REACTIONS OF SUBSTITUTED N-PHENYLPYRIDINIUM SALTS WITH METHOXIDE AND ETHOXIDE IONS

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Equilibrium constants of reactions of N-(3- and 4-substituted phenyl)pyridinium salts with methoxide and ethoxide ions have been measured. The alkoxide ion always attacks the 2-position of the pyridine ring. The dependence log K *vs* σ^0 constants is linear with the slope 3.27 ± 0.10 and 3.05 for the reactions with methoxide and ethoxide ions, respectively. Reaction of more concentrated solutions of phenylpyridinium salts with excess ethoxide ion brings about reduction of pyridine ring to N-phenyl-1,4-dihydropyridine. Structure of the addition products and 1,4-dihydro derivative has been determined by NMR spectra.

N-Alkyl- and N-arylpyridinium salts (I) react with nucleophiles to give complexes II and III (refs[1-3]) (Scheme 1). If the nucleophile contains an α-proton which can be split off $(R' = H)$, then the complex II can undergo pyridine ring opening to form the substance IV.

In previous reports we described reactions of substituted N-phenylpyridinium salts with hydroxyl ions[4], primary amines[5], and secondary amines[6-8]. In all these cases the subsequent reaction of primary complexes II was so rapid that they could not be detected even spectrophotometrically, and, therefore, it was impossible to determine equilibrium constants of their formation. The present paper deals with the reaction of substituted N-phenylpyridinium salts with methoxide and ethoxide ions. Under
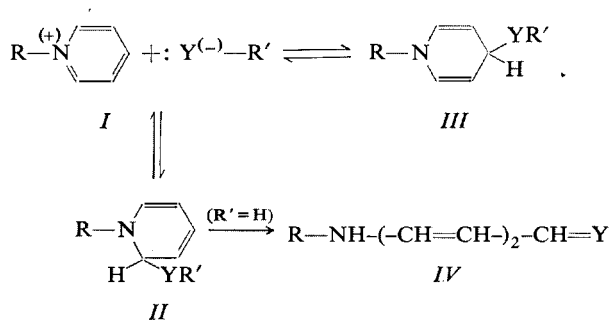
SCHEME 1

appropriate reaction conditions the complexes of the type *II* are practically the only reaction products.

$$\text{Br}-\text{C}_6\text{H}_4-\text{N}(\text{H}_1\text{H}_2\text{H}_3\text{H}_4\text{H}_5)(\text{OCH}_3)$$

IIc   *V*
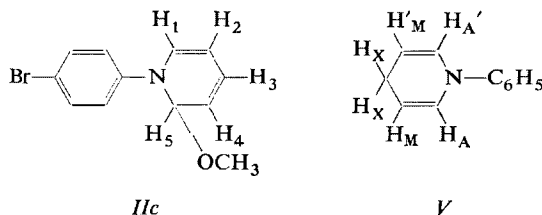
EXPERIMENTAL

Reagents. N-(3-resp. 4-Substituted phenyl)pyridinium chlorides *Ia—d* (*a* = 4-CH$_3$, *b* = H, *c* = 4-Br, *d* = 3-Cl) resp. bromides *Ie—f* (*e* = 3-NO$_2$, *f* = 4-NO$_2$) were prepared by the method described previously[4]. Anhydrous ethanol was prepared by repeated distillation of 96% ethanol with sodium. The other chemicals were commercial reagents of *p.a.* purity grade. For the proper measurements 1M and 3M methanolic sodium methoxide solutions and 0·5M ethanolic sodium ethoxide solution were prepared by dissolving sodium in the respective alcohols. These stock solutions were used also for preparation of more diluted solutions. Stock solutions of the compounds *Ia—f* in anhydrous methanol and ethanol (concentration $1 . 10^{-3}$M) were kept in cold and dark.

