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REACTION OF ALKYL-3-NITROPYRIDINIUM SALTS WITH DIMETHYLFORMAMIDE DIETHYLACETAL

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Alkyl-3-nitropyridinium salts react with DMF diethylacetal to give β-aminovinyl derivatives under considerably milder conditions than with the corresponding bases. The regioselectivity of this process has been studied in dependence on the structure and positions of the alkyl substituents in the initial salt.

It was observed some years ago that polyalkyl-3-nitropyridinium salts (I) are useful and potential synthons for the preparation of various carbo-and heterocycles (e.g., [1]). This resulted from their ability to undergo attack by nucleophiles at positions 2, 4 and 6 of the nucleus (with a variety of subsequent conversions) and attack by electrophiles at the CH acidic alkyl substituents in these positions.

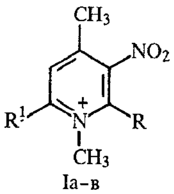
Among the observed reactions of salts I under the influence of ketones in the presence of bases, some apparently go via the initial condensation of the electrophile (ketone) with the 4-CH_3 group (in the case of 3-nitropyridinium salts containing a 4-methyl group). An example of a conversion via the intermediate formation of a 4-vinyl-3-nitropyridinium salt may be the preparation of 2,2-bis(4-indolyl)propane by the reaction of salt I with acetone in the presence of secondary amines and its conversion into cyclic nitrodieneamines under the influence of dialkylketones and methylamine (schemes for these reactions are presented in a review [1]). However in neither case was the intermediate vinyl derivative isolated and its intermediate formation remains a postulate only.

One may surmise that this conversion is not unique and the chemistry of vinyl-3-nitropyridinium salts promises to be very interesting. We have therefore tackled the problem of the synthesis of 3-nitropyridinium salts with vinyl groups in various positions on the ring.

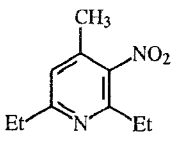
We chose DMF diethylacetal (II) as the electrophile for formation of the double bond by condensation with the CH acid alkyl group of salt I.

There is no report of the condensation of salts of type I with DMF acetals. Only reactions of alkyl-3-nitropyridine bases are known and these occur at 80-95°C [2-8].

Salts Ia-c, containing one to three methyl groups capable of condensation, were used to study reactions with the acetal II, plus the base 1-methyl-2,6-dimethyl-3-nitropyridine (III) for comparison. This choice of salts allowed the regioselectivity of the condensation with an electrophile to be studied, taking both steric and electronic factors into account.



Ia-в



III

I a $R = R^1 = Et$; b $R^1 = H, R = Me$; c $R^1 = R = Me$

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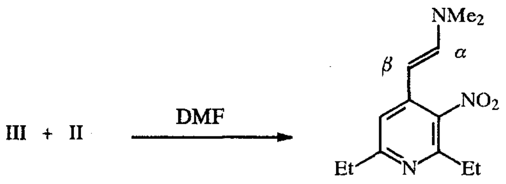
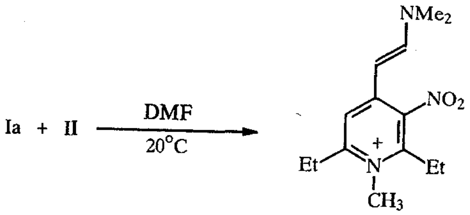
It is known that the CH acidity of α- and γ-alkyl substituents of 3-nitropyridine is increased on conversion to the salts as a result of the acceptor power of the quaternized nitrogen atom.

In fact, when condensation of base III with acetal II at 140-150 °C gave the corresponding 4-(2-dimethylaminovinyl)-3-nitropyridine IV in 32% yield, whereas reaction with all the salts Ia-c with acetal occurred at room temperature in practically quantitative yield.



IV

Because of the high activity of both the methylene and carbonyl functions a high selectivity of the condensation in the presence of several methyl groups in salts I was not expected. The reaction with 1,4-dimethyl-2,6-diethyl-3-nitropyridinium salt (Ia) was the most selective. As in the case of base III, condensation occurred only at the 4-methyl group. Not even traces of other regioisomers were observed in the ^{1}H NMR spectrum.



