FORMATION OF THE MEISENHEIMER SPIRO ADDUCT OF N-(2,4,6-TRINITROPHENYL)ALANINE METHYLAMIDE AND ITS REARRANGEMENT TO 2-AMINO-N-METHYL-N-(2,4,6-TRINITROPHENYL)PROPANAMIDE

Vladimír MACHÁČEK[a], Makky M. M. HASSANIEN[a], Vojeslav ŠTĚRBA[a] and Antonín LYČKA[b]

[a] *Department of Organic Chemistry, Institute of Chemical Technology, 532 10 Pardubice and*
[b] *Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví*

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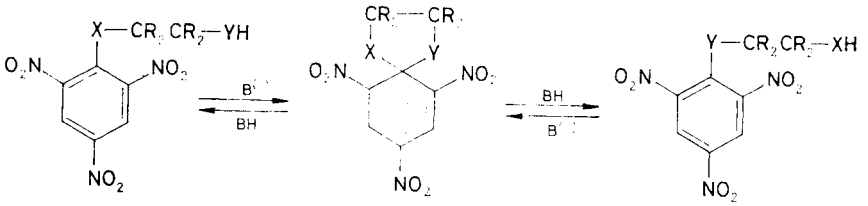
N-(2,4,6-trinitrophenyl)alanine methylamide (*I*) undergoes base-catalyzed cyclization in methanol to give the spiro adduct *II*. In aniline–anilinium chloride buffers, the spiro adduct is protonated at the oxygen atom of 2-nitro group to give the neutral compound *III*. In 4-bromoaniline buffers or by action of methanolic hydrogen chloride, the compound *III* is opened to *E* and *Z* isomers of 2-amino-N-methyl-N-(2,4,6-trinitrophenyl)propanamide hydrochloride (*IV*). The rate-limiting step of cyclization of compound *Z*—*IV* to compound *III* consists in the isomerization *Z*—*IV* → *E*—*IV*. At higher pH values (acetate buffers), the rate-limiting step is gradually changed to the isomerization of 2-amino-N-methyl-N-(2,4,6-trinitrophenyl)propanamide (*Z*—*V* → *E*—*V*).

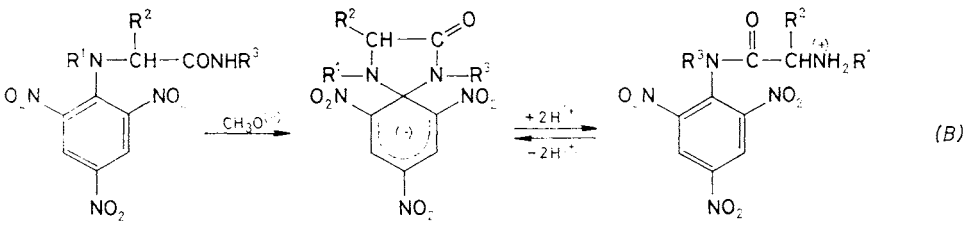
The compounds type *VI* having the benzene nucleus activated with one or several strongly electron-attracting groups at the alternating positions undergo the base-catalyzed Smiles rearrangement (*A*). The rearrangement intermediates are spiro compounds *VII* of the type of the Meisenheimer adducts. Their stability is increased with increasing number and electron-acceptor ability of the substituents in the ring[1]. Literature presents a large number of kinetic studies of the Smiles rearrangement for X = O, S, NR, and Y = OH, SH, NHR (for a review see ref.[1]).



VI *VII* (*A*)

We studied[2] the reaction of N-methyl-N-(2,4,6-trinitrophenyl)glycine methylamide *I* with sodium methoxide and found it to produce the spiro adduct whose structure

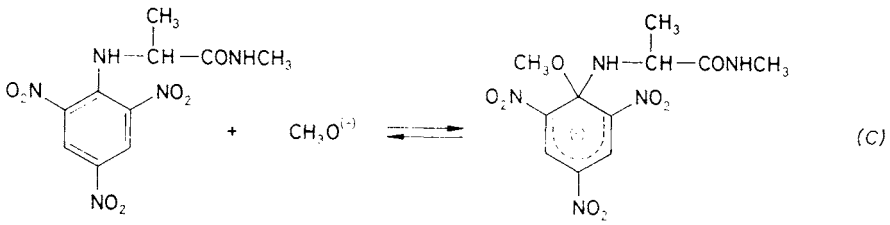
was confirmed by ^1H and ^{13}C NMR spectra and elemental analysis. In acid media the spiro adduct is opened[2] to give the salt of 2-methylamino-N-(2,4,6-trinitrophenyl)-acetamide ((*B*), $R^1 = R^3 = CH_3$, $R^2 = H$).



(B)

I, $R^1 = H$; $R^2 = R^3 = CH_3$ *II*, $R^1 = H$; $R^2 = R^3 = CH_3$ *IV*, $R^1 = H$; $R^2 = R^3 = CH_3$

On the contrary, Boulton states[3-5] that the compound *I* ($R^2 = R^3 = CH_3$, $R^1 = H$) adds the methoxide ion at 1-position of the 2,4,6-trinitrophenyl group (*C*).



