SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS. 1. RECYCLIZATION OF 4-ALKYL-2,6-DIMETHYL-3-NITROPYRIDINE METHIODIDES IN THE PRESENCE OF KETONES

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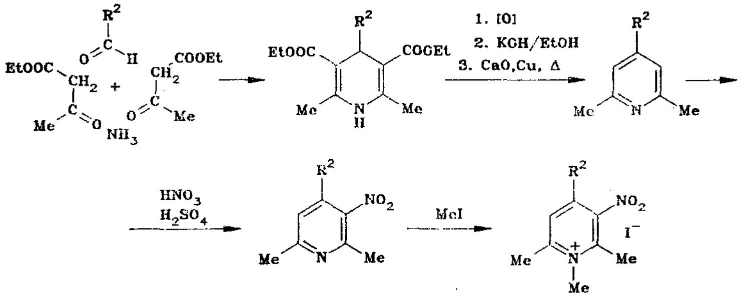
A method for the synthesis of 4-alkylpolymethylindoles by recyclization of 4-alkyl-2,6-dimethyl-3-nitropyridine methiodides in the presence of ketones was developed. A method for establishing the structures of the polyalkylindoles on the basis of data from the PMR spectra and the proton-coupled ^{13}C NMR spectra is proposed.

A fundamentally new approach to the synthesis of the indole ring, viz., the reaction of alkyl-3-nitropyridinium salts with ketones in the presence of amines, was recently discovered [1, 2]. On the basis of the previously conducted study [1] of the products of the reactions of 2,4,6-trimethyl- and 2,4- and 4,5-dimethyl-3-nitropyridines with ketones, it is impossible to unambiguously establish which fragments of the starting molecules participate in the construction of the benzene and pyrrole rings of the resulting indoles.

In order to shed some light on this problem we used the "chemical label" method, selecting pyridinium salts with ethyl or propyl groups in the 4 position as the starting compounds. We assumed that the modification or retention of this alkyl group in the resulting indoles would make it possible to evaluate the degree of its participation in the formation of the indole ring.

The establishment of the positions of the substituents in polyalkylindoles is not a simple task, inasmuch as they are difficult to distinguish by ordinary spectral methods. This made it imperative that we develop a method for the reliable establishment of the structures of the resulting polyalkylindoles on the basis of a combination of data from the PMR and ^{13}C NMR spectra.

Starting pyridinium salts Ia,b were obtained via the scheme



Ia,b

Salts Ia,b were also subjected to recyclization with acetone and methyl ethyl ketone. The process takes place under very mild conditions in an excess amount of the corresponding ketone, saturated with methylamine, at room temperature in the course of a few days [1]. The resulting indoles are isolated by chromatography with a column packed with silica gel.

Absorption maxima that are characteristic for indole structures [λ_{max} 276-278 nm (log ε 3.9-4.01)] [3] are observed in the UV spectra of IIa-d. The fact that structures II belong to the indole series is also confirmed by their mass-spectral fragmentation: A low-intensity

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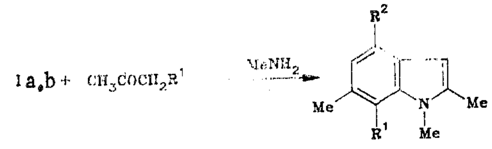


IIa-d

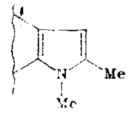
Ia IIa,b R^2=Et; Ib, IIc,d R^2=Pr; IIa,c R^1=H; b,d R^1=Me

but characteristic triplet of ion peaks* at 117, 116, and 115 [4] is present in the spectra of all of the compounds. The molecular ions of II are quite stable with respect to electron impact: IIa 187 (63), IIb 201 (51), IIc 201 (38), and IId 215 (31). The maximum peaks in all cases are the peaks corresponding to the elimination of a methyl radical in the 4 position for IIa,b to give ions at 172 and 186 and to the elimination of an ethyl radical for IIc,d to give ions at 172 and 186, respectively. In the mass spectra of IIc,d this process is confirmed by metastable ions with apparent masses of 147.2 and 160.9, respectively.

$$\underset{201\ (38)}{M^+\ \text{IIc}} \xrightarrow{147.2} \underset{172\ (100)}{[M-Et]}$$

$$\underset{215\ (31)}{M^+\ \text{IId}} \xrightarrow{160.9} \underset{186\ (100)}{[M-Et]}$$