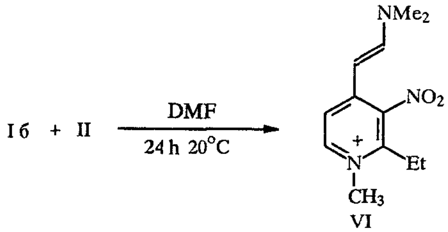
V

As expected the activity of the methylene group in the case of base III and salt Ia is considerably lower than the methyl group due to electronic (lower CH acidity of the methylene group because of the +I effect of the methyl substituents) and steric factors.

The nitropyridylenamine IV obtained is exclusively the *trans* isomer as indicated by the value of $J_{\alpha\beta}$ = 17.06 Hz in its ^{1}H NMR spectrum. The vinyl group appears as an AX system (α-H 4.80 and β-H 7.09 ppm). The identification of the signals of the α- and β-protons was by analogy with the ^{1}H NMR spectrum of the nitroenamines [9].

All of the signals in the ^{1}H NMR spectrum of compound V are shifted to weaker field in comparison with the spectrum of compound IV. The signals of the 5-H and β-H protons are shifted by 1.14 and 1.59 ppm respectively while that of the α-H is shifted by only 0.09 ppm. However the presence in the ^{1}H NMR spectrum of compound V (Table 1) of proton signals for two nonequivalent ethyl groups at 3.05 and 2.74 (q, 2-CH_2 and 6-CH_2) and 1.39 and 1.36 ppm (t, 2-CH_3 and 6-CH_3) and for the vinyl protons β-H (8.68) and α-H (4.70 ppm) fully confirm the proposed structure. With respect to the non-equivalence of the protons of the methyl groups on nitrogen, the signals were observed at 2.97 and 3.71 ppm.

In salt Ib, which contains both 2- and 4-methyl groups, there are two alternative sites for condensation with an α-methyl group. However, according to ^{1}H NMR spectroscopic data (Table 1), reaction with acetal II occurs entirely at the 4-methyl group.



VI

Evidently this regioselectivity is explained by the greater steric availability of this methyl group.

TABLE 1. Parameters of the ^1H NMR Spectra of the Initial Salt Ic and Compounds

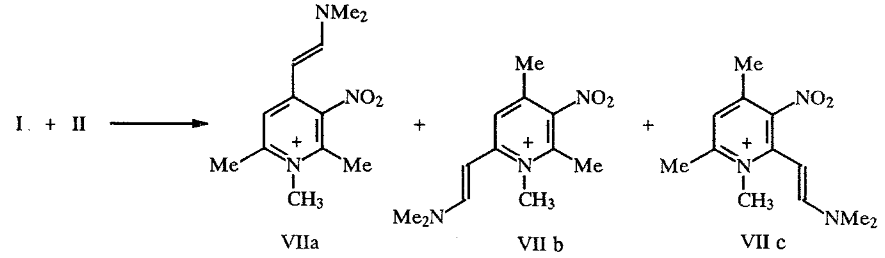
Compound	Position of substituent	Chemical shift, δ, ppm, and coupling constant, J, Hz								
		$1\text{-}CH_3$	2-R	$4\text{-}CH_3$	5-H	6-R	α-H	β-H	NMe_2	$J_{\alpha\beta}$
V	4	3,81	1,29 3,05	—	8,06	1,36 2,74	4,70	8,68	2,99 3,71	12,14
VI	4	4,01	2,48	—	8,10 J_{56} = 7,56 Hz	8,44	4,85	8,80	3,02 3,55	12,45
VIIa	4	3,74	2,43	—	8,01	2,57	4,63	8,50	2,94 3,32	12,30
VII b	6	3,72	2,32	2,50	8,05	—	5,30	8,50	3,12 3,37	12,20
Ic		4,08	2,48	2,71	8,22	2,84	—	—	—	—