(C)

I

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured at 99·602 and 25·047 MHz, resp., using a JNM FX-100 (JEOL) spectrophotometer. For the measurements used were 10–20% solutions of the compounds in hexadeuteriodimethyl sulphoxide and tetradeuteriomethanol, resp. The $\delta(^{13}C)$ chemical shifts are related to the central peak of the multiplet of hexadeuteriodimethyl sulphoxide (δ 39·60) and tetradeuteriomethanol (δ 49·00), resp., the $\delta(^1H)$ chemical shifts are related to hexamethyldisiloxane (δ 0·05).

N-(2,4,6-*Trinitrophenyl)alanine methylamide* (I): 1·4 g (10 mmol) alanine methylamide hydrochloride[6], 2·4 g (9·7 mmol) 1-chloro-2,4,6-trinitrobenzene, and 3 g (36 mmol) $NaHCO_3$ in 20 ml methanol was stirred at room temperature 5 h. The separated solid was collected by suction, mixed with 100 ml 0·2 mol l^{-1} HCl, again collected by suction, and washed with water. Yield 2·3 g (76%), m.p. 170–172°C (ethyl acetate) (ref.[4] m.p. 172°C). ^1H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CHNH) 9·72 (broadened doublet, J = 7·4 Hz); δ(Pi) 9·02 (singlet); $\delta(NHCH_3)$ 8·41 (broadened quartet); δ(CH) 4·05 (multiplet); $\delta(NHCH_3)$ 2·69 (doublet, J = = 4·8 Hz); $\delta(CHCH_3)$ 1·30 (doublet, J = 6·9 Hz). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CO) 170·36; δ_i 140·58; δ_o 137·03; δ_m 127·23; δ_p 133·71; δ(CH) 53·34; $\delta(NCH_3)$ 25·90; $\delta(CCH_3)$ 19·42.

Spiro adduct II: 5 ml 1 mol l^{-1} sodium methoxide (5 mmol) was added drop by drop to a suspension of 1·56 g (5 mmol) compound *I* in 10 ml methanol with stirring. After about 10 min, the product was precipitated by addition of dry ether, collected by suction under argon, and dried by passing dry argon therethrough and subsequent drying in vacuum (300 Pa) at room temperature. Yield 1·3 g (78%). The substance is slowly decomposed on heating at 150°C. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(Ar) 8·58 and 8·49 (AB quartet, J_{AB} = = 2·9 Hz); δ(NH) 4·07 (doublet, J = 7·3 Hz); δ(CH) 3·74 (multiplet); δ(NCH_3) 2·46 (singlet); δ ($CHCH_3$) 1·17 (doublet, J = 6·8 Hz); δ(CH_3OH) 3·21 (singlet). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CO) 174·57; δ_1 78·56; $\delta_{2,6}$ 132·44 and 130·51; $\delta_{3,5}$ 127·41 and 126·65; δ_4 118·05; δ(CH) 55·75; δ(NCH_3) 25·62; δ(CCH_3) 17·02; δ(CH_3OH) 48·96. A sample of compound *II* was dissolved in 5 ml tetrahydrofurane, filtered with charcoal, precipitated by addition of dry ether, and dried in the above-mentioned way. The ^{1}H NMR spectrum lacks the signal with δ 3·21 (CH_3OH) and contains additional multiplets of the tetrahydrofurane protons (δ 1·77 and 3·62). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CO) 174·41; δ_1 78·44; $\delta_{2,6}$ 132·40 and 130·45; $\delta_{3,5}$ 127·28 and 126·50; δ_4 117·92; δ(CH) 55·58; δ(NCH_3) 25·52; δ(CCH_3) 16·94.

2-*Amino*-N-*methyl*-N-(2,4,6-*trinitrophenyl*)*propanamide hydrochloride* (IV): 3·13 g (10 mmol) compound *I* was suspended in 20 ml ethanol, and 10·5 ml 1 mol l^{-1} sodium ethoxide (10·5 mmol) was added thereto drop by drop. After 15 min, methanolic 4·4 mol l^{-1} hydrogen chloride was added dropwise to the solution of compound *II* until decolourization. The separated NaCl was filtered off after addition of charcoal. The solution of compound *IV* was concentrated in vacuum to one third of its original volume. The raw compound *IV* was precipitated by addition of dry ether. The solid was collected by suction and dissolved in a minimum volume of ethanol with a drop of methanolic hydrogen chloride, then it was filtered with charcoal, and again precipitated with ether. The crystals were collected by suction and dried in vacuum at room temperature. Yield 2·7 g (77%). The compound is gradually cyclized on heating at 100°C. ^{1}H NMR spectrum (tetradeuteriomethanol + one drop of trifluoroacetic acid): δ(Pi) 9·13 (9·23) (two singlets); δ(NCH_3) 3·47 (3·18) (two singlets); δ(CH) 4·65 (4·05) (two quartets, J = 6·8 Hz); δ (CH_3) 1·57 (1·22) (two doublets). The values in brackets denote chemical shifts of the protons of the less populated *E*—*IV* isomer. ^{13}C NMR spectrum (tetradeuteriomethanol + one drop of trifluoroacetic acid): δ(CO) 172·09; δ_1 148·28; $\delta_{2,6}$ 149·16 and 149·28; $\delta_{3,5}$ 125·87 and 125·75; δ_4 135·58; δ(CH) 48·41; δ(NCH_3) 38·35; δ(CCH_3) 15·83 (only given are the signals of the predominating *Z*—*IV* isomer).

