INDOLES FROM 3-NITROPYRIDINIUM SALTS
9.* METHYL ETHYL KETONE N-METHYLIMINE IN THE INDOLIZATION OF 1-METHYL-3-NITROPYRIDINIUM SALTS

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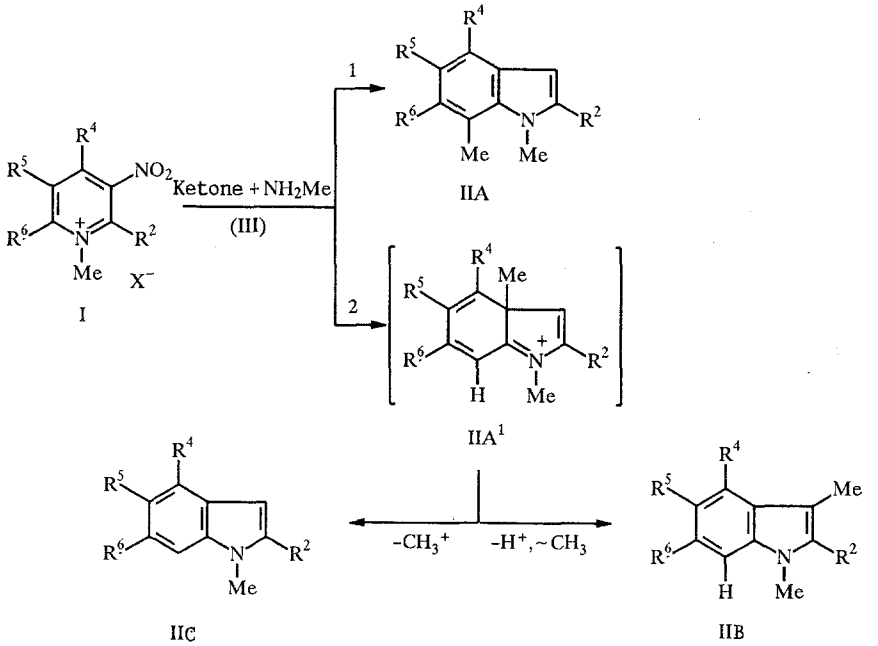
In a study of the direction of the indolization of alkyl-substituted 3-nitropyridinium salts in reaction with methyl ethyl ketone N-methylimine as a function of the structure of the salts, it has been established that in the presence of a substituent at position 4, initial attack at position 6 by the most substituted enamine form of the imine leads to preferential formation of 7-methylindole whereas in its absence the regioselectivity of the process is reduced and in the indole mixture the fraction of 3-methylindole increases.

It has been reported previously that the action of an excess of an unsymmetrical ketone and methylamine on the 3-nitropyridinium salt I gives a mixture of the 3-unsubstituted indole IIA, the 7-unsubstituted indole IIB, and the 3,7-unsubstituted indole IIc according to the scheme [2]:



It has also been established that it is the enamine form of the N-alkylketimine, formed from the corresponding ketone and amine, which enters into reaction with the 3-nitropyridinium cation. The use of prepared ketimines leads to an increase in the yield of indole and a reduction in both the reaction time and the number of secondary products [3]. The process by which indoles are formed from N-alkylketimines of unsymmetrical ketones has not hitherto been studied.

Since the ratio of the indoles formed depends on the regio-orientation of the enamine form of the unsymmetrical ketone N-alkylimines III, which in its turn is determined by the structure of the initial 3-nitropyridinium cation, we selected, as subjects for study, salts Ia-i with different number, location, and structure of alkyl substituents (Table 1). The selection of these salts was determined by the fact that the initial step of the process is evidently 4,6-meta-bonding of the electron-deficient 3-nitropyridinium cation with the enamine form of the ketimine which acts in this case as a 1,3-bis-C,C-nucleophile [4]. We therefore varied the

*For Communication 8, see [1].

