NUCLEAR MAGNETIC RESONANCE SPECTRA OF POLYALKYLINDOLES OBTAINED BY TRANSFORMATIONS OF 3-NITROPYRIDINIUM SALTS*

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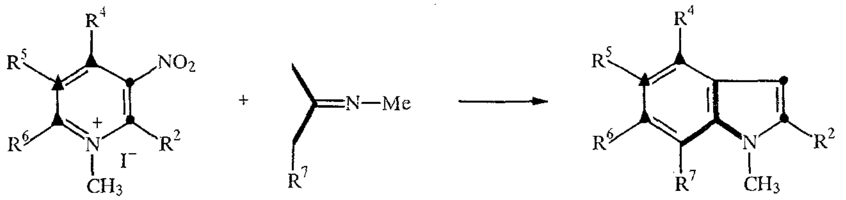
Data are correlated on the ^1H and ^{13}C NMR spectra of a representative series of polyalkylindoles obtained by the reaction of alkyl-substituted 3-nitropyridinium salts with ketimines. It has been shown that the use of a combined approach to the interpretation of the ^1H and ^{13}C NMR spectra enables reliable information to be obtained on the structure of these previously unknown indole derivatives. The long range $^{13}C-H$ coupling constants give particularly valuable information. A reliable demonstration of the structure of the reaction products is the basis for establishing the route of the indolization.

In 1984 a new route was discovered for the synthesis of polyalkylindoles, viz. the transformation of polyalkyl-3-nitropyridinium salts by the action of ketimines (or mixtures of ketones and amines (see [1-5] for example). This process has no analogy in the literature and was so unusual that a clear determination of the structure of the alkylindoles formed in the reaction was demanded in order to establish the formal course of the reaction. Only a comparison of the disposition of the alkyl substituents (serving as chemical markers) in the initial and final structures can serve as a basis for such a scheme, subsequently leading to an understanding of the mechanism of the indolization process. Only NMR spectra can give an answer to this problem.

The formal process may be represented as follows:



(1)

In the reaction the 3-nitropyridinium cation is ruptured at the $C_{(3)}-C_{(4)}$ bond, the $C_{(2)}-C_{(3)}$ fragment participates in the formation of the pyrrole ring of the indole, the $C_{(4)}-C_{(5)}-C_{(6)}$ fragment forms part of the benzene ring, and the triangular ketimine unit is inserted between them taking part in the formation of both rings of the bicyclic compound [2].

In the case of imines of unsymmetrical ketones (R^7 = Alk), it is possible to form indoles with the R^7 substituent in position 3 [3] [see compound (XXIII), Table 1, for example] in addition to the main reaction product which corresponds to Scheme (1).

The complexity of establishing the structure is caused by the fact that the PMR spectra of polyalkylindoles are relatively poorly informative due to the absence of fine structure. The aromatic protons couple with the α protons of alkyl groups located in the ortho, meta, and para positions [9, 10]. All these constants are less than 1 Hz as a rule and are close in size to one another (see the data for toluene in [10]). When two or three alkyl groups are present in the benzene ring coupling with all the

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*Dedicated to Professor A. R. Katritzky on his 65th birthday.

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TABLE 1. Proton Magnetic Resonance Spectra of Polyalkylindoles in Acetone-d_6

