium Constants of the Reaction of (**1d**) *and* (**3c**) *with* CH_3O^-.—A solution of sodium methoxide (1.6 ml; c = 8 × 10^{-4}—0.5M) was placed in the cell of the spectrophotometer and a solution of (**1d**) or (**3c**) (0.4 ml; c = 4 × 10^{-4}M) was injected therein, and the absorbance was measured at 445 nm for 60 s. The equilibrium constants were calculated from the absorbance values extrapolated to zero time.

Results and Discussion

Addition of 0.1M-sodium methoxide (20 μl) to a methanolic solution of the ester (**3a**) (2 ml; c = 6 × 10^{-5}M) results in the formation of a compound (with a half-life of several seconds) which exhibits a sharp band in visible spectrum ($\lambda_{max.}$ 390 nm).

Acidification of this solution with 0.5M-acetic acid or HCl (20 μl) causes a rapid change in the spectrum followed by a further much slower change to the spectrum of a compound with $\lambda_{max.}$ 435 nm (Figure 1). The reaction is complete within about 40 min. The esters (**3c**) and (**3d**) react similarly, but the reaction with methoxide is slower by *ca.* 2—3 orders of magnitude.

The electronic spectra of the product (**4**) prepared on a preparative scale (see the Experimental section) from the ester (**3b**) have, in both neutral and methoxide medium, the same shape as the spectra 2 and 1 in Figure 1. The ^{1}H n.m.r. spectrum of this product exhibits two doublets of the same intensity due to protons at sp^2 carbons (*J* 2.9 Hz), which indicates the

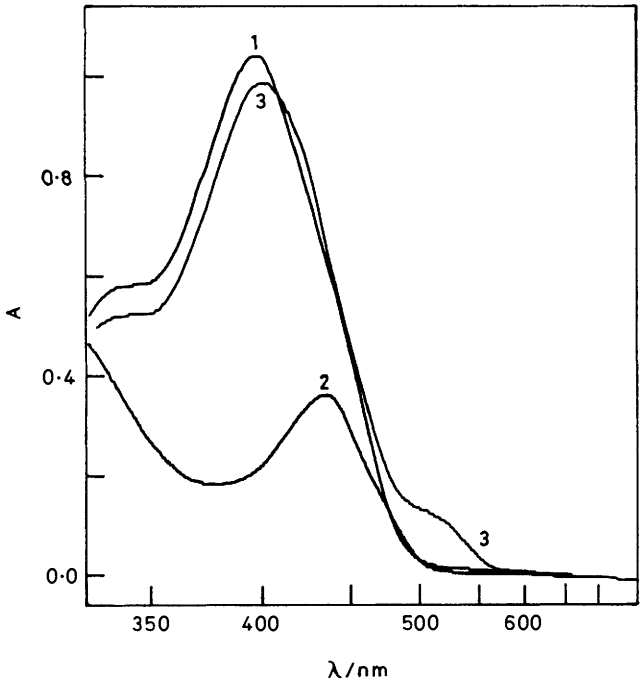


Figure 1. Electronic spectra of compound (**4**) (6×10^{-5} mol l^{-1}) in methoxide solution (10^{-3} mol l^{-1}) (spectrum 1) and in acetate buffer (spectrum 2). Electronic spectrum of a mixture of compounds (**4**) and (**2d**) formed from the amide (**1d**) (6×10^{-5} mol l^{-1}) in methoxide solution (10^{-3} mol l^{-1}) (spectrum 3)