1-Phenyl-2-methoxy-1,2-dihydropyridine solution in CCl$_4$. 1·25 ml 1M-CH$_3$ONa was added to 0·3 g (1·55 mmol) of the substance *Ib* in 0·5 ml methanol. After 5 seconds the reaction mixture was diluted with 20 ml CCl$_4$, and the separated NaCl was filtered off. The filtrate was concentrated to about one fifth of the original volume under reduced pressure (the bath temperature max. 30°C), and the separated substances (predominantly the unreacted compound *Ib*) were again filtered off. The filtrate contained practically only the compound *IIb* and was concentrated to about 1 ml under reduced pressure and used immediately for NMR spectra measurement. In the same way the solutions of compounds *IIb* (YR′ = OC$_2$H$_5$) and *IIc* (YR′ = OCH$_3$ resp. OC$_2$H$_5$) were prepared. In preparation of complexes with ethoxide ion a double amount of CCl$_4$ was used.

N-Phenyl-1,4-dihydropyridine (V) solution. *A*) Reaction of the compound *Ib* with sodium ethoxide. 2·7 ml (4 mmol) 1·5M-C$_2$H$_5$ONa was added to a solution of 0·6 g (3·1 mmol) compound *Ib* in 3 ml anhydrous ethanol. The separated sodium chloride was filtered off. After several hours 0·2 g red crystalline compound *VI* separated from the filtrate, m.p. 164—165°C (analysis: 80·60% C, 5·59% H, 8·65% N). The compound was collected by suction, and the filtrate was mixed with 50 ml tetrachloromethane. The solution was concentrated under reduced pressure (the bath temperature max. 30°C) to about one fifth of the original volume, and the separated portions were filtered off. The filtrate was concentrated to about 1 ml and used immediately for NMR measurements.

B) By reaction of the compound *Ib* with sodium dithionite. Solution of 0·2 g (1·15 mmol) sodium dithionite in 4 ml 0·5M-Na$_2$CO$_3$ was added to a solution of 0·2 g (0·95 mmol) of the compound *Ib* in 4 ml aqueous 0·05M-Na$_2$CO$_3$. After 20 minutes the separated substance was filtered off and washed with water. M.p. 45—46°C (ref.[9] 48—50°C). The wet substance was dissolved in tetrachloromethane (1·5 ml), the solution was dried over sodium sulphate, filtered through glass wool, and used immediately for NMR spectra measurements.

Equilibrium constants of formation of the compounds *IIa—f* were measured first approximati-vely with a Unicam SP 800 spectrophotometer. Electronic spectra of the compounds *Ia—f* $(2 . 10^{-4}M)$ were measured in methanol resp. ethanol and in solutions of sodium methoxide resp. ethoxide. From these experiments the conditions were established (wavelength, alcoholate ion concentrations) for the proper measurements of equilibrium constants which were carried out with the use of a VSU 2-P spectrophotometer (Zeiss, Jena) at $25 \pm 0.1°C$. The equilibrium constants of the reactions of the compounds *Ia—e* with methoxide ions were determined in the following way. 2 ml of $1 . 10^{-3}M$ solution of the compound *I* was added to 8 ml temperated methanolic sodium methoxide solution. Such methoxide concentration was chosen to make the ratio $[I]/[II]$ within 0.2—5. A part of this solution was poured into the 1 cm quartz cell located in the temperated cell compartment of the spectrophotometer and absorbance values were measured at λ 325 nm at short time intervals within 2—3 minutes. Linear extrapolation to zero time gave the absorbance value of the moment of mixing. The absorbance value of the starting substance *I* was determined by measurement in pure methanol. The absorbances of complexes *IIc—e* were determined by measurements in 2.4M, 1.5M resp. 0.2M sodium methoxide, and those of substances *IIa* and *IIb* were measured at λ_{max} 330 nm in a solution prepared by mixing 1 ml $1 . 10^{-3}M$ methanolic solution of the compound *Ia* resp. *Ib* with 4.9 ml tetrachloromethane and 0.1 ml 3M-CH_3ONa. In this medium the equilibrium is shifted practically completely to the complex *II*. In this medium the extinction coefficient value is not changed as compared with purely methanolic solution, only λ_{max} is slightly shifted, which was verified in the case of the derivative *Id*. The measurement of equilibrium constant of formation of the complex *IIf* neces-sitated a rather different method; in this case the methoxide ion concentrations were so low that
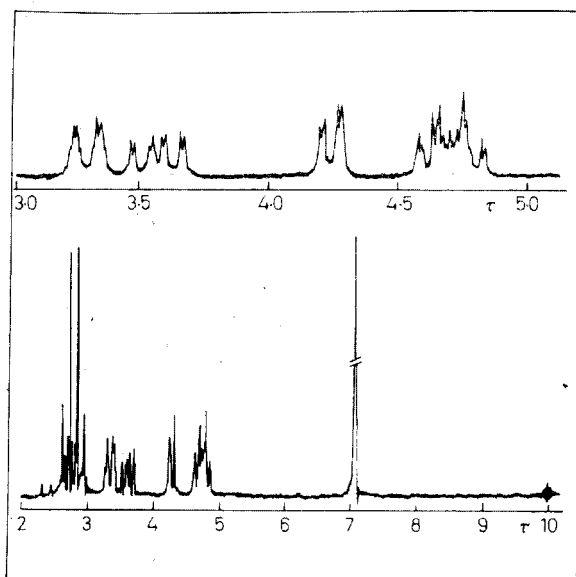