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TABLE 1. Conditions of the Indolization Reaction and Relative Content of Indoles IIA, B, C in the Mixture

I	R^2	R^4	R^5	R^6	X^-	Relative content of indoles II			Reaction time, days	Overall yield, %
						A	Б	B		
a	CH_3	CH_3	H	H	I	6,3	1	0,2	4	24
b	CH_3	H	H	CH_3	I	3,0	1	—	3	28
c	CH_3	CH_3	H	CH_3	I	38,0	1	0,6	5	80
d	CH_3	H	CH_3	CH_3	ClO_4	2,4	1	—	13	73
e	C_2H_5	CH_3	H	C_2H_5	CH_3SO_4	5,0	1	—	4	44
f	CH_3	CH_3	CH_3	CH_3	CH_3SO_4	5,0	1	0,6	13	60
g	CH_3	CH_3	i-C_3H_7	CH_3	ClO_4	1,7	—	1	5	61
h*	CH_3	C_6H_5	H	CH_3	CH_3SO_4	7,0	1	—	7	78
i	CH_3	C_2H_5	CH_3	CH_3	ClO_4	7,0	1	1,5	10	62

*Salt sample kindly supplied by F. V. Maksimova.

TABLE 2. Mass Spectra of Indoles

Compound	M/Z (I rel.)
IIaA	173 (100), 174 (15), 172 (50), 159 (13), 158 (60), 156 (13), 155 (14), 144 (8), 128 (9), 115 (14), 87 (8), 77 (7), 65 (5), 51 (6)
IIaB	173 (100), 174 (15), 172 (96), 158 (28), 156 (8), 154 (8), 142 (6), 128 (8), 115 (11), 91 (5), 79 (5), 77 (5), 51 (3)
IIbA	173 (100), 174 (11), 172 (89), 171 (10), 159 (8), 158 (50), 157 (12), 156 (11), 142 (6), 128 (6), 115 (16), 91 (7), 86 (8), 77 (5), 65 (4), 51 (4)
IIgA	229 (60), 230 (9), 215 (18), 214 (100), 199 (20), 185 (8), 56 (8), 40 (9)
IIgB	215 (62), 216 (8), 201 (10), 200 (100), 186 (30), 56 (12), 40 (5)
IIiA	215 (60), 216 (10), 201 (11), 200 (100), 185 (8), 170 (5), 40 (18)
IIiB	215 (46), 216 (6), 214 (6), 201 (10), 200 (100), 184 (5), 93 (5), 40 (46)
IIiC	201 (56), 187 (10), 186 (100), 171 (8), 40 (44)

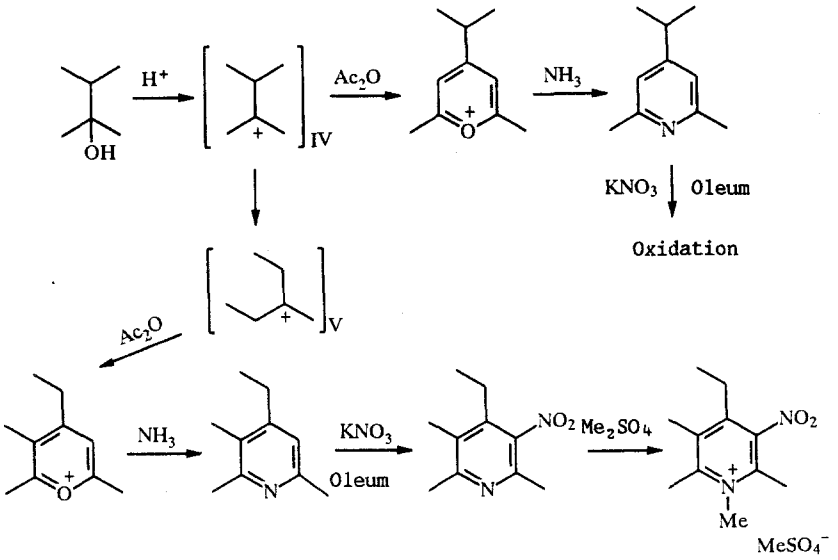
substituents at positions 4, 5, and 6 of the pyridine ring. Methyl ethyl ketone N-methylimine (III) was selected as the imine component.