Electronic spectra of compounds I—IV. 2 ml methanol was placed into a cell (d = 10 mm), whereupon 0·1 ml methanolic solution of compound *I* ($c = 10^{-3}$ mol l^{-1}) was added, and the spectrum was measured in the region of 330 to 630 nm. Then 20 µl 0·1 mol l^{-1} sodium methoxide was added, and after 10 min the spectrum of compound *II* was measured. After addition of 20 µl 0·2 mol l^{-1} methanolic HCl and after 2 min, the spectrum of compound *IV* was measured (Fig. 1).

The kinetic and equilibrium measurements were carried out in methanolic solutions at 25°C using a Specord UV VIS (Zeiss) spectrophotometer. For the measurement of the reaction rate *I* → *II* we prepared 1·9 ml sodium methoxide solution ($c = 7 . 10^{-4}$ to $2{\cdot}5 . 10^{-1}$ mol l^{-1}), added 0·1 ml methanolic solution of compound *I* ($c = 10^{-3}$ mol l^{-1}), and measured the absorbance increase at 500 nm. The kinetics of reversible reaction *III* ⇌ *IV* was measured in the following way: 1·6 ml methanolic solution of compound *II* or *IV* was placed in a cell (d = 10 mm), 0·4 ml methanolic buffer solution 4-bromoaniline–4-bromoanilinium chloride was added thereto (the final ionic strength 0·04 mol l^{-1}), and the absorbance was measured at 500 nm. In order to estimate the absorbance of the compound *III* itself, the solution of 1·6 ml compound *II* was

treated with 0·4 ml methanol (the *II* and *III* compounds have the same absorbance coefficients at 500 nm). The buffers were prepared by mixing methanolic solutions of 4-bromoaniline and 4-bromoanilinium chloride ($c = 1$ mol l^{-1}) at various ratios and adding methanol to make the final volume correspond to resultant hydrochloride concentration of 0·2 mol l^{-1}. The solution of compound *II* was prepared by mixing 1 ml methanolic solution of *I* ($c = 1{\cdot}6 \cdot 10^{-3}$ mol l^{-1}), 20 μl sodium methoxide (1 mol l^{-1}), and adjusting the volume to 20 ml by addition of methanol after 5 min. The solution of compound *IV* was prepared immediately before starting the kinetic runs: 30 μl methanolic HCl (1 mol l^{-1}) was added to 21 ml solution of compound *II* prepared in the above-described way. The solution prepared in this way was used for one hour at the most.

Isomerization kinetics. To 1·6 ml solution of compound *IV* prepared as above, 0·4 ml methanolic acetate buffer (the buffers were prepared in similar way as the 4-bromoaniline–4-bromoanilinium chloride buffers, the final acetate concentration being 0·2 mol l^{-1}) or 0·4 ml sodium methoxide (0·04 to 0·2 mol l^{-1}) was added, and the absorbance was measured at 500 nm.

Study of equilibrium II ⇌ III. 1·6 ml solution of compound *II* ($c = 6 \cdot 10^{-5}$ mol l^{-1}) was treated with 0·4 ml aniline–anilinium chloride buffer, and immediately the absorbance measurement was started at 422 nm and continued for 2 min. The reference cell contained the same buffer solution with 1·6 ml methanol. The absorbance of pure compound *II* was estimated after addition of 0·4 ml methanol to 1·6 ml solution of compound *II*.

RESULTS AND DISCUSSION

Compound *I* reacts with methanolic sodium methoxide rapidly and produces the red compound *II* with λ_{max} 420 and 500 nm. The shape of spectrum of this compound is characteric for the Meisenheimer adducts[7] (Fig. 1). From the ^{1}H NMR spectrum of compound *II* it is obvious that *II* is a spiro adduct and not a 1,1 or 1,3 adduct of compound *I* with methoxide ion. The NCH_3 group exhibits a singlet in ^{1}H NMR spectrum of compound *II*, whereas it gives a doublet with $J = 4{\cdot}8$ Hz in the spectrum of the starting compound *I*. The signal with δ 3·21 in the spectrum of compound *II* is due to methanol, which was confirmed by addition of methanol to the