FIG. 1
^1H—NMR Spectrum of 1-(4-Bromophenyl)-2-methoxy-1,2-dihydropyridine in CCl_4

their decrease due to absorption of atmospheric carbon dioxide during handling was not negligible. Therefore, 1 ml $2 . 10^{-3}$M solution of *Ie* and 1 ml $2 . 10^{-3}$M solution of *If* were added to 8 ml sodium methoxide solution, and absorbances were measured at 325 and 385 nm (λ_{max} of *IIe* and *IIf*, respectively). From these values and absorbance values of individual substances *I* and *II* at the same wavelengths and concentrations the concentrations of all the substances present in the reaction mixture and therefrom the ratio of equilibrium constants of formation of the compounds *IIe* and *IIf* were computed. In the case of formation of complexes with ethoxide ion it was possible to measure the equilibrium constants of formation of the complexes *IIa—c*. The determination of the equilibrium constant of formation of the compound *IIa* was carried out in the same way as that of the compounds *IIc—e* in methanol. The constants of *IIb* and *IIc* were determined as follows: a sodium ethoxide stock solution was prepared, and, immediately, the derivatives *Ia—c* were dissolved therein, and absorbances of the solutions were measured at 325 nm one after the other. From the values obtained the equilibrium constants of formation of the complexes were computed. The measurements were repeated with six various concentrations of sodium ethoxide, and then the average values of equilibrium constants ratio were computed.

Spectral measurement of formation of 1-*phenyl*-1,4-*dihydropyridine* (V). 0·2M solution of the compound *Ib* in 0·25M sodium ethoxide was prepared. During one hour six samples were withdrawn, diluted thousand times with 0·01M-C_2H_5ONa, and their spectra were measured in the range $250 - 550$ nm.

NMR spectra of the complexes *IIb* and *IIc* (with CH_3O^- resp. $C_2H_5O^-$) and compound *V* were measured in tetrachloromethane. Their preparation is described above. Spectrum of the compound *V* was measured in dimethyl sulphoxide. The measurements were carried out with a Tesla BS 487 B apparatus at 80 MHz at room temperature. Hexamethyldisiloxane (9·95τ) was used as a standard for solutions in tetrachloromethane.

RESULTS AND DISCUSSION

Reactions of substituted N-phenylpyridinium salts with alkoxide ions are very rapid. Even the Durrum stopped-flow spectrometer could catch only the absorbances of reaction products, which means that the half-life of the alkoxide addition must be shorter than 0·5 ms, and even an eventual isomerization (Scheme 1) must be practically finished within 2 ms (the dead time of the apparatus). The attempts to isolate the reaction products *II* or *III* ($YR' = OCH_3$ resp. OC_2H_5) failed. After removing the last residues of solvent by vacuum distillation at about 20°C, the originally yellowish solution turns dark very rapidly to give finally a viscous oil (with eventual solid portions) having quite a different electronic spectrum from that expected[1] for the substances *II* and *III*. Therefore, the structure of reaction products was determined by means of NMR spectra of fresh solutions (about $10 - 20\%$) in tetrachloromethane.