On attempting the synthesis of the sterically hindered 1,2,6-trimethyl-4-isopropyl-3-nitropyridinium salt via the corresponding pyrrylium salt (from dimethylisopropylcarbinol and acetic anhydride), the 1,2,5,6-tetramethyl-4-ethyl-3-nitropyridinium salt Ii was unexpectedly obtained. This occurs because in a strongly acid medium bis-acylation of the cationic particle IV precedes the sigmatropic rearrangement stage, leading to the formation of the carbocation V.

The pyridinium salts Ia-i were reacted with imine III in DMF.*

The composition of the indole mixtures which were obtained was established by a combination of GLC, chromatography—mass spectrometry, and PMR spectroscopy. In the aromatic region of the PMR spectrum, the isomeric indoles IIA and IIB have characteristic signals, assigned to protons in the 3 and 7 positions, at 6.01 to 6.40 and 6.70 to 7.21 ppm, respectively; for indole IIC two signals are characteristically present in the same aromatic region of the PMR spectrum and hence an accurate determination of the ratio of the indoles in the mixture is not possible on the basis of the PMR spectrum. Identification of the 3,7-unsubstituted indole IIC from chromatography—mass spectrometry is fairly straightforward, the chief problem in this case being the determination of the difference in the dissociative ionization of the isomeric indoles IIA and IIB.

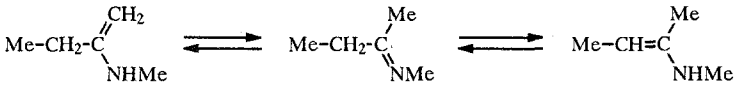
*A study of the influence of the solvent on the ratio of the reaction routes will be the subject of a further publication.



To solve this problem we proceeded on the assumption that although the fragmentation of the indole isomers IIA and IIB was similar the relative intensities of ions of the same type was different. In the case of 3-methylindoles IIB the characteristic fragmentation process was the loss of a hydrogen atom from the molecular ion leading, via rupture of the ring, to the formation of a stable quinoline cation. For the fragmentation of the 7-methyl indoles IIA, a process involving loss of a methyl group from the benzene ring leading via rupture of the ring to the formation of a tropyl system was more characteristic. The ratio of the intensities of the $I[M-H^+]/I\ M^+$ and $I[M-CH_3]^+/I\ M^+$ peaks could serve as quantitative characteristics of these processes. For 3-methylindoles, the first-mentioned value was close to unity and the second did not exceed 0.5 whereas for 7-methylindoles the first was 0.5 and the second between 0.6 and 0.7. The observed fragmentation was characteristic for polyalkylindoles and corresponded to literature data [5]. The mass spectra of several indoles are detailed in Table 2.

Data for the relative concentration of indoles IIA, B, and C in the mixtures, obtained from a combination of these physicochemical methods, are set out in Table 1. A discussion of the results need to be prefaced by the following theoretical comments.

1. Methyl ethyl ketone N-methylimine (III), as with all imines of unsymmetrical ketones, is capable of existing in three tautomeric forms, two of which are enamines:



a III b

Enamines of type b are more thermodynamically stable and more nucleophilic [6].

2. The process of 4,6-meta-bonding mentioned above, leading to the formation of indoles, proceeds stepwise [7], and the site of the initial attack plays a deciding role in the regio-orientation of the addition of the enamine form of the ketimine (III) to the cation I.

3. It is known from quantum-chemical calculations for the 1,2,4,6-trimethyl-3-nitropyridinium cation that position 6 has the maximum electrophilicity. Apparently, this position also retains maximum electrophilicity in other cations having alkyl substituents in positions 2, 4, and 6 [8]. The initial attack by the enamine form IIIb at position 6 leads to the formation of 7-methylindole IIA (route 1); attack by form IIIa at this position leads to a nonaromatic cationoid intermediate II^1 which, depending on the method of aromatization, gives 3-methylindole IIB and the 3,7-unsubstituted indole IIC (route 2).

