SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS.

8.* PREPARATION OF A FREE ANHYDRO-BASE FROM THE 1,2,5,6-TETRAMETHYL-3-NITROPYRIDINIUM CATION, AND ITS INVOLVEMENT IN THE SYNTHESIS OF INDOLES FROM 3-NITROPYRIDINIUM SALTS

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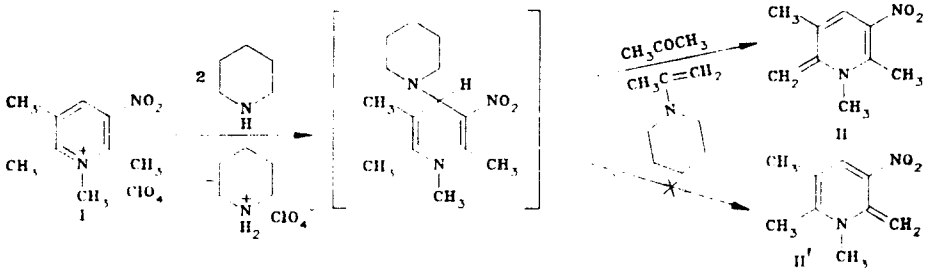
UDC 547.821.3'753:543.422: 541.124

The reaction of 1,2,5,6-tetramethyl-3-nitropyridinium perchlorate with acetone and piperidine on a solid carrier has given the novel, relatively stable 3-nitropyridine anhydro-base, 1,2,5-trimethyl-3-nitro-6-methylene-1,6-dihydropyridine, which bears alkyl groups only. This anhydro-base has been shown not to be an intermediate in the synthesis of indoles from 3-nitropyridinium salts.

It has been reported that the conversion of 3-nitropyridinium salts into indoles takes place in basic media, either in the presence of mixtures of a ketone and a primary amine [2, 3], or of ready-prepared ketimines whose basicity is not more than an order of magnitude less than that of the corresponding amines [5]. In view of the foregoing, and bearing in mind the CH-acidity of the α- and γ-methyl groups in 3-nitropyridinium cations, this reaction could occur via the anhydro-base. In order to test this possibility, we sought to isolate the anhydro-base in the free state and to react with a ketimine, although attempts to isolate and examine the unstable anhydro-bases of the pyridine series had been unsuccessful [6]. Attempts to obtain the anhydro-base by the usual method (deprotonation of 3-nitropyridinium salts with various bases) were unsuccessful. We were able to obtain the anhydro-base (II) only by carrying out the reaction of 1,2,5,6-tetramethyl-3-nitropyridinium perchlorate (I) with piperidine and acetone on Silpearl as a solid carrier, in a yield of 57%. The formation of (II) may be shown as follows:



It appears that on mixing the salt (I) applied to the carrier with excess piperidine, nucleophilic addition of the piperidine to the free 4-position of the salt occurs to give a carrier-bound adduct which is not eluted by methanol, and the piperidine salt which is eluted completely. Subsequent elution with acetone results in cleavage of the piperidine from the 1,4-dihydroadduct as the enamine, deprotonation occurring at the 6-CH_3 group as shown by PMR and ^{13}C NMR spectroscopy.

The suggested mode of formation of the anhydro-base (II) is supported by the lack of success of attempts to use this method to obtain anhydro-bases from 2,4,6-trialkyl-3-nitropyridinium salts.

The PMR spectrum of (II) shows signals for the protons of both the aromatic methyl groups (1.884 and 2.687 ppm), the N-methyl group (3.249 ppm), the exocyclic methylene group (4.032 ppm), and the 4-H proton (6.942 ppm). The ^{13}C NMR spectrum shows signals for the carbon atoms of the two aromatic methyl groups (18.547 and 19.668 ppm), the N-methyl

*See [1] for Communication 7.

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1214-1216, September, 1990. Original article submitted December 22, 1989.

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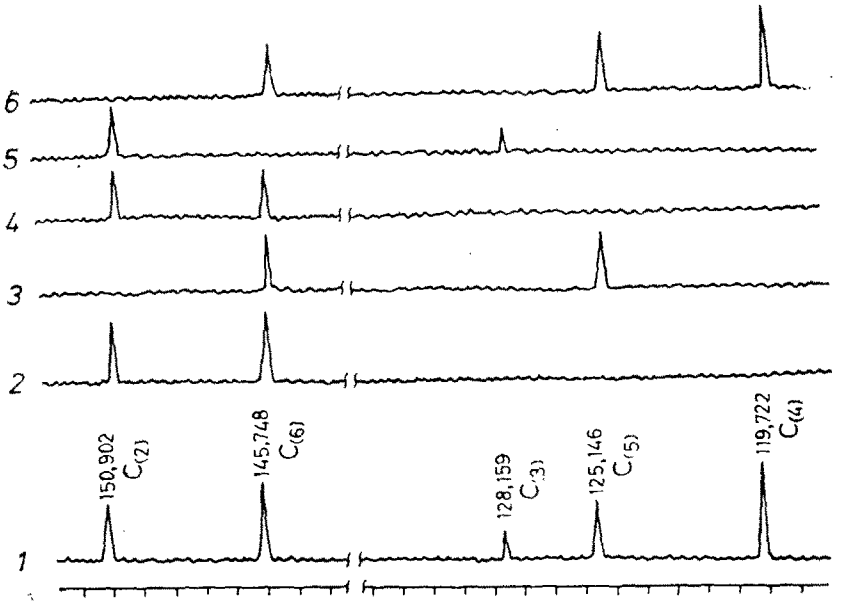


Fig. 1. ^{13}C NMR spectra (aromatic region) for (II): 1) $^{13}C\{^1H\}$ spectrum; 2-6) RPT difference spectra with selective excitation of the proton groups; 2) 4-CH; 3) 6-CH_2; 4) N–Me; 5) 2-Me; 6) 5-Me.

group (30.604 ppm), the exocyclic methylene group (83.063 ppm), the tertiary atom $C_{(4)}$ (119.802 ppm), and the four quaternary carbon atoms (125.160, 128.242, 146.888, and 150.726 ppm) (Fig. 1, curve 1). In order to make a choice between structures (II) and (II'), this information was inadequate, and we therefore resorted to the ^{13}C–^1H remote coupling constants, which established the mode of coupling of the ^{13}C and ^1H nuclei.