We established the structures of IIa-d unambiguously by using a combination of data from the PMR and ^{13}C NMR spectra. The presence of lone signals at 3.2-3.8 ppm (Table 1) of protons of N—CH_3 groups is characteristic for the PMR spectra of II. Characteristic multiplets of the protons of ethyl groups are observed in the spectra of IIa,b, whereas characteristic multiplets of protons of n-propyl groups are observed in the spectra of IIc,d. The signals of the protons of the remaining methyl groups are found at 2.2-2.5 ppm, which is the region characteristic for methyl groups bonded to aromatic rings. From the magnitude of its chemical shift, the signal at 6.09-6.13 ppm should be assigned to the 3-H proton [5]. In the case of IIb,d these signals have the form of quartets (Fig. 1a) due to splitting by the protons of the adjacent methyl group (J = 1.0 Hz); this is confirmed by the collapse of this signal to a singlet in the case of irradiation with a second radiofrequency field at a frequency of 224 Hz from tetramethylsilane (2-CH_3) (Fig. 1b). Thus, the presence of signals of protons of N—CH_3 groups and the position [5] and multiplicity of the signal of the 3-H proton make it possible to assign the structure given below to the pyrrole part of the IIa-d molecules:



For IIa,c irradiation of the signal of the 2-CH_3 group leads to conversion of the signal of the 3-H proton to a doublet (J = 0.85 Hz) (Fig. 2b), and a similar constant is characteristic for coupling of the 3-H and 7-H protons in indoles [5, 6].

In the case of IIa-d the protons of the benzene part of the molecule in the monoresonance PMR spectra are broadened or have a complex multiplet structure due to spin—spin coupling (SSCC) with the protons of the alkyl groups (Figs. 1a and 2a).

In the double-resonance PMR spectra of IIa in the case of irradiation of the signal of the CH_3 group of the benzene part of the molecule (237 Hz from TMS) the multiplet structure of the signals of these protons is simplified somewhat (Fig. 2c) and makes it possible to single out the SSCC between these protons (J = 1.4 Hz), which is characteristic for protons in the meta position. Thus the protons are in the 5 and 7 positions in the benzene ring of IIa.

We obtained more detailed information regarding the structures of the resulting indoles by a study of the ^{13}C NMR spectra; substantial information may be provided by the $^{13}C—^1H$ SSCC of the carbon atoms of the alkyl groups with the protons of the benzene ring and, on the other

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*Here and subsequently, the m/z values are given for the ion peaks (the intensities in percent relative to the maximum ion peak are given in parentheses).

TABLE 1. Chemical Shifts of the ^1H Nuclei (ppm with respect to tetramethylsilane) for Indoles IIa-e

Compound	Ring									
	2-H	3-H	5-H	6-H	7-H	1-CH$_3$	2-CH$_3$	4-CH$_3$	6-CH$_3$	7-CH$_3$
IIa	—	6,09	6,63	—	6,77	3,32	2,19	—*	2,37	—
IIb	—	6,09	6,59	—	—	3,66	2,24	—*	2,26	2,44
IIc	—	6,13	6,63	—	6,84	3,46	2,28	—†	2,36	—
IId	—	6,13	6,61	—	—	3,75	2,28	—†	2,28	2,50
IIe‡	7,17	6,44	6,82	7,04	7,21	3,80	—	2,48	—	—

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*The chemical shifts of the protons of the CH$_2$ and CH$_3$ groups of R^2 are as follows: 2.77 and 1.25 (IIa) and 2.71 and 1.23 ppm (IIb).

†The chemical shifts of the protons of the α-CH$_2$, β-CH$_2$, and γ-CH$_3$ groups of R^2 are as follows: 2.72, 1.69, and 0.92 (IIc), 2.68, 1.68, and 0.93 ppm (IId).

‡The spin-spin coupling constants (SSCC) are as follows: J_{23} = 3.17, J_{26} = 0.40, J_{37} = 0.95, J_{57} = 1.05, J_{56} = 6.89, and J_{67} = 8.11 Hz.

TABLE 2. Chemical Shifts of the ^{13}C Nuclei (ppm from TMS) of the Aromatic Atoms for Indoles IIa-e (the chemical shifts of the carbon atoms calculated by an additive scheme are given in parentheses)

