SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS. 7.* STERICALLY HINDERED ALKYL-3-NITROPYRIDINIUM SALTS IN THE SYNTHESIS OF INDOLES

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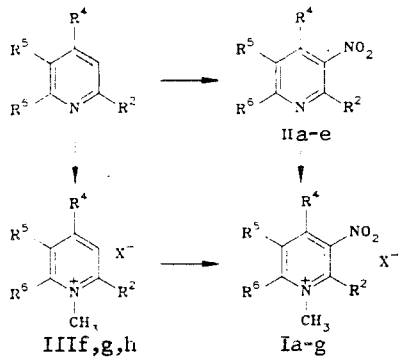
The introduction of bulky alkyl substituents (iso-Pr,tert-Bu) into any positions of the starting 3-nitropyridinium salt only increases the reaction time and decreases the yields of the corresponding alkylindoles somewhat.

The developed method for the synthesis of indoles from 3-nitropyridinium salts and N-methylketimines (or mixtures of ketones with amines) makes it possible to obtain polyalkylindoles with different numbers and orientations of unbranched alkyl substituents [2, 3]. 3-Nitropyridinium salts that contain branched bulky substituents have not been investigated in this reaction.

In the case of such salts we wanted to trace the effect of bulky substituents in various positions of the starting salt on the formation of indoles in the reaction with N-methylacetoneimine. In addition, we hoped that in would be possible to isolated intermediates of the process stabilized by such substituents.

For the investigation we selected N-methyl-3-nitro-pyridinium salts Ia-g, which contain alkyl substituents with increasing steric hindrance in various positions of the molecule (Et, CH_2—tert-Bu, iso-Pr, tert-Bu). For comparison, we used 2,4,6-trimethyl-3-nitropyridine methiodide (Ia, $R^2 = R^4 = R^6 = Me$) as a sterically unhindered model.

Starting salts I were obtained by two methods that differ with respect to the sequence of the nitration and quaternization steps:



I a–c $X^- = I$, d,f,g $X^- = ClO_4$, e $X^- = MeSO_4$; III h $R^2 = R^6 = i$-Pr, $R^4 = t$-Bu, $R^5 = H$; see Table 1 for radicals that are identical for I-IV.

The first method involves nitration of the corresponding polyalkylpyridines with subsequent quaternization with methylating agents and is suitable for obtaining salts Ia-e, which contain the simplest unbranched substituents (Me, Et) in the α position. In contrast to 2,6-dimethyl-3-nitropyridines IIa-c with a free 5 position, which are quaternized by methyl iodide (100°C, 10-15 h), 2,6-diethyl-4-methyl-3-nitropyridine (IIe) does not react with it at all even when the reaction time is increased substantially (50 h). The use of a more active methylating agent, viz., dimethyl sulfate, is required for the quaternization

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TABLE 1. Indoles IVa-g

Indole*	Empirical formula	R^2	R^4	R^6	mp, °C	t_{react}, days	M·	Yield, %	Literature cited
IVa		Me	Me	Me		1		62	[3]
IVb		Me	CH_2—*t*-Bu	Me		1		64	[8]
IVc	$C_{15}H_{21}N$	Me	*t*-Bu	Me	173...174	7	215	36	
IVd	$C_{15}H_{21}N$	Me	Me	Me	94...95	3		43	
IVe		Et	Me	Et		1		70	[8]
IVf	$C_{16}H_{23}N$	*i*-Pr	Me	*i*-Pr	Oil	5	229	9	
IVg	$C_{18}H_{27}N$	*i*-Pr	*i*-Pr	*i*-Pr	Oil	5	257	37	

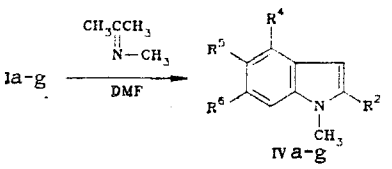
*In the case of IVa-c, e-g R^5 = H, whereas R^5 = iso-Pr for IVd.