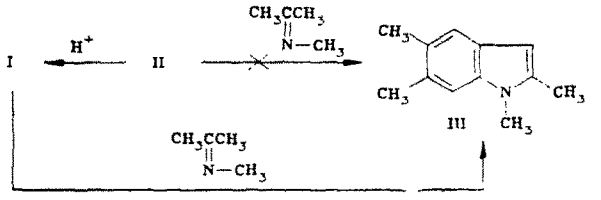
For this purpose, we utilized the spin echo method with selective excitation (SESE), which is a modification of two-dimensional J-resolving spectroscopy with selective excitation [7, 8] for the unidimensional case. This gave a series of ^{13}C NMR spectra (in the spin echo mode) with successive excitation of the individual groups of protons. Presentation of the series of these spectra in the difference mode (relative to the control echo spectra without excitation) enables the signals for the ^{13}C nuclei with large ^{13}C–^1H coupling constants with the excited protons (from 3 to 10 Hz, D2 = 0.1 sec) to be readily discerned.

For example, in Fig. 1, curve 2, excitation of the 4-H proton gives rise to signals for the two lowest-field quaternary atoms only, and similar behavior is seen when the N–CH_3 protons are excited (Fig. 1, curve 4). This enables these low-field signals to be assigned to the ring $C_{(2)}$ and $C_{(6)}$ atoms, which have vicinal constants with these protons. Detailed concurrent examination of the series of spectra (Fig. 1, curves 2-6), which correspond to successive excitation of the 4-H, 6-CH_2, N–CH_3, 2-CH_3, and 5-CH_3 protons, enabled full assignment of the signals to be made.

In order to choose between structures (II) and (II'), it was sufficient to consider spectra (5) and (6) (Fig. 1). Since these spectra show no coincident signals, structure (II') may be rejected, since this possesses two ortho-CH_3 groups, and on excitation the spectra should have shown coincident signals for $C_{(5)}$ and $C_{(6)}$. These observations provide clear confirmation of structure (II).

The anhydro-base (II) is stable in the solid state, but decomposes slowly in solution. This is the first example of the preparation of a relatively stable free anhydro-base of the 3-nitropyridine series bearing alkyl groups only.

On reaction of the anhydro-base (II) with N-methylacetonimine in DMF, it was found that, in contrast to the salt (I), 1,2,5,6-tetramethylindole (III) was formed extremely slowly (TLC), although if a protonating agent (an amine salt or acetic acid) was first added, formation of the indole commenced immediately.



This enables the participation of the anhydro-base in the formation of indoles to be excluded. It appears that the electrophilicity of the anhydro-base, which is considerably less than that of the salts, is insufficient for reaction to occur.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Varian VXR-400 in $CDCl_3$, internal standard TMS. Infra-red spectra were obtained on a UR-20 (in Vaseline grease), and UV spectra on a Cary-219 spectrophotometer (in ethanol).

1,2,5-Trimethyl-3-nitro-6-methylene-1,6-dihydropyridine (II). A solution of 0.48 g (1.71 mmoles) of the salt (I) in 5 ml of acetonitrile was added with stirring to 4 g of Silpearl as carrier, and the solvent removed at 150°C. To a separate portion of the carrier was applied piperidine at a rate of 10 g of carrier to 1 ml of reagent (salt:amine ratio 1:5). The applied reactants were mixed, shaken for 10-20 min, and the piperidine perchlorate eluted with methanol. The orange zone which then appeared was eluted quickly with acetone, the solution evaporated under reduced pressure at 15-20°C, the residue dissolved in benzene, dried over sodium sulfate at 20°C, concentrated under reduced pressure to a volume of 2 ml, hexane added until turbidity appeared, cooled to 0°C, and the solid filtered off. There was obtained 0.175 g (57%) of the anhydro-base (II) as deep red crystals, decomp. 80°C. UV spectrum: λ_{max} (log ε): 460 (4.16); 350 (4.14); 341 sh (4.14); 236 nm (4.28). IR spectrum: 1382 (s_{NO_2}); 1550 cm^{-1} (as_{NO_2}). PMR spectrum: 1.884 (3H, s, 5-CH_3); 2.687 (3H, s, 2-CH_3); 3.249 (3H, s, N–CH_3); 4.032 (2H, s, 6-CH_2); 6.942 ppm (1H, s, 4-H). ^{13}C NMR spectrum: 18.55 (2-CH_3); 19.67 (5-CH_3); 36.60 (N–CH_3); 83.06 (6-CH_2); 119.80 ($C_{(4)}$); 125.16 ($C_{(5)}$); 128.24 ($C_{(3)}$); 145.79 ($C_{(6)}$); 150.73 ppm ($C_{(2)}$).

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