Compound	Ring						Ring						
	C$_{(2)}$	C$_{(3)}$	C$_{(4)}$	C$_{(5)}$	C$_{(6)}$	C$_{(7)}$	C$_{(8)}$	C$_{(9)}$	1-CH$_3$	2-CH$_3$	4-CH$_3$	6-CH$_3$	7-CH$_3$
IIa	135,93 (137,95)	98,17 (96,88)	135,12 (134,60)	120,05 (118,73)	130,24 (130,33)	107,42 (106,34)	125,66 (126,95)	138,62 (139,84)	29,67	12,56	*	21,97	—
IIb	136,76 (137,55)	98,64 (97,23)	132,27 (132,22)	121,50 (119,14)	128,93 (130,39)	116,75 (115,36)	127,15 (126,61)	137,68 (140,06)	33,04	13,33	*	20,47	14,52
IIc	135,94 (137,95)	98,33 (96,88)	133,49 (133,31)	121,01 (119,11)	130,11 (130,43)	107,44 (106,29)	126,04 (127,33)	138,66 (139,94)	29,31	12,57	†	21,93	—
IId	136,85 (137,55)	98,86 (97,23)	130,71 (130,93)	122,55 (119,52)	128,89 (130,49)	116,82 (115,31)	127,60 (126,99)	137,80 (140,17)	33,19	13,40	†	20,49	14,62
IIe	129,14 (128,28)	99,71 (99,44)	130,26 (129,97)	122,11 (121,53)	119,99 (119,37)	107,77 (107,15)	129,36 (129,06)	136,27 (137,62)	32,92	—	18,73	—	—

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*The chemical shifts of the carbon atoms of the CH$_2$ and CH$_3$ groups of R^2 are as follows: 26.88 and 15.40 ppm (IIa), 26.49 and 15.40 ppm (IIb).

†The chemical shifts of the carbon atoms of the α-CH$_2$, β-CH$_2$, and γ-CH$_3$ groups of R^2 are as follows: 36.13, 24.48, and 14.41 ppm (IIc), 35.80, 24.47, and 14.45 ppm (IId).

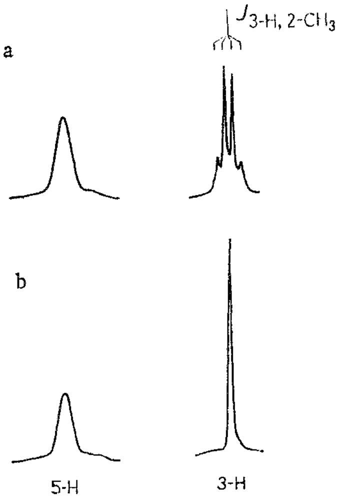


Fig. 1

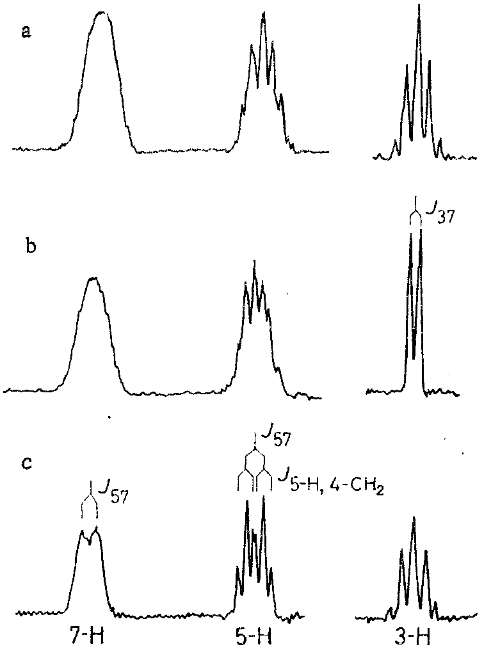
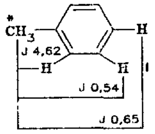


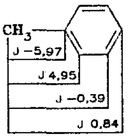
Fig. 2

Fig. 1. PMR spectra of IIb (aromatic-proton region): monoresonance spectrum (a) and double resonance with spin decoupling of the protons of the 2-CH_3 group (b).

Fig. 2. PMR spectra of IIa (aromatic-proton region): monoresonance spectrum (a) and double resonance with spin decoupling of the protons of the 2-CH_3 (b) and 6-CH_3 (c) groups.

hand, by the ^{13}C—^1H SSCC of the protons of the alkyl groups with the carbon atoms of the benzene ring. According to the data in [7], they are as follows:





Close values of the long-range ^{13}C—^1H SSCC are observed in the spectra of 2- and 3-methylthiophenes and 2-methylfuran [8].

We recorded the proton-coupled ^{13}C NMR spectra of key compounds IIa,b. The signal of the carbon atom of the methyl group of the benzene ring of IIa* has the form of a quartet of triplets; the direct ^{13}C—^1H constant is 124.8 Hz. The triplet splitting with a constant of 4.7 Hz constitutes evidence for the presence of two ortho protons adjacent to this methyl group. This enables us to unambiguously assign the 1,2,6-trimethyl-4-ethylindole structure (IIa) to the product of the reaction of salt Ia with acetone.