of pyridine IIe. In general, the quaternization of 2,6-disubstituted pyridines is extremely sensitive to electronic and steric factors [4]. We demonstrated that even the introduction of an isopropyl substituent (IId) into the 5 position of the sym-3-nitrocollidine molecule substantially hinders the reaction and that only 20% of the base is quaternized under very severe conditions (methyl iodide, 130°C, 6 h), and dimethyl sulfate was therefore also used in this case as the methylating agent (for convenience in the purification the methylsulfate salt was converted to perchlorate Id). The introduction of an isopropyl group into the 5 position evidently increases the shielding of the pyridine nitrogen atom by the adjacent 6-CH_3 group and hinders attack by the methylating agent. In an attempt to use dimethyl sulfate for the quaternization of 2,6-diisopropyl-4-methyl-3-nitropyridine (IIf) it was found that the base is recovered unchanged under the conditions used to obtain salt Id and undergoes resinification under more severe conditions (140°C, 6 h). In this connection, for the synthesis of salts If, g that contain isopropyl groups in the 2 and 6 positions we used a second method based on the proven fact of nitration of alkylpyridines in the cationic form [5, 6].

In contrast to nitro derivative IIf, starting 4-methyl-2,6-diisopropylpyridine is quaternized by dimethyl sulfate with the formation of methylsulfate salt IIIf, which we nitrated in the form of the hydrosulfate salt formed after hydrolysis. We were able to obtain maximally sterically hindered salt Ig only when we used almost exhaustive methylation of sym-collidine methiodide under interphase-catalysis conditions [7] with subsequent nitration. Sym-Collidine methiodide could not be throughly methylated (to completion) under the conditions in [7] — a mixture of cations IIIg and IIIh is formed, and only salt IIIg undergoes subsequent nitration with a mixture of HNO_3 and nitronium tetrafluoroborate in 20% oleum; the sterically more hindered salt IIIh is recovered unchanged even under more severe conditions. We developed a special method for the isolation of 3-nitropyridinium cations that contain lipophilic alkyl substituents; this method is based on the efficient extraction with chloroform of the resulting tetrafluoroborates from the diluted (with an equal volume of water) reaction mixture with subsequent isolation in the form of perchlorates on an anion-exchange resin.

It should be noted that when isopropyl or tert-butyl substituents are present in the α and γ positions nitration proceeds in low yields as a consequence of the easy oxidation of these branched radicals.

All of the 3-nitropyridinium salts Ia-g obtained react with N—methylacetoneimine in DMF [3] to give the corresponding indoles IVa-g:



IVa-g

TABLE 2. PMR Spectra of Indoles IV in $(CD_3)_2CO$

Indole	δ, ppm (J, Hz)						
	N—CH_3,	R^2	3-H	R^4	R^5	R^6	7-H, s
IVc	3,59	2,40 s	6,39 s	1,48 s	6,83 s	2,47 s	6,92
IVd	3,55	2,33 s	6,10 s	2,45 s	1,33 d (J=7 Hz); 3,36 sept	2,45 s	6,87
IVf	3,77	1,25 d (J=7,6 Hz); 3,10 sept	6,16 d.d. ($J_{37}=J_{3,2\text{-Me}}$ = =0,9 Hz)	2,42 s	6,51 s	1,32 d (J=7,6 Hz); 2,96 Sept	7,28
IVg	3,69	1,33 d (J=7,0 Hz) 3,14 sept	6,27 s	1,34 d (J=6,9 Hz); 3,29 Sept	6,82 s	1,29 d (J=6,95 Hz); 3,29 Sept	7,02

TABLE 3. 3-Nitropyridines II

Compound*	Treact, °C**	bp, °C (mm)	PMR spectrum, δ, ppm				Yield, %
			2-R	4-R, s	5-R	6-R	
IIc	105...110	139...140 (14) 50...51 (from aqueo MeOH)***	2,47 s	1,33	6,64 s	2,36 s	40
IId	110...115	146...148 (20)	2,54 s	2,22	1,34 d (J=7,6 Hz); 3,41 Sept	2,35 s	70
IIf	100...105	130...135 (17)	1,24 d (J=6,8 Hz); 2,97 Sept	2,20	6,80	1,24 d (J=6,8 Hz); 2,97 Sept	51

*Compound IIc was nitrated by method A, while IId, f were nitrated by method B.
**The reaction time for IIc, f was 60 h, while the reaction time for IId was 70 h.
***Melting point.