4. In the case where substituents are absent from position 4 but present at positions 2 and 6 it is the unsubstituted position which has the highest electrophilicity and the initial addition of the enamine form IIIa to it leads to the formation of indoles IIB and C while enamine IIIb gives indoles IIA.

It can be seen from the data in Table 1 that indolization of the salts Ia, c, e-i predominantly forms IIa. This means that the more substituted and more nucleophilic form of the ketimine IIIb attacks position 6. On comparison of the ratio of the indoles formed in reaction with salts Ia (R^6 = H) and Ic (R^6 = CH_3), one observes a sharp increase in the selectivity of the process, the ratios of the indoles IIA:(IIB + IIC) amounting to 5.2:1 and 23:1, respectively. Apparently, the selectivity of the process

increases with a reduction in the electrophilicity of position 6 on introducing an electron—donor substituent. Some reduction in the selectivity of the reaction on moving from salt Ic ($R^4 = CH_3$) to salt Ih ($R^4 = C_6H_5$) is apparent as a reduction in the concentration of indole IIA in the indole fraction, apparently as a result of the specific electron effect of the aromatic substituent.

Until now, electronic factors have been the chief concern in discussing of the results but account should be taken of the possibility of steric factors. The preferred initial attack by form IIIb at the 6-position of 4,6-dialkyl-substituted 3-nitropyridinium cations is evidence that the N-methyl group in the ortho-position to the point of attack creates less steric hindrance than does the ortho-nitro group to attack at position 4. The latter group, moreover, on account of electrostatic interactions, hinders attack by the nucleophile. These considerations do not conflict with the possibility of attack at position 4 by the less sterically hindered form IIIa enamine, which would also lead to enrichment of the final mixture in indoles IIA. As was shown previously for the example of indolization of salt Ie under the action of N-methylacetonimine, an ethyl substituent at position 6 does not create significant steric hindrance [9]. However, reaction with methyl ethyl ketone N-methylimine (III) is found to be more sensitive to steric requirements in comparison with its 2,6-dimethyl analog (salt Ic) and the probability of initial attack at position 6 by the enamine IIIb is somewhat reduced. We have suggested that introduction of an alkyl substituent at position 5 must create additional steric hindrance to attack at position 6 leading to a reduction in the selectivity of the process. In fact, on moving from salt Ic ($R^5 = H$) to salt If ($R^5 = CH_3$) the ratio of indoles IIA:(IIB + C) decreases to 3:1. Introduction of a bulky isopropyl substituent at position 5 (salt Ig) has a further significant effect on the selectivity (1.7:1).

For the 4-unsubstituted salts Ib, d, a considerable reduction in selectivity is observed which could be the result of concurrent attack by the IIIb enamine at the free 4 position and at the substituted 6 position.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-467A (60 MHz) instrument with TMS internal standard. GLC analyses were carried out on a Crom-5 instrument with a 12.5 m quartz capillary column, helium carrier gas, drop 1:60, flow 1.2 ml/min, injection temperature 180-200°C, flame ionization detector. Chromatography—mass spectrometry was effected on a Finnigan MAT-112 unit at 70 eV, septum temperature 250°C, vaporization temperature 200°C, SPB-5 quartz capillary column 0.25 mm × 30 m, helium carrier gas, column temperature 150-260°C at 10°C/min.

The results of elemental analyses were in agreement with those calculated.

Methyl ethyl ketone N-methylimine (III) was prepared by the method of [10], bp 87.5-88.5°C.

1-Methyl-3-nitropyridinium salts Ia-g were prepared from the corresponding 2-nitropyridines by the method of [11].

1,2,6-Trimethyl-4-phenyl-3-nitropyridinium methylsulfate Iz was prepared by the method of [4].