Compound	R^2	R^4	R^5	R^6	R^7	δ, ppm							Coupling constant, Hz							Ref.
						N—CH₃	R^2	R^3	R^4	R^5	R^6	R^7	J_{23}	J_{26}	J_{37}	J_{56}	J_{57}	J_{67}	J^{*5}	
I*1	H	H	H	H	H	10,07	7,34	6,59	7,71	7,15	7,23	7,52								
II	H	H	H	H	H	3,73	7,15	6,52	7,67	7,15	7,25	7,38								
III	H	Me	H	H	H	3,80	7,17	6,44	2,48	6,82	7,04	7,21	3,17	0,40	0,95	6,89	1,05	8,11		[6]
IV	H	Me	Me	H	H	3,66	7,04	6,39	2,30	2,37	6,94	7,03	3,17	0,35	0,73			8,30		
V	H	Me	H	Me	H	3,72	7,06	6,37	2,43	6,67	2,40	6,98	3,10		0,79		1,34			[6]
VI*2	Me	H	H	Me	H	3,52	2,32	6,03	7,23	6,73	2,42	6,98							0,95	[6]
VII	Me	H	Me	Me	H	3,53	2,33	6,01	7,13	2,26	2,33	7,00								[3]
VIII	Me	H	Me	Me	Me	3,74	2,22	5,97	7,02	2,30	2,30	2,56								[7]
IX	Me	Me	H	H	H	3,55	2,34	6,17	2,42	6,77	6,96	7,07			0,79	6,95	1,35	8,35	0,92	[6]
X	Me	Me	H	Me	H	3,47	2,29	6,09	2,37	6,61	2,37	6,84			0,84		1,41		0,95	[1]
XI	Me	Me	H	Me	Me	3,80	2,26	6,02	2,31	6,49	2,31	2,54								[6]
XII	Me	Me	H	Me	Et	3,80	2,32	6,11	2,32	6,58	2,32	1,19 (CH₃) 3,00 (CH₂)								
XIII	Me	Me	Me	Me	H	3,55	2,34	6,09	2,33*3	2,19*3	2,34	6,90			0,73		1,40		0,95	[7]
XIV	Me	Me	Me	Me	Me	3,80	2,30*3	6,05	2,30	2,20*3	2,30	2,56								[8]
XV	Me	Et	H	Me	H	3,32	2,19	6,09	1,25 (CH₃) 2,77 (CH₂)	6,63	2,37	6,77			0,85		1,40		0,95	[2]
XVI	Me	Et	H	Me	Me	3,66	2,24	6,09	1,23 (CH₃) 2,71 (CH₂)	6,59	2,26	2,44								[2]
XVII	Me	Pr	H	Me	H	3,46	2,28	6,13	0,93 (CH₃) 1,68 (β-CH₂) 2,68 (α-CH₂)	6,63	2,36	6,84.								[2]
XVIII	Me	Pr	H	Me	Me	3,75	2,28	6,13	0,93 (CH₃) 1,68 (β-CH₂) 2,68 (α-CH₂)	6,61	2,28	2,50								[2]
XIX	Me	t-Bu	H	Me	H	3,59	2,40	6,39	1,48	6,83	2,47	6,92								[4]
XX	Me	t-BuCH₂	H	Me	H	3,48	2,23	6,11	0,93 (CH₃) 2,67 (CH₂)	6,57	2,36	6,85								[4]
XXI	Me	t-BuCH₂	H	Me	Me	3,78	2,49	6,10	0,91 (CH₃) 2,58 (CH₂)	6,37	2,29	2,51								[4]
XXII	Me	Me	i-Pr	Me	H	3,55	2,33	6,10	2,45	3,36 (CH) 1,33 (CH₃)	2,45	6,80								[4]
XXIII*4	Me	H	Me	Me	H	3,68	2,09	2,15	7,06	2,20	2,20	6,90								[3]
XXIV	Et	Me	H	Et	H	3,59	1,24 (CH₃) 2,60 (CH₂)	6,15	2,42	6,66	1,30 (CH₃) 2,72(CH₂)	6,93								[4]
XXV	i-Pr	Me	H	i-Pr	H	3,77	1,25 (CH₃) 3,10 (CH)	6,16	2,42	6,51	1,32 (CH₃) 2,96 (CH)	7,28			0,90				0,90	[4]
XXVI	i-Pr	i-Pr	H	i-Pr	H	3,69	1,33 (CH₃) 3,14 (CH)	6,27	1,34 (CH₃) 3,29 (CH)	6,82	1,30 (CH₃) 3,29 (CH)	7,02								[4]

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*1Indole NH.

*2J_{45} = 8.5 Hz.

*3Possible alternative assignment of signals.

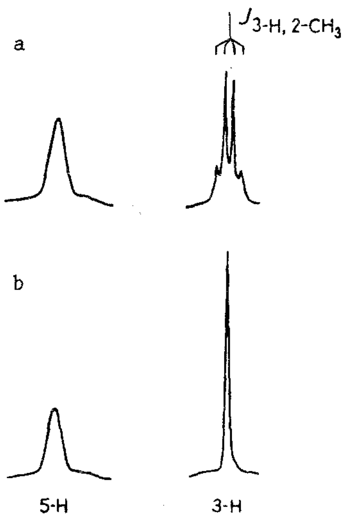

Fig. 1. PMR spectra of compound (XVI) (aromatic proton region): (a) single resonance spectrum and (b) double resonance spectrum with spin decoupling from the protons of the 2-CH_3 group.