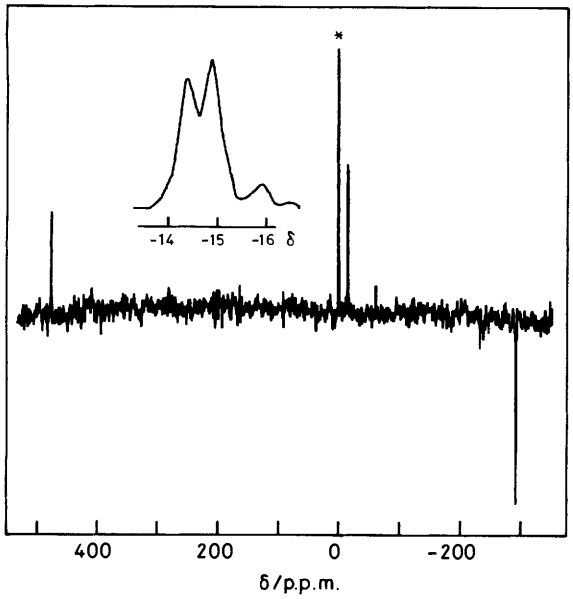


Figure 2. ^{15}N N.m.r. spectrum of compound (**4**) in $[^2H_6]Me_2SO$. The signal marked with an asterisk is due to the external nitromethane reference

presence of two different protons in the *meta* position. The absorption of two acidic protons (δ 10.53 and 8.97 at 25 °C) can be assigned to the amino group. The two signals coalesce at about 60 °C. The ^{13}C n.m.r. spectrum exhibits only six signals for the carbon atoms of the benzene ring, four of them assignable to quaternary carbon atoms and two to CH groups. In the ^{15}N n.m.r. spectrum (Figure 2), the two signals due to the nitro groups (δ −14.4 and −14.9 p.p.m.) were found with

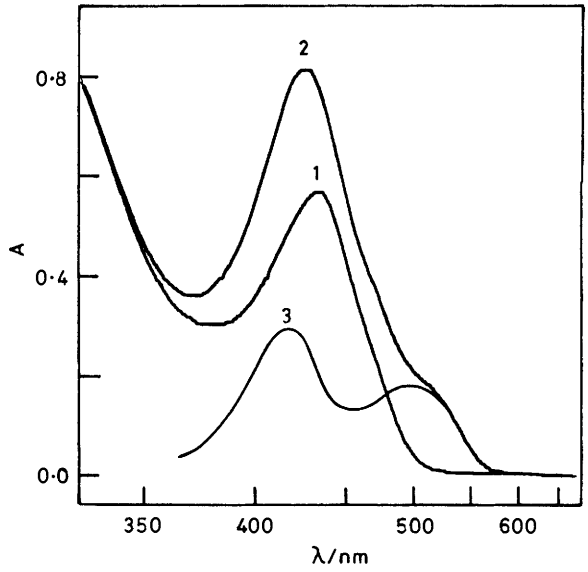
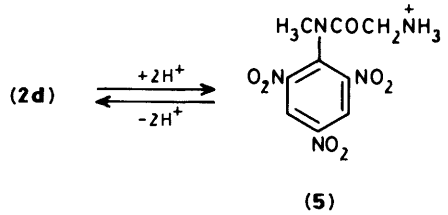


Figure 3. Electronic spectrum of (1) a mixture of compounds (**4**) and (**5**) in methanolic HCl, (2) a mixture of compounds (**4**) and (**2d**) in acetate buffer, and (3) the difference between the two spectra.

chemical shifts close to those of nitrogen atoms of nitro groups in 2,4,6-trinitroaniline[6] [δ_N −14.4 (N-2) and −16.8 (N-4)]. The signal with negative amplitude (due to negative gyromagnetic moment of ^{15}N nucleus and nuclear Overhauser effect; δ −293.9 p.p.m.) belongs to the amino group (in 2,4,6-trinitroaniline[6] the NH_2 group has δ_N −286.4 p.p.m.). The chemical shift δ_N 473.9 p.p.m. is typical[7] of a nitroso group. The ^1H, ^{13}C, and ^{15}N chemical shifts given above, as well as the observed M^+ 212, indicate that the compound synthesized is 4,6-dinitro-2-nitrosoaniline (**4**). Comparison of the electronic spectra of the solution of the prepared pure (**4**) and of that of (**4**) prepared by the reaction of methoxide with ester (**3b**) ($c = 6 \times 10^{-5}$M) shows that (**4**) is formed in the yield of 98 ± 2%.