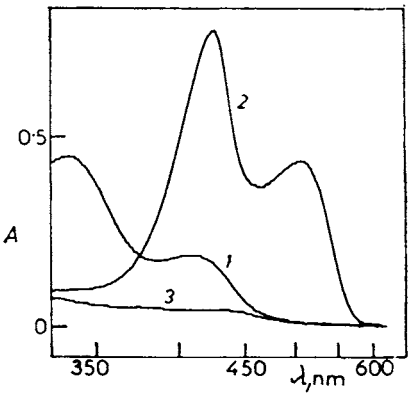


FIG. 1

Electronic spectra of compound *I* (*1*), *II* (*2*), and *IV* (*3*) at concentrations of $4{\cdot}8 \cdot 10^{-5}$ mol l^{-1} in methanol

sample measured. The spectrum of the compound *II* prepared by reprecipitation from tetrahydrofurane lacks the signal with δ 3·21 and contains additional multiplets of the tetrahydrofurane protons with δ 1·77 and 3·62 (Fig. 2). Neither methanol nor tetrahydrofurane can be removed from samples of compound *II* even by long-term drying in vacuum (300 Pa) at room temperature, the solvents being probably bound to the Na^+ cation. The spiro adduct structure is also confirmed by the ^{13}C NMR spectra. The chemical shift of methanol is δ 48·96 in the spectrum of compound *II*, whereas the methoxy groups of the Meisenheimer adducts with methoxide ion have[8,9] the chemical shifts δ 53 to 56.

The methanolic sodium salt *II* is transformed to compound *IV* on acidification with methanolic hydrogen chloride, the compound *IV* exhibiting no absorption in visible region (Fig. 1). From the ^1H NMR spectrum of compound *IV* in tetradeuteriomethanol with one drop of trifluoroacetic acid it can be seen that the substance represents a mixture of *Z* and *E* isomers of 2-amino-N-methyl-N-(2,4,6-trinitrophenyl)propanamide hydrochloride (*IV*), the isomer ratio being $[Z-IV]/[E-IV] \doteq 10$ (Pi = 2,4,6-trinitrophenyl). Even after several hours drying at 300 Pa at room temperature, the compound *IV* prepared contains hydrogen chloride and methanol

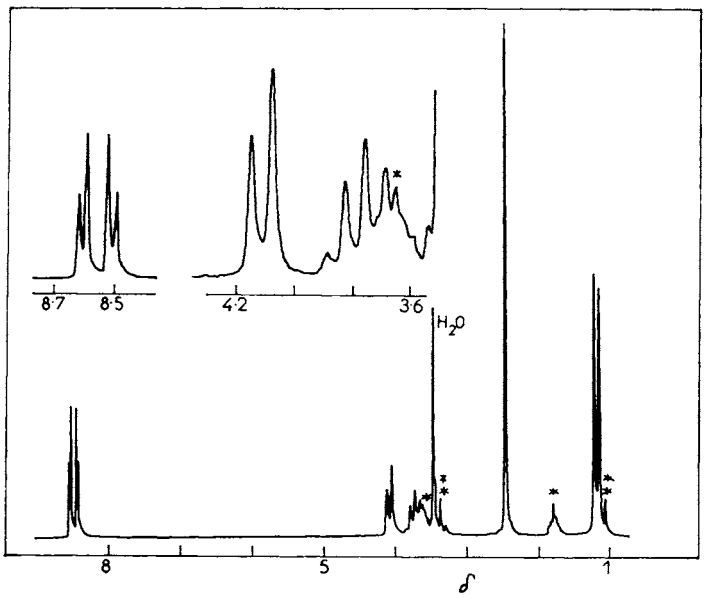
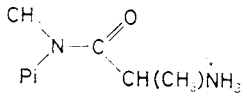


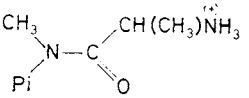
FIG. 2

^1H NMR spectrum of compound *II* in hexadeuteriodimethyl sulphoxide. The denoted signals belong to tetrahydrofurane (*) and diethyl ether (⁂)

in which it exhibits almost unlimited solubility. The attempts to dry the compound *IV* at 50°C result in partial splitting off of hydrogen chloride and cyclization of *IV*. Therefore, it was impossible to obtain a pure sample of *IV* for elemental analysis.



E - *IV*

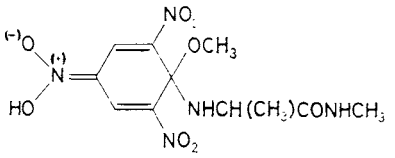


Z - *IV*

By its high solubility in ethanol the compound *IV* considerably differs from 2-methylamino-N-methyl-N-(2,4,6-trinitrophenyl)acetamide hydrochloride[2] which is little soluble in ethanol at room temperature. Addition of methanolic sodium acetate to solution of compound *IV* causes very rapid formation of the spiro adducts *II*.