2,5,6-Trimethyl-4-ethylpyridine. To 33.6 ml (0.6 mole) concentrated H_2SO_4 was added, with stirring, 169.8 ml (1.8 mole) freshly distilled acetic anhydride and the mixture kept for 30 min at 80°C. A solution of 30.6 ml (0.3 mole) dimethylisopropylcarbinol in 237 ml (2.52 moles) acetic anhydride was added and the mixture kept at 80-85°C for 2 h and then cooled to 20°C. The cooled mixture was hydrolyzed with 150 ml water, washed with ~300 ml ether, separated, and the organic layer washed several times with water. The aqueous solution was run dropwise into a vigorously stirred excess of 25% aqueous ammonia over 2-2.5 h. This was then extracted with benzene, the extract dried over Na_2SO_4, evaporated in vacuum, and the residue distilled, collecting the fraction with bp 79-82°C/12 mm. 29 g (70%) 2,5,6-trimethyl-4-ethylpyridine was obtained with 2,6-dimethyl-4-isopropylpyridine as impurity; according to the PMR spectrum the isomer ratio was 10:1. PMR spectrum (CCl_4, δ, ppm): 1.20 (3H, t, $CH_2\underline{CH_3}$), 2.12 (3H, s, 5-CH_3), 2.20 (3H, s, 6-CH_3), 2.51 (3H, s, 2-CH_3), 2.57 (2H, q, $\underline{CH_2}$ CH_3), 6.70 (1H, s, 3-H).

2,5,6-Trimethyl-4-ethyl-3-nitropyridine. To a solution of 18.2 g (0.15 mole) 2,5,6-trimethyl-4-ethylpyridine in 20 ml concentrated H_2SO_4 was added, with cooling and stirring, 60 ml 18% oleum. After the salt which initially precipitated had redissolved, 37 g (0.38 mole) dry $NaNO_3$ was added in small portions so that the reaction temperature did not exceed 110°C. It was then kept at this temperature for 6 h. The reaction mixture was then cooled, neutralized with ammonia, and extracted with ether. The combined ether extracts were dried over Na_2SO_4, the solvent distilled off, and the residue used in the quaternization reaction without further purification.

1,2,5,6-Tetramethyl-4-ethyl-3-nitropyridinium Perchlorate (Ii, $C_{11}H_{17}ClN_2O_6$). To a solution of 3.88 g (0.02 mole) 2,5,6-trimethyl-4-ethyl-3-nitropyridine in 5 ml acetonitrile was added 2.3 ml dimethylsulfate. The reaction mixture was held at 100°C for 3 h, cooled, washed with ether, and dissolved in 10-15 ml water. A saturated aqueous solution of magnesium perchlorate (10-15 ml) was added to the aqueous solution and the mixture left for 1 day at 0°C. The crystals which deposited were filtered off and washed with ether. After recrystallization, first from absolute alcohol, then from acetonitrile, 5.2 g (85%) salt Ii was obtained with mp 220°C (with decomposition). PMR spectrum (DMSO-d_6, δ, ppm): 1.08 (3H, t, $CH_2\underline{CH_3}$); 2.51 (3H, s, 5-CH_3), 2.75 (3H, s, 6-CH_3), 2.85 (2H, q, $\underline{CH_2}CH_3$), 2.87 (3H, s, 2-CH_3), 4.08 (3H, s, N-CH_3).

Indolization of 3-Nitropyridinium Salts by Reaction with a Methyl Ethyl Ketone N-Methylimine (General Method). To a solution of 0.003 mole 3-nitropyridinium salt in 3 ml DMF was added 0.075 mole imine III. The reaction mixture was kept for several days at room temperature and then poured into a 1:1 mixture of benzene and water. The benzene was separated and the aqueous layer extracted three times with benzene. The combined benzene extracts were washed with a small amount of water and dried over Na_2SO_4. The benzene was distilled off and the residue chromatographed on a column of 40 × 100 μ silica gel using 1:1 benzene—hexane as eluent.

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