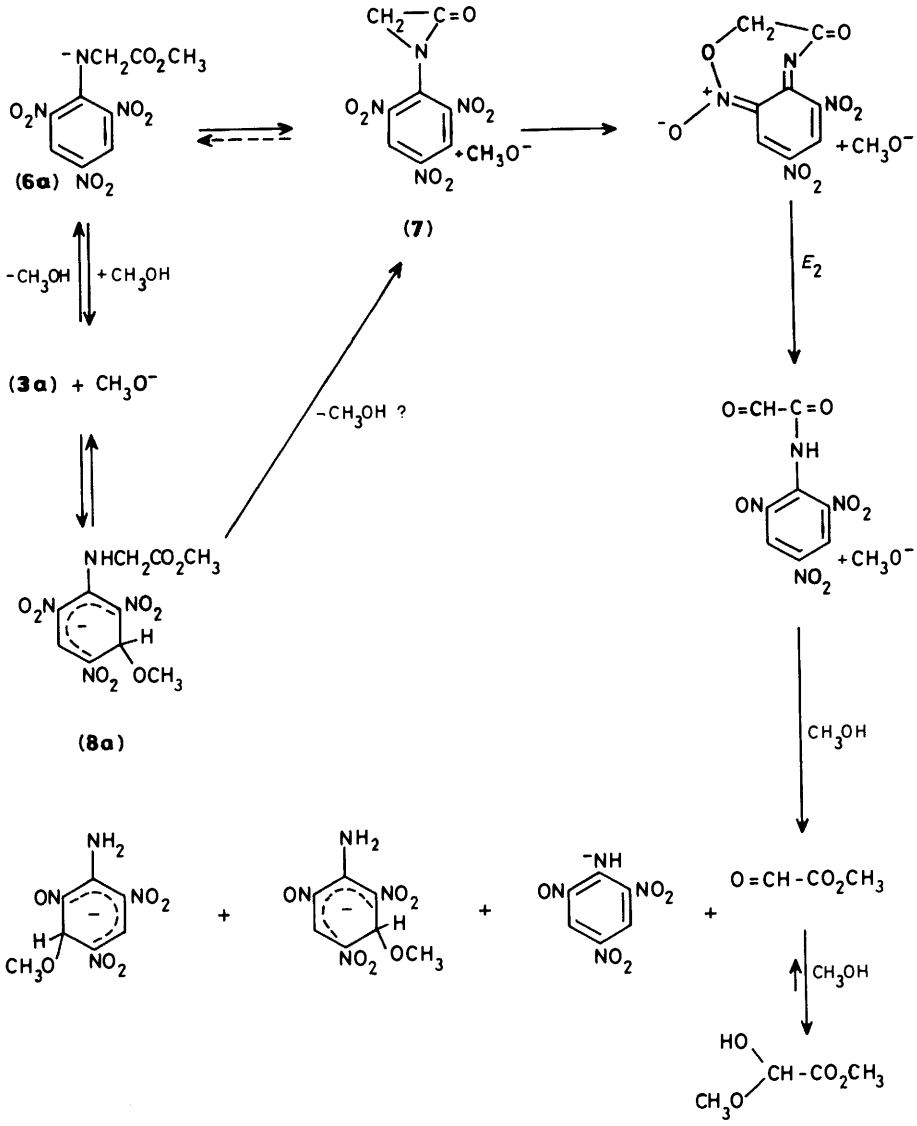
The reaction of amide (**1d**) with methanolic methoxide again gives the anion of nitroso compound (**4**) as the main product (Figure 1, spectrum 3) besides the spiro adduct (**2d**). Acidification of the mixture of these compounds with HCl causes ring opening of the spiro adduct and formation of compound (**5**) (Scheme 1), which does not absorb in visible region,[1-3] and the



Scheme 1.

neutral nitroso compound (Figure 3, spectrum 1). Addition of sodium acetate results in rapid cyclization of compound (**5**) into the spiro adduct (**2d**) (Figure 3, spectrum 2). Subtraction of spectrum 1 from 2 gives a typical spectrum of the spiro adduct (Figure 3, spectrum 3). If the absorbance coefficients of the spiro adducts (**2c**) and (**2d**) are presumed to have the same values, then the reaction of amide (**1d**) with methanolic methoxide produces spiro adduct (**2d**) (12 ± 2%) and the nitroso compound (**4**) (86 ± 2%).

A mechanism of formation of nitroso compound (**4**) from the



Scheme 2.

ester (**3a**) is suggested in Scheme 2. The individual reaction intermediates can undergo proton transfer and addition of methoxide ion to the aromatic ring.