The establishment of the structure of IIb is a more complex problem. Six signals of carbon atoms in the aliphatic region and eight signals of carbon atoms in the aromatic region of the spectrum are present in the $^{13}C\{^1H\}$ NMR spectra of IIb. On the basis of data on the chemical shifts of methylindoles [9], only the signals of the $C_{(3)}$, $C_{(7)}$, and 1-CH_3 carbon atoms can be assigned unambiguously at this stage (Table 2). An examination of the multiplet structure of the carbon signals in the proton-coupled ^{13}C NMR spectra of IIb made it possible to refine the initial assignment significantly. Thus the signal at 33.04 ppm, which has direct constant ^1J = 138.0 Hz, is related to the methyl group in the 1 position. All of the remain-

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*The assignment of this signal was made on the basis of the $^{13}C\{^1H\}$ double resonance NMR spectra with selective decoupling of the protons of the CH_3 groups.

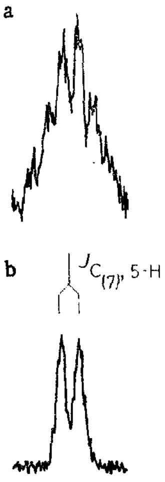


Fig. 3

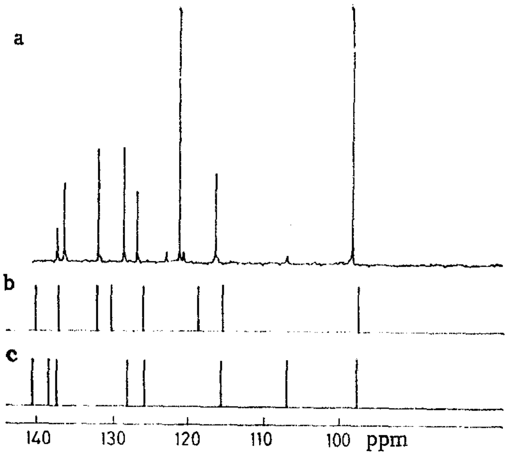


Fig. 4

Fig. 3. Proton-coupled ^{13}C NMR spectra of the $C_{(7)}$ atom of IIb: monoresonance spectrum (a) and double-resonance spectrum with selective decoupling of the protons of the methyl groups (b).

Fig. 4. $^{13}C\{^1H\}$ NMR spectra of IIb (in the region of the aromatic carbon atoms): experimental (a) and calculated by the additive scheme for structures IIb (b) and III (c).

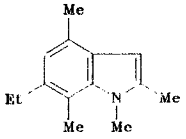
ing signals of the carbon atoms of the methyl groups have SSCC from 125.1 to 127.0 Hz. An analysis of the fine multiplet structure made it possible to assign the signal at 15.40 ppm to the CH_3 group of the ethyl fragment (triplet splitting with J = 4.6 Hz by the protons of the CH_2 group, which is typical for ethyl derivatives [10]). A similar constant of ~4.3 Hz, which is observed for the signal at 26.49 ppm, characterizes the spin–spin coupling of the carbon atoms of the CH_2 group with the protons of the CH_3 group of the ethyl fragment. For the same signal we observe a long-range SSCC (4.3 Hz) with an aromatic proton. We observe a constant with a close value (4.9 Hz) for the signal of the methyl group at 20.47 ppm. At the same time, the signal at 14.52 ppm does not display a long-range constant, whereas the signal at 13.33 ppm displays a relatively small SSCC (2 Hz). On the basis of these data it may be concluded that the signal at 13.33 ppm belongs to the 2-CH_3 group of the pyrrole ring and that the ethyl and methyl groups (20.47 ppm) are in the ortho position relative to the aromatic proton.

The fact that an alkyl group is actually located in the 7 position of IIb also follows from the character of the multiplet structure of the signal of the 3-H proton in the PMR spectrum — for it, we do not observe an interring SSCC with the proton of the benzene ring, which should have a value of 0.8-0.9 Hz [5, 6] and was noted in the PMR spectra of IIa,c (see above). Furthermore, it follows from the magnitude of the chemical shift of the signal of the quaternary $C_{(7)}$ atom (116.75 ppm) in the ^{13}C NMR spectrum of IIb that it is bonded precisely to the methyl group. In fact, the methyl and ethyl groups have a large difference in the increments of ipso substitution of the benzene ring ($\Delta\delta_{CH_3}$ = 9.22 ppm and $\Delta\delta_{C_2H_5}$ = 15.59 ppm) [11]. If the ethyl group were located in the 7 position, on the basis of the data in [9], one should have expected the appearance of a $C_{(7)}$ signal at about 120-122 ppm.

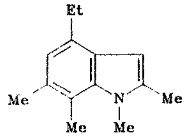
Thus the lone proton of the benzene part of the IIb molecule can be located only in the 5 or 6 position of the indole ring.