This very fact provides evidence that the formation of indoles from 3-nitropyridinium salts does not make severe demands: even the presence of a tert-butyl radical in the 4 position or isopropyl radicals in the 2 and 6 positions does not hinder the reaction but only slows it down somewhat.

Unfortunately, we were unable to isolate stabilized intermediates in any of the cases examined.

A concrete examination of the transformations of sterically hindered 3-nitropyridinium salts to the corresponding indoles presented in this research (Table 1) makes it possible to ascertain the effect of the orientation, number, and structure of the alkyl radicals on the effectiveness of the process; it should be noted that other pathways of the transformations of salts I were not investigated within the framework of this research.

We have proposed [8] that the first step in the transformation of 3-nitropyridinium salts I to indoles is meta bonding of the enamine form of the ketimine, which here acts as a 1,3-bis-C,C nucleophile, with respect to the 4 and 6 positions of the electron-deficient 3-nitropyridinium ring. In this connection an increase in the volume of the substituent in the 5 position should hinder the indolization reaction. In fact, in the series of 1,2,4,6-tetramethyl-5-R-3-nitropyridinium salts the yields of the corresponding indoles in the reaction with N-methylacetoneimine in DMF are 62% when R^5 = H [3], 55% when R^5 = Me [3], and 43% when R^5 = iso-Pr; the reaction time in the latter case increased to 3 days (as compared with 1 day in the first two cases).

It is apparent that the presence of bulky substituents directly in the sites of meta bonding (the 4 and 6 positions) should have an even greater effect. Replacement of the methyl group in the 4 position (sym-3-nitrocollidinium salt Ia) by a 4-tert-butyl group (salt Ic) leads to a decrease in the yield of the corresponding indole IVc to 36% (after 7 days). Distancing of this tert-butyl substituent by one methylene group from the site of bonding (4-neopentyl salt Ib) leads to elimination of steric hindrance to indolization (the yield of indole IVb after 1 day is 64% [9]).

To examine the effect of α substituents we selected 4-methyl salts Ia,e,f, which contain methyl, ethyl (the yield of indole IVe was 70%), and isopropyl groups (the yield of indole IVf was 9%) in the 2 and 6 positions; it was found that only α-isopropyl groups hinder the formation of the corresponding indole. However, this sharp decrease in the yield of 1,4-dimethyl-2,6-diisopropylindole (IVf) cannot be unequivocally linked only with steric factors, since in the reaction of 2,4,6-triisopropyl salt Ig the yield of the corresponding indole is 37% for the same reaction time (5 days). That combination of steric and electronic factors which favors different pathways (in addition to indolization) of the transformation processes is evidently realized for salt If. In this case a number of polar brightly colored compounds, the structures of which have not yet been established, are formed in the reaction. However, the certain increase in the yield of 1,4-dimethyl-2,6-diethylindole (IVe) as compared with 1,2,4,6-tetramethylindole (IVa) is probably due to suppression of competitive condensation processes when the α-methyl groups are replaced by methylene groups.

In conclusion, it should be noted that at the present time the method that we developed for the synthesis of indoles from 3-nitropyridinium salts is the only possible method for obtaining previously unknown and inaccessible (by other methods) polyalkylindoles with bulky substituents in predesignated positions.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with Varian T-60 and Varian XL-300 spectrometers with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the purity of the indoles formed were monitored by TLC on Silufol in a benzene—hexane system (1:3).