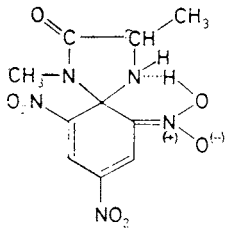
The ^{1}H NMR spectrum of the compound *IV* dissolved in hexadeuteriodimethyl sulphoxide exhibits, besides the signals of compound *IV* (the chemical shifts are very close to those found in tetradeuteriomethanol), additional signals with the character similar to that of the proton signals of the spiro adduct *II* but with higher chemical shifts. The differences in chemical shifts of the mutually corresponding protons of the two compounds are : $\Delta\delta(\mathrm{Pi}) = 0{\cdot}22$ and $0{\cdot}27$ ppm; $\Delta\delta(\mathrm{NCH_3}) = 0{\cdot}05$ ppm; $\Delta\delta(\mathrm{CH}) = 0{\cdot}49$ ppm; $\Delta\delta(\mathrm{CHCH_3}) = 0{\cdot}37$ ppm. Gradual addition of trifluoroacetic acid to the solution of the compounds mixture in hexadeuteriodimethyl sulphoxide is accompanied by gradual transformation of this compound to compound *IV*. The spectrum of compound *IV* dissolved in trifluoroacetic acid only contains the proton signals of compound *IV*.

Boulton[3] found that addition of one equivalent of methanolic hydrogen chloride to a solution of compound *I* with methoxide ion produces a compound with $\lambda_{max} =$ = 394 and 500 nm which is decomposed to the starting compound *I* with a half-life of 40 min. The author ascribed structure *VIII* (which can be derived by protonation of the adduct in Eq. (*C*)) to the new substance.



VIII

From our measurements it follows that the substance is, in fact, the protonated spiro adduct *III*. The protonation caused the greatest changes in chemical shifts of the $\mathrm{CH{-}CH_3}$ protons and the least changes in those of $\mathrm{NCH_3}$ protons.



III

In pure tetradeuteriomethanol without added trifluoroacetic acid it is impossible to measure the spectrum of compound *IV*, because the little soluble compound *I* separates within several minutes. In the presence of one drop of trifluoroacetic acid the spectrum only contains the signals of compound *IV*. The different behaviour of compound *IV* in the solutions of hexadeuteriodimethyl sulphoxide and tetradeuteriomethanol is due to two facts: different basicity of the two solvents and different stability of the Meisenheimer adducts therein.

Kinetics of Cyclization I → II

The spectral investigation of the cyclization course (λ = 330 to 630 nm) revealed that the spectrum of compound *I* does not cross the isosbestic point formed by the other spectral lines after addition of methoxide ion. The absorbance difference at the wavelength of the isosbestic point is increased with increasing methoxide concentration. This fact is due to the pre-equilibria in which the compound *I* with methoxide ion form the anion *IX* and 1,3 adduct *X* (ref.[10]) (Scheme 1).

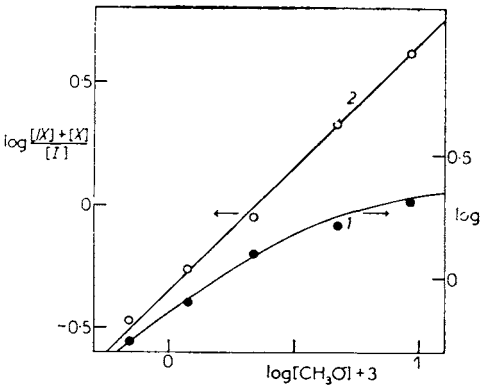
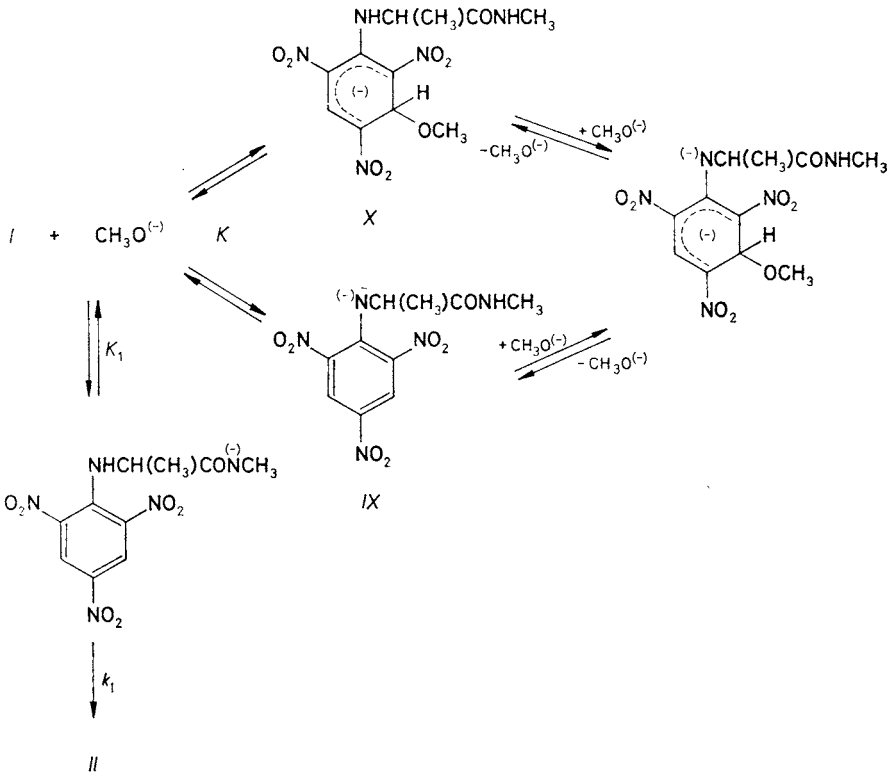