The key aziridinone intermediate (**7**) is probably formed by an attack of the negatively charged nitrogen of anion (**6**) on the carbonyl carbon atom. However, this intermediate may also be formed by attack on the carbonyl by a neutral nitrogen atom whose nucleophilicity is strongly increased by the addition of methoxide ion [adduct (**8**)].

The other reaction product is methyl glyoxylate hemiacetal, which was isolated by the procedure given in the Experimental section and identified by means of ^1H and ^{13}C n.m.r. spectroscopy and by comparison with the spectra of methyl glyoxylate dimethyl acetal. The relation between δ_C of CH groups of the hemiacetal and acetal of methyl glyoxylate (δ_C 93.9 and 99.1 respectively) is similar to that between the CH_2 groups of formaldehyde hemiacetal and acetal (δ_C 89.6 and 96.6[8,9]).

The formation of an oxime and an aldehyde during the splitting of the alkyl nitronates formed by intermolecular alkylation of $=NO_2^-$ group of the Meisenheimer adducts has already been described.[10,11]

The kinetics of the reaction of amide (**1d**) and the esters (**3c**) and (**3d**) with methoxide ion were studied in solution with sodium methoxide. The reactions of esters (**3a**) and (**3b**) were found to be too fast in this medium, therefore their reaction was studied in methanolic 4-bromophenol–sodium 4-bromophenoxide buffer. In all cases the reaction obeyed simple pseudo-first-order kinetics, the only exception being the reaction of the amide (**1d**) at $[CH_3O^-] > 0.5$M. The rate constants for the reactions of (**3a**) and (**3b**) in bromophenolate buffer (5:1) are $k = 2.7 \times 10^{-2}$ and 2.2×10^{-2} s^{-1}, respectively, and in bromophenolate buffer (3:1), $k = 4.6 \times 10^{-2}$ and 3.65×10^{-2} s^{-1}, respectively. The rate constant ratio of the esters (**3a**) and (**3b**) is 1.24 ± 0.04.

In Figure 4, the logarithm of the experimental rate constant ($\log k_{obs.}$) of the reaction of amide (**1d**) (curve 1) and ester (**3c**) (curve 2) with methoxide ion is plotted against $\log [CH_3O^-]$. The ethyl ester (**3d**) and methyl ester (**3c**) do not differ (within experimental error) in their reaction rates under the same experimental conditions. The data given and the dependences shown in Figure 4 allow the following conclusions to be made: the amide (**1d**) reacts by 2 orders more slowly than the esters (**3a**) and (**3b**), which means that the reaction rate of amide (**1d**) is limited by the attack of nitrogen on the carbonyl carbon. The

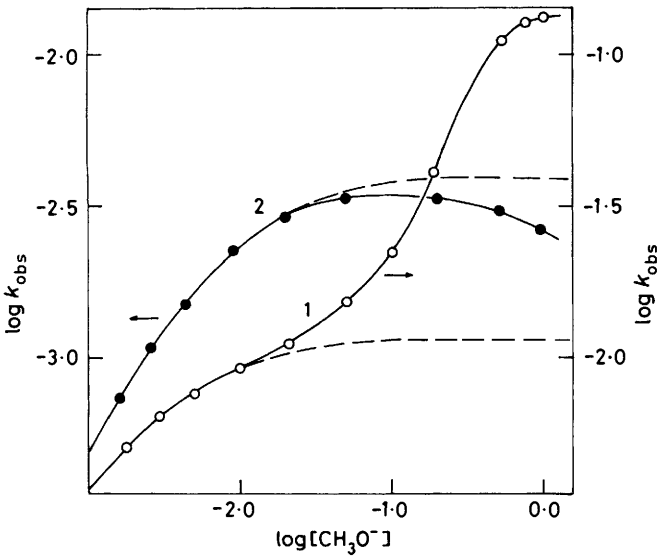


Figure 4. Dependence of log $k_{obs.}$ of the reaction of (1) the amide (**1d**) and (2) the ester (**3c**) with methoxide ion on log [CH_3O^-]

same step must be rate-limiting for esters (**3a**) and (**3b**). If the formation of the intermediate (**7**) were a pre-equilibrium of the rate-limiting step, a rapid re-esterification of (**3b**) to (**3a**) would take place and the rate constants would be the same for the two esters.