The preparation of 1,2,6-trimethyl-4-neopentyl-3-nitropyridinium iodide (Ib) and 1,4-dimethyl-2,6-diethyl-3-nitropyridinium methylsulfate (Ie) was described in [8]. 2,6-Dimethyl-4-tert-butylpyridine was obtained from 2,6-dimethyl-γ-pyrone through the corresponding pyrylium salt [10]. 4-Methyl-2,6-diisopropyl- [11] and 2,4,6-trimethyl-3-isopropylpyridine [12] were also obtained from the pyrylium salts, which were synthesized by diacylation of the corresponding olefins.

Indoles IVa-g were obtained from the corresponding 3-nitropyridinium salts Ia-g and N-methylacetoneimine in DMF by the method in [3].

The reaction conditions and the characteristics of the indoles are presented in Tables 1 and 2, while the same information for 3-nitropyridines II is presented in Table 3. The results of elementary analysis of salts Id,f,g for Cl and of indole IVd for C, H, and N, as well as the M^+ values for indoles IVc,f,g, were in agreement with the calculated values.

Nitration of Polyalkylpyridines (General Method). The polyalkylpyridines were nitrated either with a mixture of HNO_3 (d = 1.5) with concentrated H_2SO_4 (method A) or with KNO_3 in 20% oleum (method B). The cooled reaction mixture was poured over ice, and the aqueous mixture was neutralized with 10% KOH solution or concentrated ammonium hydroxide. The nitropyridines were extracted with benzene or ether, the extract was dried with Na_2SO_4, the solvent was removed by distillation, and the residue was fractionated in vacuo.

1,2,6-Trimethyl-4-tert-butylpyridinium Iodide (Ic). A mixture of 0.127 g (0.61 mmole) of 3-nitropyridine IIc and 3 ml (21 mmole) of methyl iodide was heated at 100°C in a sealed ampul for 15 h, after which the precipitate was removed by filtration and washed with absolute ether to give 0.108 g (51%) of salt Ic with mp 168-170°C. PMR spectrum (d_7-DMF): 1.41 [9H, s, $C(CH_3)_3$], 2.92 (6H, s, 2-CH_3, 6-CH_3), 4.27 (3H, s, N—CH_3), 8.39 ppm (1H, s, 5-H).

1,2,4,6-Tetramethyl-5-isopropylpyridinium Perchlorate (Id, $C_{12}H_{19}ClN_2O_6$). A mixture of 2.57 g (12.36 mmole) of nitropyridine IId with 1.43 ml (15 mmole) of dimethyl sulfate was heated until an exothermic reaction began (~120°C), after which the temperature was raised to 130°C, and the mixture was maintained at this temperature for 1 h. It was cooled, washed with dry ether, and dissolved in 2 ml of water. The solution was treated with 2 ml of 70% perchloric acid, and the precipitate was washed with small portions of cold water and methanol. The yield of salt Id, with mp 176-179°C (from acetone), was 3.15 g (79%). PMR spectrum (d_6-DMSO): 1.42 [6H, d, $CH(CH_3)_2$, J = 7.5 Hz], 2.52 (3H, s, 4-CH_3), 2.73 (3H, s, 6—CH_3), 2.93 (3H, s, 2-CH_3), 3.59 [1H, sept, $CH(CH_3)_2$], 4.17 ppm (3H, s, N—CH_3).