FIG. 3

Dependence of $\log k_{obs}$ of cyclization of compound *I* to compound *II* in methanolic methoxide solutions on $\log [CH_3O^{(-)}]$. The curve *1* was calculated according to Eq. (*1*), *2* the dependence of $\log (([IX] + [X])/[I])$ on $\log [CH_3O^{(-)}]$



SCHEME 1

Pseudo-first-order kinetics was found for the cyclization of compound *I* to the spiro adduct *II* in methoxide solution within the whole range studied (3–4 half-lives). Fig. 3 presents the dependence of log k_{obs} of the cyclization on log [CH_3ONa]. The decrease of slope of the dependence with increasing methoxide concentration is due to gradual transformation of compound *I* to anion *IX* and adduct *X*. At the methoxide concentrations above about 0·1 mol l^{-1}, formation of the adduct of anion *XI* with methoxide ion makes itself felt[10] (Scheme 1), and the cyclization k_{obs} decreases with increasing methoxide concentration.

In the methoxide concentration region where the formation of dianion *XI* is insignificant, the cyclization rate constant is defined by Eq. (*1*). The equilibrium constant *K* is defined by Eq. (*2*). The theoretical dependence of k_{obs} *vs* [$CH_3O^{(-)}$],

$$k_{obs} = k_1 K_1 [CH_3O^{(-)}]/(1 + K[CH_3O^{(-)}]) \qquad (1)$$

$$K = ([IX] + [X])/[I]\,[CH_3O^{(-)}] \qquad (2)$$

given in Fig. 3, was calculated from Eq. (*1*) with application of the values $k_1K_1 = 11{\cdot}0 \pm 0{\cdot}5\ \mathrm{l\,mol^{-1}\,s^{-1}}$ and $K = (4{\cdot}4 \pm 0{\cdot}2) \cdot 10^2\ \mathrm{l\,mol^{-1}}$. The K values given for 1-alkylamino-2,4,6-trinitrobenzenes in ref.[10] are lower by more than one order of magnitude. The difference is obviously due to the inductive effect of amidic group in compound *I*. The rate constant found for the cyclization of compound *I*, $k_1K_1 = 11{\cdot}0\ \mathrm{l\,mol^{-1}\,s^{-1}}$, is almost twenty times smaller than the cyclization rate constant of N-methyl-N-(2,4,6-trinitrophenyl)glycine methylamide[2]. Extrapolation to $t = 0$ of the time dependence of the absorbances for the individual methoxide concentrations gave the absorbance values of compounds *IX* and *X*, which enabled calculation of the ratios $([IX] + [X])/[I]$. Fig. 3 presents the dependence of $\log([IX] + [X])/[I]$ on $\log[CH_3O^{(-)}]$. The equilibrium constant value ($K = 4{\cdot}45 \cdot 10^2\ \mathrm{l\,mol^{-1}}$) found from this dependence agrees with the K value found directly from kinetic data by stepwise approximation.

In aniline–anilinium chloride buffers, the negatively charged spiro adduct *II* is protonated to the neutral spiro adduct *III* which – especially in more acidic buffers – is transformed partially to compound *IV*. The equilibrium $III + H^+ \rightleftharpoons IV$ is established with a half-life of 15 to 20 s. At the same time compound *III* is slowly transformed to the starting compound *I* with a half-life of about 30 min (Scheme 2).

$$II + H^+ \rightleftharpoons III \underset{-H^+}{\overset{+H^+,\,\mathrm{fast}}{\rightleftharpoons}} E\text{–}IV + Z\text{–}IV$$

$$III \xrightarrow{\text{slowly}} I$$

SCHEME 2

The absorbance values (at $\lambda = 422$ nm) of the corresponding equilibrium mixture $II + III + IV$ (at this wavelength the compound *II* has its λ_{max}, the compound *III* has its absorbance minimum, and *IV* does not absorb at all) were obtained by extrapolation of the linear absorbance dependence (in the time interval where the $III \rightarrow I$ transformation is small) to zero time. The extrapolated absorbance of the equilibrium mixture $II + III + IV$ (A_{ext}) is given by Eq. (*3*).

$$A_{ext} = A_{II} \cdot x + A_{III}(1 - x)\,K_{IV}/(K_{IV} + [H^+]) \qquad (3)$$

The absorbance value of pure compound *II* at the given concentration ($A_{II} = 1{\cdot}08$) was found by direct measurement. The absorbance of compound *III* at the same concentration ($A_{III} = 0{\cdot}30$) cannot be obtained by direct measurement, because compound *III* always stands in equilibrium with at least one of compounds *II* and

IV. The A_{III} value was estimated by stepwise approximation. The values x and $(1 - x)$ denote molar fraction of compound *II* in the mixture and molar proportion of compounds *III* + *IV*, resp. K_{IV} represents the equilibrium constant of the reaction $IV \rightleftharpoons III + H^+$. The fraction $P = K_{IV}/(K_{IV} + [H^+])$ gives relative proportion of compound *III* in its mixture with compound *IV*. The molar fraction x of compound *II* is defined by Eq. (*4*), and the concentration ratio $[II]/[III]$ is defined by Eq. (*5*). The pK_A^{III} value of compound *III* was calculated from Eq. (*6*), pK_A of aniline in methanol having the value 5·9 (ref.[11]). The results of measurements are given in Table I. The pK_A^{III} value is equal to 5·87 ± 0·04 at the ionic strength of 0·04 mol l^{-1}.