The esters (**3c**) and (**3d**) react at the same speed and by more than 2 orders more slowly than the esters (**3a**) and (**3b**). The re-esterification of ester (**3d**) to (**3c**), as followed by the ^1H n.m.r. spectra, is about one order faster than the formation of nitroso compound (**4**) (for the re-esterification $k = 2.4 \times 10^{-2}$ s^{-1}). This fact could indicate that the rate-limiting step, in this case, consists of an attack of the nitro group oxygen on the aziridinone carbonyl in the intermediate (**7**), the substitution of the hydrogen atom of the methylene group in this intermediate by a methyl group considerably disfavouring this attack.[12]

These conclusions also agree with the differences in the dependences of log $k_{obs.}$ on log [CH_3O^-] (Figure 4). At methoxide concentrations below about 0.02M the reaction mixture contains the starting compounds (**1d**) and (**3c**) in an equilibrium with their conjugate bases and monoadducts with methoxide. Analogous reactions proceed with *N*-alkylpicramides at higher methoxide concentrations.[13] The concentration ratio of conjuaged bases to adducts was determined by the stopped-flow method.[13] At higher methoxide concentration greater amounts of diadducts and anion adducts are formed, as with *N*-alkylpicramides. The rate constants $k_{obs.}$ of products formation are proportional to the concentration of negatively charged particles [conjugate base + adduct (equation (1)].

$$k_{obs.} = k_T \frac{K_T[CH_3O^-]}{K_T[CH_3O^-] + 1} \quad (1)$$

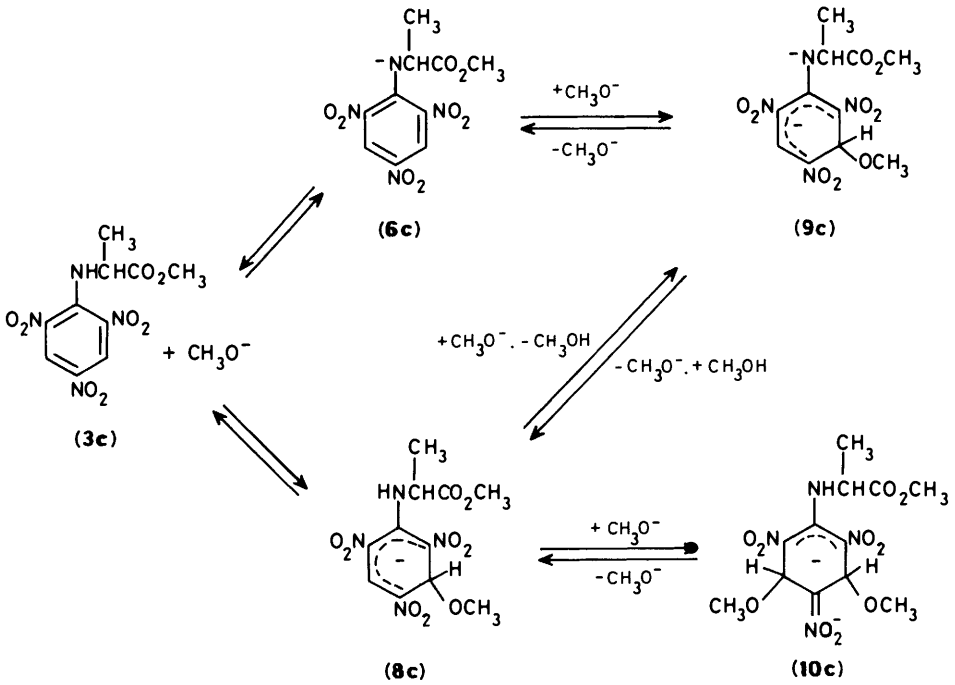
The term K_T refers to the overall equilibrium constant of the reaction of the substrate with methoxide to give (**6c**) and (**8c**) [in the case of ester (**3c**)], defined by equation (2), and k_T is the