Spectrum of heterocyclic protons of the compound *IIc* ($YR' = CH_3O^-$) (Fig. 1) consists of three multiplets (belonging to three different types of protons) and a very complicated multiplet formed by superposition of absorptions of two non-equivalent protons. Therefrom it can be deduced that the complex *IIc* must be unsymmetrical. The spectrum was partially interpreted with the presumption that the absorption at the lowest field ($v_1 = 3·31\tau$) is due to the proton H_1. Then the following chemical shifts and coupling constants can be ascribed to the other protons: $v_2 = 4·74\tau$;

$v_3 = 3.57\tau$; $v_4 = 4.67\tau$; $v_5 = 4.25\tau$; $J_{1,2} = 7.0$ Hz; $J_{2,3} = 5.7$ Hz; $J_{3,4} = 9.3$ Hz; $J_{4,5} = 5.0$ Hz; $J_{1,3} = 1.2$ Hz; $J_{2,4} = 1.3$ Hz.* The other coupling constants could not be determined due to complexity of the spectrum. Methoxy group of the complex *IIc* $\left(\text{YR}' = \text{CH}_3\text{O}\right)$ gives one sharp signal $\left(7.06\tau\right)$ and the aromatic protons absorb in the region 2·5 to 3·0τ.

Shape of absorptions of heterocyclic protons of the complex *IIc* $\left(\text{YR}' = \text{C}_2\text{H}_5\text{O}\right)$ is completely analogous to that of the complex *IIc* $\left(\text{YR}' = \text{CH}_3\text{O}\right)$. The spectrum of ethoxy group of this substance is interesting (Fig. 2). The terminal methyl group gives a simple triplet $\left(J = 7.0 \text{ Hz}\right)$. Absorption of the methylene group represents a complicated multiplet the formation of which can be explained by non-equivalence of the methylene protons. The whole ethoxy group thus represents an ABX_3 system where $\Delta v_{\text{AB}} = 16.7$ Hz, $J_{\text{AB}} = 8.8$ Hz and $J_{\text{AX}} = J_{\text{BX}} = 7.0$ Hz. This analysis was also supported by measuring spectrum of the compound at 60 MHz. This spectrum agrees well with that calculated on the basis of the parameters found at 80 MHz.
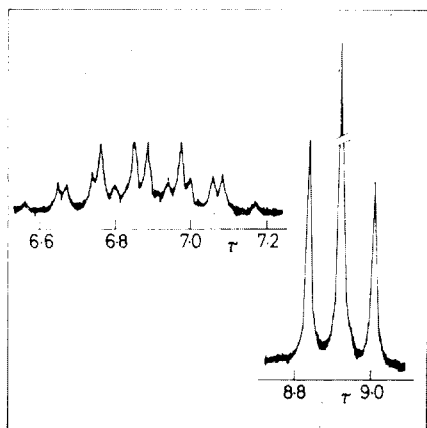

FIG. 2

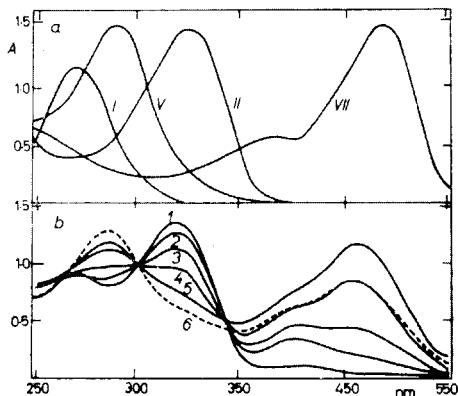^{1}H—NMR Spectrum of Ethoxy Group of 1-(4-Bromophenyl)-2-ethoxy-1,2-dihydropyridine in CCl_4