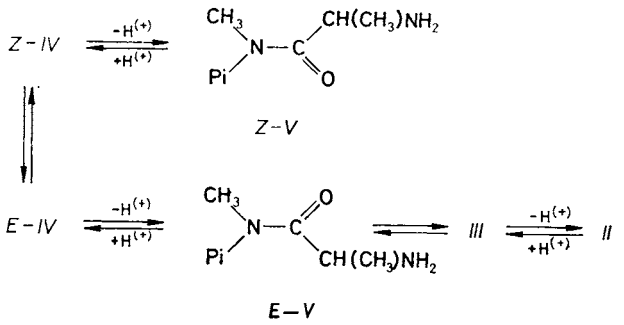
$$x = (A_{ext} - 0{\cdot}30P)/(1{\cdot}08 - 0{\cdot}30P) \tag{4}$$

$$[II]/[III] = P(1 - x)/x \tag{5}$$

$$pK_A^{III} = pK_A - \log \frac{[C_6H_5NH_3^+]}{[C_6H_5NH_2]} + \log \frac{[III]}{[II]} \tag{6}$$

Study of Reaction III + $H^+ \rightleftharpoons$ IV

Compound *III* is reversibly transformed to a mixture of compounds *Z–IV* and *E–IV* in 4-bromoaniline–4-bromoanilinium chloride buffers. At higher pH values the mixture, at the same time, also contains compound *II*. The reaction sequence is described by Scheme 3.



SCHEME 3

In bromoaniline buffers the concentrations of compounds *Z–V* and *E–V* are lower by several orders of magnitude than those of the other compounds. The rate of establishing of the equilibrium was followed from both sides, *i.e.* that starting from compound *IV* as well as that from compound *II*. The reactions proceed kinetically in two steps. After injection of buffer into the solution of compound *II* or into that of the isomer mixture *Z–IV* + *E–IV*, the equilibrium between compounds

E−*IV* and *III* is established very quickly (the reaction half-life below 1 s; the equilibria involving the proton transfer are usually established immediately). The second, far slower step (half-lives 5 to 15 s) consists in establishing of equilibrium between the isomer *Z*−*IV* and the equilibrium mixture *E*−*IV* + *III* + *II* (Eq. (*D*)).

$$Z\text{-}IV \underset{\overleftarrow{k}}{\overset{\vec{k}}{\rightleftharpoons}} E\text{-}IV + III + II \qquad (D)$$

The rate-limiting step consists in the isomerization $Z\text{-}IV \rightleftharpoons E\text{-}IV$, which is similar case to that of 2-methylamino-N-methyl-N-(2,4,6-trinitrophenyl)acetamide hydrochloride[2]. After establishing of the equilibrium, the concentration ratio $[IV]/([III] + [II])$ is defined by Eq. (7).

$$[IV]/([III] + [II]) = (A_{II} - A_{\infty})/A_{\infty} \qquad (7)$$

The absorbance coefficients of compounds *II* and *III* are the same at $\lambda = 500$ nm, and compound *IV* does not absorb at 500 nm. The rate constant k_{eq} of formation of the equilibrium mixture is the sum of the rate constants in both directions (Eq. (*8*)).

$$k_{eq} = \vec{k} + \overleftarrow{k} = k^{+}_{iso}\left(1 + \frac{[Z\text{-}IV]}{[E\text{-}IV] + [III] + [II]}\right) =$$

$$= k^{+}_{iso}\left(1 + \frac{[IV]}{[II] + [III]} \cdot \frac{K_{iso}}{([IV]/([II] + [III])) + K_{iso} + 1}\right) \qquad (8)$$

TABLE I

Estimation of equilibrium constant of the reaction $III \rightleftarrows II + H^{+}$ in methanolic buffers aniline–anilinium chloride

$\frac{(+)}{[C_6H_5NH_3]}$ / $[C_6H_5NH_2]$	A_{ext}	$\frac{[III]}{[II]}$	pK_A^{III}
8	0·31	6·8	5·84
4	0·41	3·8	5·88
2	0·54	1·93	5·89
1	0·70	0·95	5·85
0·5	0·82	0·48	5·89
0·25	0·95	0·20	5·80

k_{iso}^{+} denotes the isomerization rate constant of compound $Z-IV$ to compound $E-IV$ ($k_{iso}^{+} = \bar{k}$) and its value $3{\cdot}15 \cdot 10^{-2}$ s^{-1} was determined by direct measurement at higher pH values, where the reaction is practically irreversible ($k_{obs} = k_{iso}^{+}$). The equilibrium constant K_{iso} of the reaction $E-IV \rightleftharpoons Z-IV$ has a value of 10. The proportion of both the isomers was established by integration of the ^1H NMR spectrum of compound IV in tetradeuteriomethanol.