$$K_T = \frac{[(6c)] + [(8c)]}{[(3c)][CH_3O^-]} \quad (2)$$

overall rate constant for the transformation of compounds (**6c**) and (**8c**) into the nitroso compound (**4**) (Scheme 3). Similar relationships are also true for the amide (**1d**); however, in this case the rate constant $k_{obs.}$ is a sum of the rate constants for the formation of the nitroso compound (**4**) and spiro adduct (**2d**). The quilibrium constants K_T for (**1d**) and (**3d**) were determined spectrophotometrically according to equation (3), where A_{SH}

$$K_T = (A_{exp.} - A_{SH})/(A_{S^-} - A_{exp.}) \quad (3)$$

is the absorbance of the substrate (**1d**) or (**3c**), A_{S^-} is the absorbance of the mixture (**6c**) + (**8c**) [in the case of ester (**3c**)] or of the corresponding anions [in the case of amide (**1d**)]. At the wavelength used (445 nm), the equilibrium mixture of the anion and adduct showed the same absorbance coefficient as the



Scheme 3.

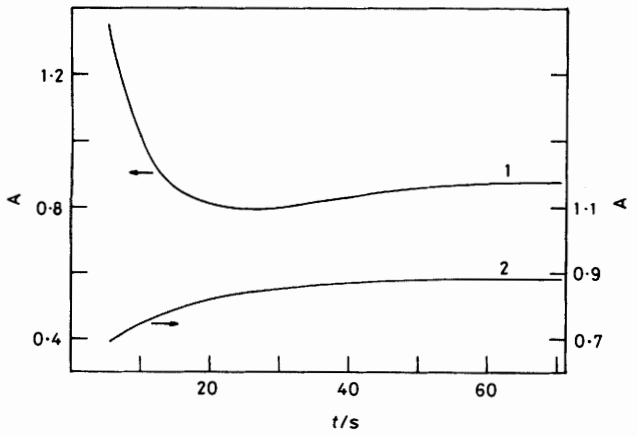


Figure 5. Changes in absorbance with time of the reaction of the amide (**1d**) (curve 1) and the nitroso compound (**4**) (curve 2) with sodium methoxide (1 mol l^{-1}).

anion adduct and diadduct. The ester (**3c**) reacts with methoxide ion to give substantial amounts of the anion adduct (**9c**) and the diadduct (**10c**) (Scheme 3) at methoxide concentrations at which the free ester (**3c**) is also present. Therefore, the measured K_T values had to be corrected with respect to the presence of (**9c**) and (**10c**). At the highest methoxide concentration used (0.08M), the correction was 18% of the K_T value. The equilibrium constants K_T have the values of 145 ± 5 l mol^{-1} and 500 ± 30 l mol^{-1} for the ester (**3c**) and the amide (**1d**), respectively. The values are much higher than those of *N*-alkylpicramides[13] due to the electron-attracting effect of amide and ester group respectively. The dominant interaction in these cases is probably proton transfer from the amino group. The rate constants k_T calculated from equation (1) with application of the K_T values are (4.0 ± 0.2) × 10^{-3} l mol^{-1} s^{-1} and (1.10 ± 0.05) × 10^{-2} l mol^{-1} s^{-1} for the ester (**3c**) and amide (**1d**), respectively.

At higher methoxide concentrations, formation of anion and diadducts is increasingly significant (Scheme 3).

From the absorbances of the reaction mixtures of the ester (**3c**) in methoxide solutions (at λ 488 nm) extrapolated to zero time it could be assessed that, at [CH_3O^-] 0.05, 0.2, and 0.5M, about 10, 40, and 80% substrate, respectively, is transformed into compounds carrying two negative charges. Formation of these dianions increases the nucleophilicity of the nitrogen atom, which [in the case of amide (**1d**)] results in an acceleration of the reaction roughly proportional to the concentration of these particles. On the other hand, the reaction of ester (**3c**) is slightly retarded (Figure 4), because the rate-limiting step is the subsequent step—the attack on aziridinone carbon in (**7**) by the oxygen atom of the nitro group.