TABLE 2. Conditions for the Formation of Salts V-VII and Some of Their Constants

Compound	Anion	Molecular formula	Solvent	Reaction time, h	Isomer ratio, 4:6:2	M.p., °C	UV spectrum, λ_{max}, nm (log ε)
V	$MeSO_4^-$	$C_{15}H_{25}N_3O_6S$	DMF	5	4 only	176...178	
VI	I^-	$C_{11}H_{16}IN_3O_2$	DMF	24	4 only	145...147	398 (4,98) 600 (2,98)
VII	I^-	$C_{12}H_{18}IN_3O_2$	DMF	4	2,13 : 1 : 0	192...195	396 (4,54) 601 (3,45)
	I^-		Ethanol	240	4 only	243...245	
	ClO_4^-	$C_{12}H_{18}ClN_3O_6$	CH_2Cl_2	10	1,35 : 1 : 1,12	186...188	400 (4,45) 600 (3,45)

We carried out the reaction of 2,4,6-trimethyl-3- nitropyridine iodomethylate (Ic) (with acetal II in different solvents: DMF, CH_2Cl_2 and ethanol). The reaction occurred most slowly in ethanol (Table 2) and only one of the three possible isomers, VIIa, was formed.

C



The reaction went fastest in DMF but only isomers VIIa and VIIb were observed to be formed with isomer VIIa predominating. The reaction was only slightly slower but was the least selective in methylene chloride: all three possible isomers were formed.

The three methyl groups of cation Ic have approximately equal ability to condense with electrophiles so that fine steric and electronic characteristics must be called into play to distinguish them. For example, the 2-methyl is the most sterically hindered and condensation is least likely despite its considerable CH acidity. Although the steric requirements for condensation at the 4- and 6-methyl groups are approximately the same, electronic factors evidently make attack at position 4 preferable.

The structures of isomers VIIa-c have been determined by NMR spectroscopy. The ^1H and ^{13}C NMR spectra of compounds VIIa and VIIb have been studied in detail. A characteristic of their ^1H NMR spectra is the absence of proton–proton multiplet structures (except for $J_{\alpha\beta}$ constants) which is characteristic of the ^1H NMR spectra of polyalkyl

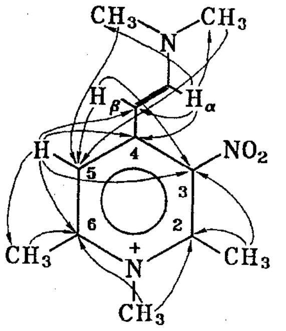


Fig. 1

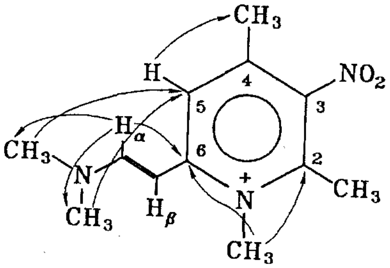


Fig. 2

Fig. 1. Correlation diagram for the protons and ^{13}C nuclei in compound VIIa from ^{13}C–H coupling constants.

Fig. 2. Correlation diagram for the protons and ^{13}C nuclei in compound VIIb from ^{13}C–H coupling constants.