Fig. 3

a Electronic Spectra of $2 . 10^{-4}$M Solutions of Compounds *Ib*, *IIb* (YR) = $\text{C}_2\text{H}_5\text{O}$), *V* in Ethanol and Solution of 3 mg of Compound *VI* in 25 ml 0·01 M-$\text{C}_2\text{H}_5\text{ONa}$, *b* Spectral Record of Reaction of Compound *Ib* with Sodium Ethoxide Giving Compounds *V* and *VI*

1 0·5 min; *2* 5 min; *3* 10 min; *4* 20 min; *5* 40 min; spectrum *6* is a record taken after 60 min when the compound *VI* separated.

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*   The coupling constants found agree well with those found[10] for 2-butyl-1-deuterio-2-hydropyridine.

A similar shape of spectrum of ethoxy group was observed also with the compound *IIb* $\left(\text{YR}' = C_2H_5O\right)$, the respective coupling constants $J_{AX}(J_{BX})$ being also 7·0 Hz, whereas $\Delta\nu_{AB}$ was somewhat smaller (about 12 Hz).

In preparations of solutions of the complexes *IIb* and *IIc* for NMR spectra measurements an excess of tetrachloromethane was added into the reaction mixture after mixing the both components. Besides its acting as solvent for the NMR spectra measurements, tetrachloromethane shifted the equilibrium in favour of formation of the product *II* and suppressed side reactions (*e.g.* formation of the aldehyde *VII*). Under these conditions the respective complex *II* was practically the only reaction product. However, a quite different reaction course was observed with excess of ethoxide ion in absence of tetrachloromethane. The respective reaction course is recorded in Fig. 3 (for description of the experiment see Experimental). Immediately after mixing of the solutions, practically all substance *Ib* was transformed into *IIb*. Then concentration of the compound *IIb* (*i.e.* absorbance at λ 325 nm) slowly decreased with simultaneous increasing of the absorbances at λ 285 and 475 nm (the absorbance maximum at λ 400 nm observed in the first spectra is caused by the presence of a small amount of the aldehyde *VII*). After this change was mostly finished (about 1 hour), the solution began to separate red crystals and, at the same
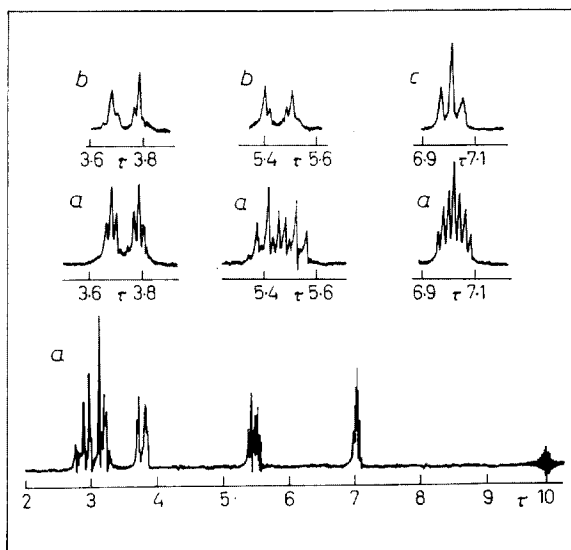

Fig. 4

a ^{1}H—NMR Spectrum of 1-Phenyl-1,4-dihydropyridine and Parts of Spectrum after Spin Decoupling from H_x (*b*),resp H_a (*c*) in CCl_4