At methoxide concentrations of 0.75M and 1M, the reaction of the amide (**1d**) with CH_3O^- proceeded as a typical stepwise reaction. The half-life of the slower, second reaction was $t_{\frac{1}{2}}$ 11 s in 1M-CH_3ONa (Figure 5, curve 1). The given reaction course could be due either to accumulation of some of the intermediates in the reaction mixture at high methoxide concentration or to the equilibrium established relatively slowly between the adducts, diadducts, and anion adducts of the reaction product (**4**). The absorbance of a solution of the nitroso compound (**4**) of the same concentration as that of the substrate in the above described experiment (1M-CH_3ONa) is changed with practically the same half-life (Figure 5, curve 2), which confirms that the same reaction is observed in the two cases [*viz.* the establishing of an equilibrium between the products of the reaction of the nitroso compound (**4**) with methoxide].

The amide (**1d**) gives only 12% of the spiro adduct (**2d**) in the reaction with methanolic methoxide, the rest being the nitroso compound (**4**). The amide (**1c**), which differs from (**1d**) by a methyl group, gives quantitative yields of the spiro adduct (**2c**) under the same conditions.[2] The rate constant of formation of the spiro adduct (**2d**) from amide (**1d**) is $k = 0.12 \times 1.1 \times 10^{-2} = 1.3 \times 10^{-3}$ s^{-1}; the corresponding rate constant[2] of formation of spiro adduct (**2c**) is 2.5 × 10^{-2} s^{-1}. This means that replacement of a hydrogen in CH_2 group by a methyl group speeds up the cyclization by a factor of *ca.* 20. The effect of the methyl group on the rate of formation of the aziridinone ring (Scheme 2) can be assessed from the rate of re-esterification of (**3d**) to (**3c**) and rate of formation of the nitroso compound from the ester (**3a**), where the formation of the intermediate (**7**) is also rate-limiting. The rate of formation of (**4**) from the ester (**3a**) was measured in 4-bromophenolate buffer only. It can be estimated that the methyl group retards the attack on the carbonyl carbon by almost 2 orders. Therefore, it follows that in the case of the amide (**1c**), the rate of formation of the nitroso compound is *ca.* 2 orders lower than that of formation of the spiro adduct (**2c**).

It was impossible to prepare the nitroso compound (**4**) from the ester (**3c**) on a preparative scale {[(**3c**)] ~ 5 × 10^{-2}M}, and formation of methyl pyruvate could not be proved by ^1H n.m.r. spectroscopy. On the other hand, at spectroscopic concentrations {[(**3c**)] ~ 5 × 10^{-5}M} the nitroso compound (**4**) is formed from both esters (**3c**) and (**3d**) practially quantitatively. The amount of the nitroso compound (**4**) in the reaction products (as followed spectrophotometrically) rapidly decreases with increasing concentration of the ester (**3c**). Obviously, subsequent reactions take place between the products, products and starting compounds, or products and some intermediates. In the reactions of the amide (**1d**) and esters (**3a**) and (**3b**), to give (**4**) and methyl glyoxylate hemiacetal, these subsequent reactions take place to a small extent even on a preparative scale. It was therefore supposed that the subsequent reactions of the esters (**3c**) and (**3d**) involved methyl pyruvate which is the second reaction product. The reactions of compounds (**3c**) and (**4**) ($c = 5 \times 10^{-5}$M) with methyl pyruvate ($c = 10^{-3}$—5×10^{-2}M) were studied spectroscopically in the presence of methoxide in methanol, and it was found that (*i*) pyruvate reacts rapidly with compound (**4**) and still faster with the ester (**3c**) or with some intermediate leading to compound (**4**), (*ii*) at pyruvate concentration *ca.* 3 × 10^{-3}M, the reaction with (**3c**) is faster than the transformation of (**3c**) to (**4**) under the same conditions. Therefore, it was impossible to prove the formation of methyl pyruvate by ^1H n.m.r. spectroscopy, and the nitroso compound could not be isolated from the products either. Methyl glyoxylate also caused side reactions, but to a small extent only, the reason being that methyl glyoxylate is present in the reaction mixture almost exclusively as the non-reactive hemiacetal, whereas methyl pyruvate is present to a considerable extent (the equilibrium constants of formation of the hydrates in water being 300 for glyoxylic acid[14] and 2.6 for ethyl pyruvate[15]).

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