substituted aromatic compounds. Apparently the spin–spin coupling between aromatic protons and the protons of alkyl groups is small and generally does not exceed 1 Hz (see results reviewed in [10]). Recording of these potentially very important parameters requires special experiments. However very useful information can be obtained from long range ^{13}C–^{1}H coupling constants, but the coupled spectra of molecules of the type studied here have complex multiplet structures which are difficult to record and to interpret. We have used the SESE (Spin Echo with Selective Excitation) method successfully in the past to solve similar problems [11]. This new method allows qualitative information on long range ^{13}C–^{1}H coupling constants to be obtained relatively quickly and it is particularly effective for the identification of quaternary carbon atoms and for the direct determination of the position of protons relative to the carbon skeleton of a molecule. In the first stage of deciphering the NMR spectra we used results from the ^{13}C–^{1}H COSY experiment which allows the identification of the methyl group signals in the ^{1}H and ^{13}C NMR spectra via the one bond ^{13}C–H coupling constants (J_{opt} = 140 Hz). Considerably more detailed information on the structures of these compounds was obtained via the SESE technic. The experimental long range ^{13}C–H couplings for compound VIIa are shown in Fig. 1. The arrows indicate the main responses in different ^{13}C NMR spectra obtained by selective excitation of the corresponding proton. We used a D2 delay of 0.2 s which is optimal for ^{13}C–H constants of the order of 5 Hz for protons in methine and methyl groups. The most important couplings are those between the protons of 1-CH$_3$ and carbon atoms C$_{(2)}$ and C$_{(6)}$; 2-CH$_3$ and carbon atoms C$_{(2)}$ and C$_{(3)}$; 6-CH$_3$ and C$_{(6)}$; the β-H and carbon atoms C$_{(3)}$, C$_{(4)}$ and C$_{(5)}$; α-H and C$_{(4)}$; and the pyridine ring proton 5-H and C$_{(\beta)}$, C$_{(3)}$, C$_{(4)}$, C$_{(6)}$ and 2-CH$_3$. All of these interactions correspond to our predictions for ^{13}C–H constants which "should have the largest values when the proton is separated by two or three bonds from the carbon atom with which it is coupled" [13]. The long range coupling constants between the aliphatic N-methyl group and C$_{(5)}$ should be noted. The appearance of such a long range coupling — through six bonds — is not surprising since the zigzag configuration (taking into account the *trans*-substitution at the double bond) is favorable for spin–spin interaction.

We obtained far fewer correlations for the minor isomer VIIb because of the lower signal to noise ratio (Fig. 2) but there were sufficient for unambiguous identification of the signals and for the establishment of the structure.

The final results for the ^{1}H and ^{13}C NMR spectroscopic parameters for compounds VIIa and VIIb are given in Tables 1 and 3. These tables also contain results we obtained for the 1,2,4,6-tetramethyl-3-nitropyridinium iodide (Ic) starting material which we analyzed in detail to obtain unambiguous assignment of the ^{13}C NMR signals. These results can serve as a sound foundation for estimating the electronic effects accompanying the replacement of a CH$_3$ group by the –CH=CH-NMe$_2$ group in going from compound Ic to compound VIIa and VIIb. The ^{13}C NMR data provide the clearest picture (Table 3). These results show that there is a non-trivial electron density redistribution throughout the pyridine ring on replacing the CH$_3$ group by –CH=CH–NMe$_2$. The signal for C$_{(5)}$ underwent the greatest perturbation, shifting by about 16-17 ppm to weak field in both isomers VIIa and VIIb. A considerable effect was observed for C$_{(3)}$ (6-7 ppm to strong field) and a weaker effect for C$_{(2)}$ (3-3.5 ppm to strong field). Screening effects were also observed for C$_{(6)}$ ($\Delta\delta$ 7.1) for compound VIIa and for C$_{(4)}$ ($\Delta\delta$ 7.5

TABLE 3. Chemical Shifts in the ^{13}C NMR Spectra of the Starting Material Ic and Compounds VIIa and VIIb

Carbon atom.	c	VIIa	VII b	Carbon atom	I c	VIIa	VII b
$C_{(2)}$	148,87	145,71	145,12	4-CH_3	17,67	—	17,56
$C_{(3)}$	147,86	140,54	141,47	6-CH_3	21,96	20,92	—
$C_{(4)}$	147,38	144,44	139,89	1-CH_3	41,89	38,59	40,00
$C_{(5)}$	129,07	154,75	155,74	$C(\beta)$	—	114,53	117,77
$C_{(6)}$	157,89	150,78	156,01	$C(\alpha)$	—	84,17	86,74
2-CH_3	17,54	17,78	17,30	N-CH_3	—	37,47 45,43	38,21 45,56

ppm) for isomer VIIb. The effects for $C_{(4)}$ in compound VIIa and for $C_{(6)}$ in compound VIIb were relatively small (2-3 ppmto strong field). All of these effects can be explained by a strong redistribution of electrons between the donor enamine group and the nitropyridine ring as acceptor, as a result of which increased electron density (screening effect) is observed at atoms $C_{(2)}$, $C_{(4)}$ and $C_{(6)}$ in both isomers VIIa and b relative to compound Ic. Increased conjugation of the NO_2 group with the π-system of the molecule is shown by a decreased charge on $C_{(3)}$ and an increased positive charge on $C_{(5)}$.