To determine the position of the aromatic proton one can use data on the ^{13}C–^1H SSCC of the $C_{(7)}$ atom with this proton. For this, we recorded the ^{13}C–^1H double resonance spectra with selective irradiation of the protons of the CH_3 groups. In the case of irradiation at a frequency of 244 Hz from TMS with an amplitude of the irradiating field γH_2 of 36 Hz the signal of the $C_{(7)}$ atom has the form of a doublet with a splitting of 6.1 Hz (Fig. 3). This splitting can be due only to spin–spin coupling with a proton in the 5 position [the meta position relative to $C_{(7)}$], since only an intraring ^{13}C–^1H SSCC through these bonds can have such a large value (6-8 Hz), whereas ^{13}C–^1H SSCC through two and four bonds in such structural fragments should not exceed 2 Hz [12].

Thus for IIb the entire set of data makes it possible to limit ourselves to an examination of only two possible structures:



III



IIb

We chose between these structures on the basis of calculations of the chemical shifts of the ^{13}C nuclei of the benzene part of the molecule by an additive scheme. The calculations were made from the formula

$$\delta^{\text{add}}_{C\text{-}i} = \delta^{0}_{C\text{-}i} + \Delta\delta_{C\text{-}i}(R_j),$$

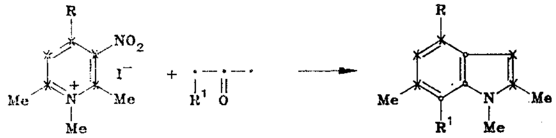
where $\delta^{\circ}_{C\text{-}i}$ is the chemical shift of the C-i nucleus in 1-methylindole,* and $\Delta\delta_{C\text{-}i}(R_j)$ is the increment of substituent R_j for the magnitude of the chemical shift of the C-i nucleus.

We used the data in [9] as the increments of substitution of methyl groups in the 2, 4, 6, and 7 positions. The increments of the ethyl and n-propyl groups were taken from [13] for the corresponding monosubstituted benzenes. The results of the calculations of the additive scheme are presented graphically (Fig. 4). It is clearly apparent from Fig. 4 that the experimental ^{13}C NMR spectrum of IIb (Fig. 4a) is in better agreement with the spectrum calculated for structure IIb (Fig. 4b) than for structure III (Fig. 4c).

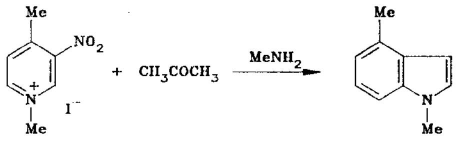
Thus, on the basis of a combination of all the data presented above, we have established the 1,2,6,7-tetramethyl-4-ethylindole structure (IIb) for the product of the reaction of salt Ia with methyl ethyl ketone.

The parameters of the PMR and ^{13}C NMR spectra of IIc and IId, with allowance for the effect of the n-propyl group in the 4 position, are in excellent agreement with the parameters of the spectra of IIa and IIb (see Tables 1 and 2).

As a result of the reliable establishment of the structure of IIa-d, it may be asserted that both starting molecules, viz., both the pyridinium salt and the ketone, participate in the construction of both the benzene and pyrrole rings of the resulting indoles.



In fact, the (Me)$C_{(4)}$—$CH_{(5)}$=$C_{(6)}$(R) fragment of the pyridinium salt is retained completely in the benzene ring of the indoles, and the transition from acetone (R^1 = H) to methyl ethyl ketone (R^1 = Me) is accompanied by the introduction of a methyl group into the 7 position of the indole. In order to confirm the proposed "molecular design" we once again had to confirm that a fragment of the pyridinium salt participates in the construction of the pyrrole ring. For this, we made a detailed study of the structure of the product of the reaction of 4-methyl-3-nitropyridine methiodide with acetone, which leads to 1,4-dimethylindole (IIe).†



IIe

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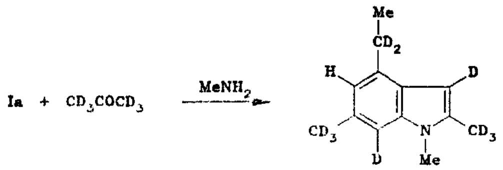
*The ^{13}C chemical shifts of 1-methylindole (in d_6-acetone) are as follows: 129.27 [$C_{(2)}$], 101.01 [$C_{(3)}$], 121.01 [$C_{(4)}$], 121.65 [$C_{(5)}$], 119.50 [$C_{(6)}$], 109.71 [$C_{(7)}$], 129.13 [$C_{(8)}$], 137.23 [$C_{(9)}$], and 32.19 ppm (N—CH_3).