time, the absorbance at λ 475 nm was decreasing, whereas that at λ 285 nm was further increasing. Rate of these reactions depends strongly on concentrations of the both components. With double concentrations the reaction was practically finished after 15 minutes, whereas a fourfold dilution caused that only a small fraction (few %) of the compound *IIb* reacted after 1 hour. Spectral records show that two compounds are formed in the reaction, their respective λ_{max} being 285 and 475 nm. (Fig. 3). Structure of the red crystalline solid could not be determined. NMR spectrum indicates only (due to slight solubility in all usual solvents) the presence of aldehydic proton (0.19τ) and aromatic and olefinic protons, but it is impossible to estimate their number. In absolute ethanol the substance *VI* is converted into another compound with λ_{max} 435 nm, the half-life of the conversion being few minutes. After addition of sodium ethoxide (up to the concentration of 0.01M) the original substance *VI* is formed practically quantitatively. In media containing higher sodium ethoxide concentrations and in ethanolic hydrogen chloride the compound *VI* is irreversibly converted into substances absorbing at lower wavelengths.

The compound $V\,(\lambda_{max}$ 285 nm) was identified to be 1-phenyl-1,4-dihydropyridine on the basis of its NMR spectrum. This finding was confirmed also by comparison with the 1-phenyl-1,4-dihydropyridine prepared by reduction of the compound *Ib* with sodium dithionite. The spectrum of heterocyclic protons of 1-phenyl-1,4-di-hydropyridine (V) represents an $AA'MM'X_2$ system (Fig. 4). An approximative interpretation was carried out according to the rules of splitting of the I. order assuming the protons X to be equivalent and neglecting the coupling constants $J_{AM'}$ and $J_{A'M}\,(\sim 0)$. The analysis gave the following data: $\nu_A = 3.74\tau$ (two triplets); $\nu_M = 5.47\tau$ (two triplets); $\nu_X = 7.02\tau$ (a septet formed by addition of two triplets with respect to the magnitudes J_{AX} and J_{MX}); $J_{AM} = 8.5$ Hz; $J_{AX} = 1.6$ Hz; $J_{MX} = 3.2$ Hz. The aromatic protons absorb between 2.5 and 3.5τ. These data agree well with those given in ref.[9] for the same substance.
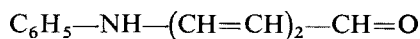
$$C_6H_5-NH-(CH=CH)_2-CH=O$$
$$VII$$

Whenever the reaction course of substituted N-phenylpyridinium salts $Ia-f$ with alkoxide ions was followed spectrophotometrically (Unicam SP 800 apparatus), the addition complex $IIa-f\,(YR' = CH_3O$ resp. $C_2H_5O)$ absorbing at 325 nm resp. 385 nm (IIf) was recorded as the primary product. In ethanolic solutions a gradual increase of absorbance at 400 nm was observed due to formation of the aldehyde *VII* by reaction of the compound *I* with OH^-. The rate of formation of the aldehyde increases with increasing concentration of alkoxide ions and with positive value of σ constant of the substituent at phenyl group. The reaction half-life was more than 10 minutes in the case of the most reactive derivative, for which the equilibrium con-

stant of its reaction with ethoxide ion was yet determined *(Ic)*. In methanolic solutions this reaction is far less significant due to methanol being more acidic than water in contrast to ethanol (which is more basic than water, so that the hydroxyl ion activity is higher in ethanolic solutions).

The equilibrium constants K (Eq. *(1)*) were determined by plotting the values log $((A - A_{\rm I})/(A_{\rm II} - A))$ (equal to log $([II]/[I])$) against log $[CH_3O^-]$ (Fig. 5).

$$K = [II]/([I] \cdot [CH_3O^-]) \tag{1}$$

If the concentrations were equal to activities, the dependence would be linear with the slope -1. In fact such a dependence was found only for solutions having $[CH_3O^-] < 1 \cdot 10^{-2}$M. Increasing methoxide ion concentration results in decrease of activity coefficients of the both compound I and methoxide ion, and thus also the value of K decreases. In the concentration range $[CH_3O^-] > 1$M the activity of methoxide ion increases faster than its concentration, and the slope assumes values higher than 1. The calculation of K was based on the equilibrium constant of formation of the compound *IIe*. The other equilibrium constants (Table I) were found by the method of step-by-step comparison from the differences of log $([II]/[I])$ at the same concentration of CH_3O^-. The values log K correlate very well with σ^0 constants (except for 4-nitro derivative) (Eq. *(2)*), correlation coefficient 0·998. The value log K