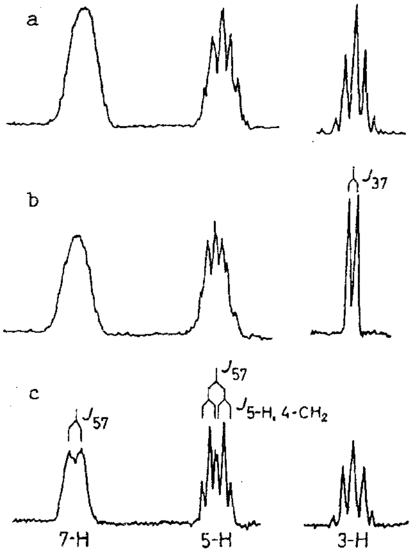

Fig. 2. PMR spectra of compound (XVI) (aromatic proton region): (a) single resonance spectrum and double resonance spectra with spin decoupling from protons of the (b) 2-CH_3 and (c) 6-CH_3 groups.

α protons of the alkyl groups is displayed simultaneously in the spectra. Coupling with the β protons of the alkyl substituents may also be displayed in the PMR spectra with constants small in absolute value (less than 0.2 Hz as a rule) (see the discussion in [11] for example). Special techniques both when recording spectra and when preparing samples are required for the display of constants so small in absolute value. However in the usual PMR spectra the simultaneous appearance of a large number of small, closely similar coupling constants may lead to complete loss of multiplicity. Lines of width 1-2 Hz may then be observed (see examples below). It is natural that in such spectra only the large constants between ortho protons ($^3J_{HH}$) may be directly displayed while the coupling constants between meta protons ($^4J_{HH}$) and between protons in the para position to one another ($^5J_{HH}$) are practically unresolved.

TABLE 2. ^{13}C NMR Spectra, Chemical Shifts δ, ppm, Solvent Acetone-d_6

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	N—CH_3	2-R	4-R	5-R	6-R	7-R
I	125,48	102,39	121,10	119,96	122,09	112,10	137,14	129,02						
II	129,77	101,36	121,35	119,82	121,99	110,10	137,71	129,56	32,70					
III	129,14	99,71	130,26	122,11	119,99	107,77	129,36	136,27	32,92	—	18,73	—	—	—
IV	129,02	99,46	129,98	126,01	124,63	107,22	127,59	136,23	32,68	—	19,20	15,36	—	—
V	128,56	99,57	129,91	121,91	13,52	107,63	127,28	137,94	32,78	—	18,62	—	21,83	—
IX	136,79	98,57	128,90	121,03	119,96	107,26	128,64	138,00	29,47	12,60	18,70	—	—	—
X	135,96	98,36	128,54	121,78	130,19	107,29	126,52	138,39	29,34	12,56	18,64	—	21,87	—
XI	136,91	98,97	125,77	123,32	128,97	116,70	127,96	137,56	33,24	13,41	18,32	—	20,38	14,61
XII	137,11	99,27	126,08	123,69	128,59	123,44	128,53	136,66	32,72	13,56	18,40	—	19,41	16,35; 21,13
XIII	135,73	98,62	127,80	125,20	129,68	108,21	126,45	136,60	29,34	12,59	15,94*	15,05*	21,69	—
XV	135,93	98,17	135,12	120,05	130,24	107,42	125,66	138,62	29,67	12,56	15,40; 26,88	—	21,97	—
XVI	136,76	98,64	132,27	121,50	128,93	116,75	127,15	137,68	33,04	13,33	15,40; 26,49	—	20,47	14,52
XVII	135,94	98,33	133,49	121,01	130,11	107,44	126,04	128,66	29,31	12,57	14,41; 24,48; 36,13	—	21,93	—
XVIII	136,85	98,86	130,71	122,55	128,89	116,82	127,60	137,80	33,19	13,40	14,45; 24,47; 35,80	—	20,49	14,69
XX	135,97	99,91	131,21	123,90	129,78	107,65	127,94	138,98	29,43	12,72	30,60; 33,35; 47,59	—	22,11	—
XXIV	142,43	96,73	126,00	120,75	137,59	106,11	128,94	130,73	29,50	13,30; 20,51	18,68	—	16,88; 20,98	—

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*The inverse assignment of signals is possible.

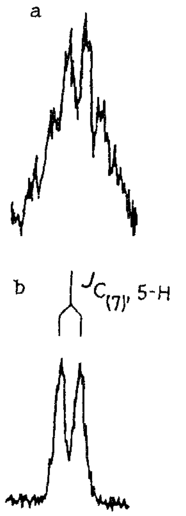


Fig. 3. Proton-coupled ^{13}C NMR spectra of the $C_{(7)}$ atom of compound (XVI); (a) single resonance spectrum and (b) double resonance spectrum with selective decoupling from methyl group protons.