†4-Methyl-3-nitropyridine methiodide was kindly provided by S. P. Gromov. The given method of synthesis was first used for IIe by S. P. Gromov, M. M. Bkhaumik, and Yu. G. Bundel'.

The absence of a methyl group in the 2 position of the resulting indole IIe is in complete agreement with the idea expressed above, that a fragment of the pyridinium salt participates in the construction of the pyrrole ring.

In the PMR spectrum of IIe (Fig. 5a) the signal of the proton at 6.44 ppm has the form of a doublet of doublets with SSCC 3.17 and 0.85 Hz, which can be unambiguously assigned to spin–spin coupling with the 2-H and 7-H protons of the indole ring [5, 6]. The multiplet structure of the signals of the remaining aromatic protons, which we deciphered by means of the SIMEQ modeling program (Fig. 5b), constitutes unequivocal evidence that the methyl group in the benzene ring is located in the 4 position (see Table 1). The ^{13}C NMR spectrum (Table 2) confirms the structure of IIe.

An experiment in which deuteroacetone was selected as the ketone component serves as a further argument in favor of the proposed pathway for the formation of the indole molecule from fragments of the pyridinium salt and the ketone. Indole IV was obtained as a result of the reaction.



IV

In the mass spectrum of IV we observe two groups of intense ion peaks, the first of which [197 (25), 196 (70), and 195 (44)] corresponds to molecular ions with different degrees of deuteration, the second of which [182 (35), 181 (100), and 180 (65)] corresponds to the principal fragmentation process, viz., elimination of a methyl group from the substituent in the 4 position, as we have already noted for the spectra of indoles IIa,b.

The location of the deuterium label was determined by means of the ^{13}C NMR spectra. In the ^{13}C NMR spectra the signals of the carbon atoms bonded directly to deuterium atoms have the form of characteristic triplets that are shifted by the magnitude of the isotopic shift (0.2-0.3 ppm) relative to the corresponding signals of the undeuterated form.

The experimental ^{13}C{^{1}H} NMR spectra of IV (Fig. 6) provide evidence for the inclusion of deuterium atoms in the 3 and 7 positions; for the 7 position the degree of enrichment is 96%, whereas it is 70% for the 3 position. An analysis of the aliphatic part of the spectrum indicates that a deuterium label with a high degree of enrichment (above 90%) is located in the methyl groups in the 2 and 6 positions, as well as in the methylene group of the ethyl

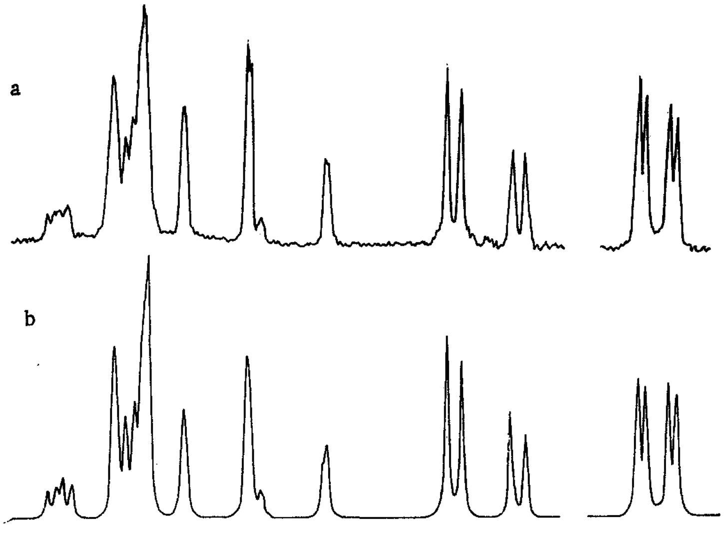


Fig. 5. Double-resonance PMR spectrum of IIe with spin decoupling of the protons of the 4-CH_3 group: a) experimental; b) theoretical (see Table 1 for the parameters).