1,4-Dimethyl-2-6-diisopropyridinium Perchlorate (If, $C_{15}H_{25}ClN_2O_6$). A mixture of 3.48 g (19.7 mmole) of 4-methyl-2,6-diisopropylpyridine and 2.2 ml of freshly distilled dimethyl sulfate was heated for ~ 1 h (until the starting pyridine has vanished according to TLC) at 120-125°C, after which it was cooled to 70-80°C, treated with 5 ml of water, and refluxed for 3 h with a short air condenser (the methanol was removed by distillation). The residual methanol and water were removed by distillation in vacuo (~100°C), and 20 ml of 20% oleum, 5 ml of HNO_3 (d 1.5), and 5 g of nitronium tetrafluoroborate were added with stirring to the residual viscous oil — a mixture of pyridinium hydrosulfate and sulfuric acid — and the mixture was heated at 100-105°C for ~ 60 h, gradually raising the temperature at the end of the process to 115°C. The cooled reaction mixture was poured over 30 g of ice, excess sodium acetate was added, and the mixture was extracted with chloroform in a continuous-operation extractor until a sample of the extract after evaporation no longer gave a red-pink coloration with acetone—piperidine. The chlorofom extract was dried with Na_2SO_4 and evaporated in vacuo, and the residual yellowish oil (a mixture of the tetrafluoroborate and the acetate) was dissolved in 2.3 ml of water. The resulting solution was stirred with a saturated solution of lithium perchlorate to give 0.9 g (14%) of salt If with mp 195-196°C (dec., from acetone). PMR spectrum (d_6-DMSO): 1.44 [12H, d, 2-, 6-$CH(CH_3)_2$, J = 6.6 Hz], 2.65 (3H, s, 4-CH_3), 3.63 [2H, sept, 3-, 6-$CH(CH_3)_2$], 4.29 (3H, s, N—CH_3), 8.04 ppm (1H, s, 5-H).

1-Methyl-2,4,6-triisopropylpyridinium Sulfate (IIIg). A mixture of 30 g (0.11 mole) of sym-collidine methiodide, 104 ml (1.7 mole) of methyl iodide, 90 ml of 50% NaOH solution, 15 ml of CH_2Cl_2, and 20 g of $Bu_4N^+OH^-$ (30% aqueous solution) was stirred for several days at 20°C until the color of the organic layer changed from dark green to light yellow. The organic layer was separated and evaporated to give 2,4,6-triisopropylpyridine methiodide [32 g (84%), mp 164-165°C (from alcohol—ether)], 4.77 g (0.129 mmole) of which was dissolved in methanol, after which the solution was passed very slowly (~2 h) through a column packed with 20 g of Pyrolite A-450 ion-exchange resin in the SO_4^{2-} form with methanol as the eluent. The eluate was evaporated in vacuo to give 3.72 g (99%) of salt IIIg (a glassy greenish mass), which was subjected to nitration without purification.

1-Methyl-2,4,6-triisopropyl-3-nitropyridinium Perchlorate (Ig, $C_{15}H_{25}ClN_2O_6$). Pyridinium sulfate IIIg (3.72 g) was dissolved in 6 ml of concentrated H_2SO_4, 5 ml of HNO_3 (d = 1.5), and 15 ml of 60% oleum, after which the solution was cooled and treated with ~4 g of nitronium tetrafluoroborate, and the mixture was heated at 80°C until everything had dissolved. The temperature was slowly raised to 90-95°C (slight gas evolution was observed). After 5 h, the temperature was raised to 105-110°C, and the mixture was maintained at this temperature for ~ 100 h. The cooled mixture was poured over 30 g of ice, and the aqueous mixture was extracted with chloroform (20 10-ml portions). The extract was dried with Na_2SO_4 and evaporated. According to the PMR spectral data, a mixture (2:3) of unnitrated and throughly nitrated tetrafluoroborates was formed. The mixture was dissolved in methanol, and the BF_4^- was exchanged for ClO_4^- by means of Pyrolite A-450 ion-exchange resin in the ClO_4^- form. The mixture of perchlorates was recrystallized several times from methanol—ether to give 0.336 g (7%) of salt Ig with mp 183-185°C (dec., from acetone). PMR spectrum ($CDCl_3$): 1.33 (6H, d, 4-$CH(CH_3)_2$, J = 7.6 Hz), 1.40 (6H, d, 6-$CH(CH_3)_2$, J = 7.6 Hz), 1.65 (6H, d, 2-$CH(CH_3)_2$, J = 7.6 Hz), 3.60 (3H, m, 2-, 4-, 6-$CH(CH_3)_2$), 4.30 (3H, s, N—CH_3), 7.60 ppm (1H, s, 5-H).

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