TABLE II

Calculated and found rate constants of establishing of the equilibrium $IV \rightleftarrows II + III$ (k_{eq}, s^{-1}) and estimation of the K^{IV} equilibrium constant of the reaction $IV \rightleftarrows III + H^+$

$\frac{[BrC_6H_4NH_3^{(+)}]}{[BrC_6H_4NH_2]}$	pH	$\frac{[IV]}{[II] + [III]}$	$k_{eq} \cdot 10^2$		pK^{IV}
			Found	Calculated	
0·26[a]	5·38	0·09	3·8	3·4	4·51
0·54[a]	5·07	$0{\cdot}25_5$	4·1	$3{\cdot}8_5$	4·57
1·11[a]	$4{\cdot}75_5$	0·58	4·8	$4{\cdot}7_5$	4·56
2·33[a]	4·43	1·28	6·3	$6{\cdot}4_5$	4·56
5·0[a]	4·10	2·80	9·4	$9{\cdot}5_5$	4·56
1·0[b]	4·80	0·56	—	—	4·58
2·0[b]	4·50	1·17	—	—	4·59
4·0[b]	4·20	2·36	9·2	$8{\cdot}7_5$	4·58
4·0[b,c]	4·20	2·30	9·0	8·75	4·57
8·0[b]	3·90	4·44	12·1	12·2	4·56

[a] Measured in the direction $IV \rightarrow III$; [b] measured in the direction $III \rightarrow IV$; [c] the buffer concentration was four times lower than in the other cases.

TABLE III

Calculated and found values of k_{obs} rate constants (s^{-1}) of $Z-IV \rightleftarrows E-IV$ isomerization in methanolic acetate buffers

$\frac{[CH_3COOH]}{[CH_3COONa]}$	k_{obs}	
	Found	Calculated
4·0	4·15	3·95
2·0	4·95	4·85
1·0	5·71	5·65
0·5	7·30	7·20
0·25	9·05	9·05

The negative logarithm of the equilibrium constant (pK^{IV}) of the reaction Eq. (*E*) was calculated from Eq. (*9*).

$$Z\text{–}IV + E\text{–}IV \rightleftharpoons III + H^+ \qquad (E)$$

$$pK^{IV} = \log([IV]/([II] + [III])) + pH - \log([H^+]/(K_A^{III} + [H^+])) \qquad (9)$$

The last term of Eq. (*9*) represents a correction to the partial transformation of compound *III* into compound *II* which takes place at higher pH values. The pH values were calculated from the ratio of buffer components, taking $pK_A = 4{\cdot}8$ for 4-bromoaniline in methanol (pK_A of 4-bromoaniline was calculated from pK_A of aniline[11] and $\Delta pK_A = 1{\cdot}1$ of the two amines in methanol[12]). Table II gives the rate constants of establishing of the equilibrium.

Kinetics of Isomerization Z–IV ⇌ E–IV

The rate constants of transformation of isomer *Z–IV* into isomer *E–IV* were measured in methanolic acetate buffers and dilute methoxide solutions. The rate constant k_{obs} of the isomerization – in the acetate buffers – was increased with increasing buffer component ratio $[CH_3CO_2Na]/[CH_3CO_2H]$, and it attained the maximum value $k_{obs} = 0{\cdot}14\ s^{-1}$ in the methoxide solution. The isomerization rate increase can be explained by increasing significance of the isomerization of the neutral species *Z–V* ⇌ *E–V* at higher pH values (Scheme 3). The isomerization rate constant is defined by Eq. (*10*), where $k_{iso}^0 = 0{\cdot}14\ s^{-1}$ is the rate constant of the isomerization *Z–V* ⇌ *E–V*.

$$k_{obs} = \frac{[Z\text{–}IV]}{[Z\text{–}IV] + [Z\text{–}V]}\, k_{iso}^{+} + \frac{[Z\text{–}V]}{[Z\text{–}IV] + [Z\text{–}V]}\, k_{iso}^{0} \qquad (10)$$

The first term of Eq. (*10*) corresponds to the isomerization of compound *Z–IV*, the second term corresponds to the isomerization of its neutral form *Z–V*, in both cases to the respective *E* isomers. Table *III* gives the results of measurements in acetate buffers. The best agreement between the measured and calculated values of the rate constants k_{obs} in Table III was reached for the ratio $K_A^{Z-IV}/K_A^{AcOH} = 0{\cdot}3$. $pK_A^{AcOH} = 9{\cdot}52$ in methanol[13], and, taking the correction for ionic strength[13] 0·04 mol l^{-1}, the value pK_A^{AcOH} of acetic acid is 9·27. Hence, at the ionic strength of 0·04 mol l^{-1} it is $pK_A^{Z-IV} = 9{\cdot}8$.

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