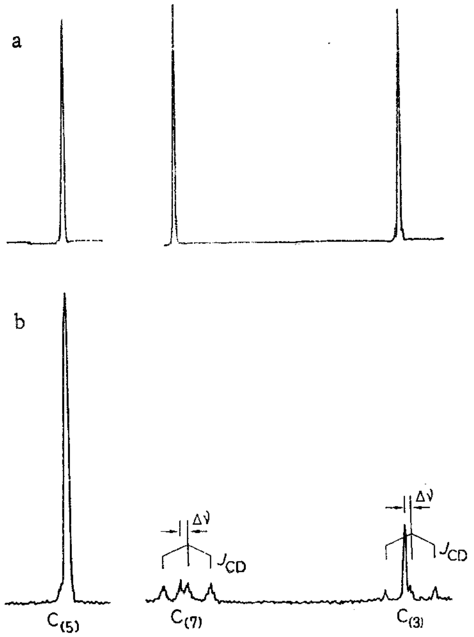


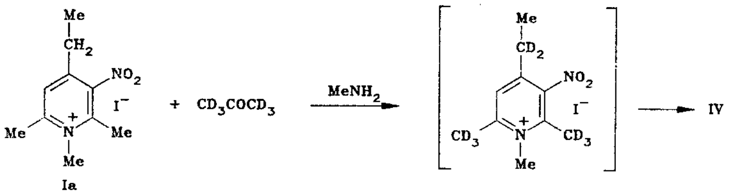
Fig. 6. Fragments of the $^{13}C\{^1H\}$ NMR spectra: a) IIa; b) IV.

TABLE 3. Constants and Yields of Polyalkylindoles IIa-e

Compound	Starting compounds		mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
	salt	ketone		C	H		C	H	
1,2,6-Trimethyl-4-ethylindole (IIa)	Ia	Acetone	50—52	82,7	9,3	$C_{13}H_{17}N$	83,4	9,2	43
1,2,6,7-Tetramethyl-4-ethylindole (IIb)	Ia	Methyl ethyl ketone	80—82	83,6	9,5	$C_{14}H_{19}N$	83,5	9,5	67
1,2,6-Trimethyl-4-propylindole (IIc)	Ib	Acetone	20—23	83,5	9,9	$C_{14}H_{19}N$	83,5	9,5	48
1,2,6,7-Tetramethyl-4-propylindole (IId)	Ib	Methyl ethyl ketone	96—98	83,8	9,8	$C_{15}H_{21}N$	83,7	9,8	76
1,4-Dimethylindole (IIe)	4-Methyl-3-nitropyridine methiodide	Acetone	Picrate 183—185 [17]						11

fragment, whereas the N—CH_3 bond and the methyl group of the ethyl fragment do not contain a deuterium label.

Since the CH acidities of both the methyl groups in the 2 and 6 positions and the methylene group of the ethyl fragment in the pyridinium salt and the CD_3 groups of deuteroacetone are quite high, it is natural to assume rapid deuterium exchange in the presence of a base:



The retention of a hydrogen atom in the 5 position of the indole IV molecule in turn confirms the participation of the $[C_{(4)}]$—$[C_{(5)}]$—$[C_{(6)}]$ fragment of the pyridinium salt in the construction of the benzene part of the indole molecule, and the inclusion of deuterium in the 7 position constitutes evidence for construction of this fragment with the participation of the ketone. The question as to the origin of the deuterium label in the 3 position may shed some light on the scheme of the formation of indoles from pyridinium salts and ketones and requires further study.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra of solutions of the compounds in d_6-acetone were recorded under pulse conditions with a Jeol FX-100 spectrometer with tetramethylsilane (TMS) as the internal standard. In recording the $^{13}C\{^1H\}$ NMR spectra we used two independent frequency generators, one of which operated continuously and ensured the necessary conditions for decoupling of the predesignated group of protons, whereas the second operated under pulse conditions. The short-lived ($\tau \sim 2 \cdot 10^{-3}$ sec) and powerful (γH_2 2000 Hz) pulses at the frequency of the protons (with noise modulation) fed in ahead of the pulses in the observation channel made it possible to efficiently increase the signal–noise ratio due to the Overhauser nuclear effect and to smooth out the components of the multiplets (see [14]). The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source (the ionizing-electron energy was 70 eV). The UV spectra were recorded with a Cary-219 spectrophotometer.

A sample of acetone with a degree of enrichment of 98% was used in the experiment with deuteroacetone in the preparation of indole IV.

2,6-Dimethyl-4-ethyl- and 2,6-Dimethyl-4-propylpyridines. These compounds were synthesized by the Hantzsch method with subsequent oxidation, hydrolysis, and decarboxylation by the methods in [15] and [16], respectively.

2,5-Dimethyl-4-ethyl-3-nitropyridine. A mixture of 41 ml of HNO_3 (d 1.51) and 123 ml of concentrated H_2SO_4 was added with cooling to 26.8 g (0.2 mole) of 2,6-dimethyl-4-ethylpyridine, and the mixture was heated at 100-110°C for about 40 h. It was then cooled and poured over ice, and the aqueous mixture was neutralized with ammonium hydroxide and extracted with benzene. The extract was dried with Na_2SO_4, and the benzene and unchanged pyridine were removed by vacuum distillation to give 24 g (67%) of 2,6-dimethyl-4-ethyl-3-nitropyridine, which was used without further purification for the next step. PMR spectrum (CCl_4): 1.20 (t, 3H, $CH_2\mathbf{CH_3}$), 2.52 (m, 8H, 2-CH_3, 6-CH_3, $\mathbf{CH_2}CH_3$), and 6.85 ppm (s, 1H, 5-H).