$$\log K = (3·27 \pm 0·1) \sigma^0 + (0·07 \pm 0·04) \tag{2}$$

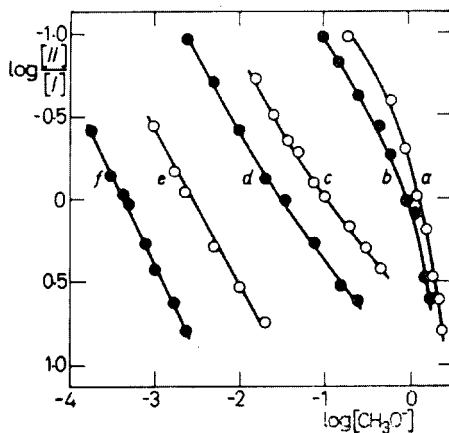FIG. 5

Dependence of log $([II]/[I])$ on log $[CH_3O^-]$ for Compounds *Ia—f*

of the 4-nitro derivative is higher than expected from σ^0. The σ value calculated from Eq. (2) equals 0·95. From structure of the compounds *I* and *II* it can be deduced that polar effect of substituents on formation of the compounds *II* will be similar to that on dissociation of anilinium ions, where the 4-nitro group has[11] the σ value 1·27. The σ value calculated from Eq. (2) is much closer to the σ^0 constant, the main reason being in that the both nuclei are not coplanar due to steric hindrance.

The calculation of equilibrium constants (Table I) of reactions of the compounds *I* with ethoxide ion was based on the value of log K of the 4-methyl derivative for which log $([II]/[I])$ showed linear dependence on log $[C_2H_5O^-]$ with the slope -1 in almost the whole range. The values log K of the unsubstituted and 4-bromo derivatives (*Ib, Ic*) were calculated from Eq. (3), where the index "a" means the

$$\log K = \log K_a + \log \frac{[II]}{[I]} - \log \frac{[IIa]}{[Ia]} \qquad (3)$$

4-methyl derivative. The ϱ constant (3·05) calculated from these three values is practically identical with the corresponding value of formation of complexes with methoxide ion.

The values of equilibrium constants of the reaction of the compounds *I* with ethoxide anion are much greater than in the case of methoxide anion. *E.g.* the ratio of the equilibrium constants of reactions of the compound *Ib* with $C_2H_5O^-$ and CH_3O^- is $4·13 . 10^2$. As the ϱ constants of the both reactions are practically the same, this ratio has similar values also for the other derivatives. The main reasons of the increase in equilibrium constants of reactions of the compounds *I* with ethoxide ion are first a higher nucleophilic reactivity of ethoxide ion in ethanol than that of methoxide ion in methanol and next the favourable influence of lower dielectric constant

TABLE I

Values of Reaction Equilibrium Constants (in $1 \, \text{mol}^{-1}$) in Methanol (K_1) and Ethanol (K_2) at 25°C

Compound	K_1	K_2
Ia	0·85	266
Ib	1·70	700
Ic	17·0	5 095
Id	40·8	—
Ie	389	—
If	2 570	—

on reaction between two ions with opposite charges. An estimate of the influence of nucleophilic reactivity on the equilibrium constant value can be based on a similar reaction of 1,3,5-trinitrobenzene with ethoxide and methoxide ions[12], the respective equilibrium constants ratio being 53. Therefrom it can be deduced, that the decrease in polarity of medium caused an increase of about one order of magnitude in ratio of equilibrium constants of the reaction studied by us. The equilibrium constant value of reaction of N-phenylpyridinium salt with ethoxide ion is only 1·7 times smaller than that of the same reaction of 1,3,5-trinitrobenzene. Therefrom it is obvious that a substitution of the grouping $C_6H_5N^+$ for C—H in benzene nucleus has practically the same effect (on the reaction with ethoxide ion) as three nitro groups.

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