The presence of strong conjugation is indicated by the very intense color of salts V-VII. They are intensely violet in the crystalline state and green in the amorphous state. The green color is retained in solution in reflected light, but it becomes red in transmitted light. Two long wavelength bands are observed in the electronic spectra (Table 2) in the region of 398-400 (lg ε 4.45-4.98) and 600-602 nm (lg ε 2.98-3.45). Evidently one reason for the appearance of a maximum at 600 nm is intramolecular charge transfer along the conjugation chain from the enamine donor to nitropyridine acceptor. In fact only one long wavelength maximum (344 nm, lg ε 4.39) is observed in the spectrum of base IV in which charge transfer of this type is considerably weakened because of the poor acceptor power of the non-quaternized pyridine ring.

Another possible reason for the intense color of the salts is formation of charge transfer complexes with the iodide anion or by intermolecular interaction of two salt molecules. To exclude the possibility of a charge transfer complex with the iodide anion in salts VII, we replaced the anion with ClO_4^-. Since the character of the spectra, the position and intensity of the maxima were unchanged it follows that the observed color is not due to complex formation with the iodide anion.

Since no change occurred in the electronic spectra occurred on dilution intermolecular charge transfer complexes are also absent. Consequently the sole reason for the intense color is intramolecular charge transfer along the system of conjugated bonds.

EXPERIMENTAL

NMR spectra in DMSO-D_6 were recorded on Bruker AC-200 and AM-360 and Varian VXR-400 spectrometers. SESE experiments were carried out with the SEL 2DJ pulse sequence [14, 15]. UV spectra of methanol solutions were recorded with a Cary-219 spectrometer.

C, H and N elemental analysis results corresponded to theoretical values.

4-(2-Dimethylaminovinyl)-2,6-diethyl-3-nitropyridine (IV, $C_{13}H_{19}N_3O_2$). A mixture of 2,6-diethyl-4-methyl-3-nitropyridine [16] (0.97 g, 5 mmol) and DMF diethylacetal (2 ml, 1.72 g, 11 mmol) in DMF (5 ml) was heated at 140-150 °C for 5 h. The solvent and remaining acetal were removed in vacuum and the residue was recrystallized from hexane, m.p. 71-73 °C, yield 400 mg (32%). UV spectrum, λ_{max} (lg ε): 246 (4.03) 3.44 nm (4.39). ^1H NMR spectrum ($CDCl_3$): 1.27 (3H, t, 6-$CH_2\underline{CH_3}$), 1.28 (3H, t, 2-$CH_2\underline{CH_3}$), 2.67 (2H, q, 6-$\underline{CH_2}CH_3$), 2.71 (2H, q, 2-$\underline{CH_2}CH_3$), 2.91 (6H, s, NMe_2), 4.80 (1H, d, α-H, $J_{\alpha\beta}$ = 17.06 Hz), 6.92 (1H, s, 5-H), 7.09 ppm (1H, d, β-H, $J_{\alpha\beta}$ = 17.06 Hz).

1-Methyl-(2-dimethylaminovinyl)polyalkyl-3-nitropyridinium salts V-VII. A mixture of a salt Ia-c (10 mmol) and DMF diethylacetal (15 mmol) in solvent (10 ml) were stirred at rom temperature for 4-240 h. The solvent and unreacted acetal were evaporated and the residue was recrystallized from 1:10 isopropanol–acetonitrile. Yields, physical constants and reaction conditions are given in Table 1.

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