2,6-Dimethyl-4-propyl-3-nitropyridine was similarly obtained in 46% yield. PMR spectrum (CCl_4): 0.8 (t, 3H, $CH_2CH_2\mathbf{CH_3}$), 1.42 (m, 2H, $CH_2\mathbf{CH_2}CH_3$), 2.32 (m, 8H, 2-CH_3, 6-CH_3, $\mathbf{CH_2}CH_2CH_3$), and 6.75 ppm (s, 1H, 5-H).

2,6-Dimethyl-4-ethyl-3-nitropyridine Methiodide (Ia). A mixture of 24 g (0.13 mole) of 2,6-dimethyl-4-ethyl-3-nitropyridine and 37 ml (0.6 mole) of methyl iodide was heated in a sealed ampul at 100°C for 15 h, after which the precipitate was removed by filtration, washed with absolute ether, and recrystallized from acetonitrile to give 35.1 g (84%) of a product with mp 210°C. Found, %: C 37.3, H 4.8. $C_{10}H_{15}IN_2O_2$. Calculated, %: C 37.3, H 4.7.

2,6-Dimethyl-4-propyl-3-nitropyridine methiodide (Ib), with mp 193-195°C (from acetonitrile), was similarly obtained in 43% yield. Found, %: C 39.2, H 5.1. $C_{11}H_{17}N_2O_2$. Calculated, %: C 39.3, H 5.1.

Preparation of Indoles IIa-e (Table 3). A 0.0037-mole sample of the methiodide of the corresponding pyridine was added with cooling to a solution of 0.016 mole of gaseous methylamine in 0.068 mole of the corresponding ketone, and the mixture was cooled for 30 min and allowed to stand at room temperature for 2 days. The excess ketone was removed by distillation, and the residue was chromatographed with a column packed with silica gel (40/100 μ) in a benzene–hexane system (1:5).

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INDOLE DERIVATIVES.

127.* INVESTIGATION OF THE ALKYLATION OF INDOLE BY POLYESTERS

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The alkylation of indole by polyesters of ω-hydroxyalkanoic acids was studied. The optimum conditions and ratios of the reacting substances were found, and a number of ω-(3-indolyl)alkanoic acids were obtained.

3-Indolylacetic acid (heteroauxin) is a plant-growth stimulator [2]. However, the known methods for the preparation of heteroauxin have substantial drawbacks, and this compels one to search for new methods for its synthesis. Thus the preparation of heteroauxin from gramine [3, 4] is carried out with the aid of cyanide salts, and the alkylation of indole by chloroacetic acid [5] is accompanied by pronounced corrosion of the apparatus because of the presence of the Cl^- ion in the reaction mixture.

The task of the present research was to find an alkylating agent that would exclude the indicated drawbacks. We initially attempted to use sodium acetoxyacetate as the alkylating agent, but the low yields obtained in its preparation from chloroacetic acid and sodium acetate [6] did not meet with our requirements. It is known that the formation of products of alkylation at both the lactone oxygen atom and at the ether bond was observed in the alkylation of indole by oxalactones [7]. We therefore decided to investigate polyglycolide, obtained by the method in [8] in 80-90% yield, as the alkylating agent.

Fusion of indole with polyglycolide under the conditions of the method in [9] showed that alkylation does take place but is accompanied by decarboxylation, which was detected from the formation of skatole and the vigorous evolution of CO_2 upon neutralization. Similar results were obtained both in the presence of air and in a nitrogen atmosphere. In accordance with the method used to prepare heteroauxin in [10] by the reaction of indole with chloroacetic acid in an alkaline medium (at an initial nitrogen pressure of 5 atm), we obtained heteroauxin in 70-85% yield when we replaced chloroacetic acid with polyglycolide. A search for the optimum ratios of the reacting substances and the optimum conditions showed that decreasing the temperature to 200°C lowers the yield to 42% and that a decrease in the concentration of the reacting substances by a factor of two also leads to a decrease in the yield of heteroauxin to 56%. A decrease in the alkali concentration also led to a decrease in the yield of heteroauxin to 13-25%. The optimum molar ratios and reaction conditions were as follows: an indole–polyglycolide–alkali ratio of 3:4:15, a reaction temperature of 250°C, and a reaction time of 6 h with an initial nitrogen pressure of 5 atm and an overall reaction pressure of 45-50 atm. The yield of heteroauxin in this case reaches 85-95%.

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*See [1] for communication 126.

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