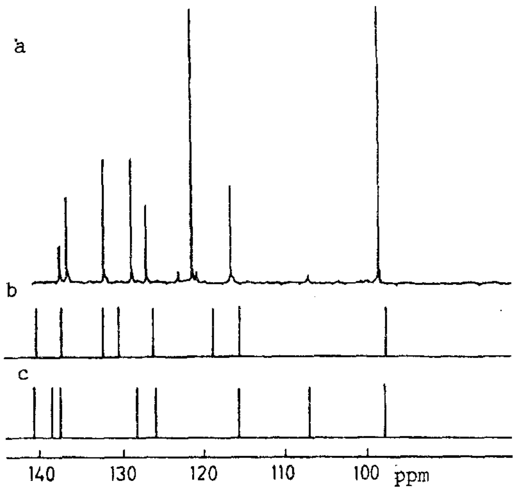
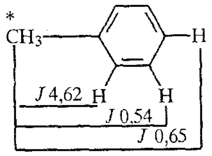


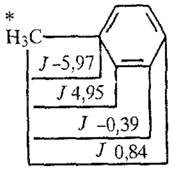
Fig. 4. The $^{13}C\{^1H\}$ NMR spectrum of compound (XVI) (aromatic carbon atom region); (a) experimental, (b) calculated using the additivity formula for structure (XVI) and (c) for structure (XXVII).

Two signals (3-H and 5-H protons) are observed in the aromatic portion of the PMR spectrum of compound (XVI) (Fig. 1). The signal of the 5-H benzene ring proton has the typical shape of a broadened singlet. When several alkyl substituents are present in the ring at the same time the simple technique of double resonance may prove to be inadequate to clarify the multiplet structure. Nonetheless we successfully achieved some improvement of the multiplicity (of the 5-H and 7-H signals) in the double resonance spectra of compound (XV) on irradiating the signal of the 6-CH_3 methyl group of the benzene portion of the molecule (2.37 ppm) (Fig. 2). The parameters of the PMR spectra of the polyalkylindoles obtained are given in Table 1.

More detailed information on the structure of the indoles formed may be obtained with the aid of ^{13}C NMR spectra. There are many data in the literature on ^{13}C NMR spectra of substituted indoles (see [12, 13] for example). However the obvious complexities when assigning signals and interpreting ^{13}C shifts [14] do not enable an unequivocal demonstration of the structure of an indole to be carried out solely on the data of ^{13}C NMR spectra with complete decoupling from protons [14].

The long range $^{13}C-H$ coupling constants of the carbon atoms of the alkyl groups with the benzene ring protons and of the alkyl group protons with the benzene ring carbon atoms may give significantly more reliable information. The constants for toluene [10] are:





Closely similar values of the long range $^{13}C-H$ coupling constants were observed for 2- and 3-methylthiophenes and for 2-methylfuran [15].

We recorded the proton-coupled ^{13}C NMR spectra for several key compounds. In the proton-coupled ^{13}C NMR spectrum of compound (XV) the signal for the carbon atom of a methyl group linked to a benzene ring (6-CH_3)† was a quartet of triplets. The size of the direct ^{13}C constant was 124.8 Hz. The triplet splitting of 4.7 Hz indicates the presence of two ortho protons in the vicinity of this methyl group, which enables a reliable conclusion to be drawn as to the structure of this compound.

The establishment of the structure of compound (XVI) was a more complex problem. There are six carbon atom signals in the aliphatic and eight in the aromatic region of the $^{13}C\{^1H\}$ NMR spectra of compound (XVI). On the basis of the data on the chemical shifts of methylindoles [12] only the signals of the $C_{(3)}$, $C_{(7)}$, and 1-CH_3 carbon atoms can be assigned unequivocally at this point (Table 2). Consideration of the multiplet structure of the carbon signals in the proton-coupled ^{13}C NMR spectra of compound (XVI) enabled the initial assignment to be made more precise. Thus the signal at 33.04 ppm with a direct constant of $^1J = 138.0$ Hz is assigned to the methyl group at position 1. All the remaining signals of methyl group carbon atoms have coupling constants between 125.1 and 127.0 Hz. Analysis of the fine multiplet structure enabled the signal at 15.40 ppm to be assigned 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 [16]). A similar constant ~4.3 Hz, observed for the signal at 26.49 ppm, characterizes the spin-spin interaction of the CH_2 carbon with the protons of the CH_3 group of the ethyl fragment. A long range coupling constant (4.3 Hz) with an aromatic proton was also displayed by the same signal. We observed a closely similar constant (4.9 Hz) for the methyl group signal at 2.47 ppm. At the same time the signal at 14.52 ppm did not display a long range constant but the signal at 13.33 ppm displayed a relatively small coupling constant (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 on the pyrrole ring but the ethyl and methyl groups (20.47 ppm) are in the ortho position to an aromatic proton. The fact that there is an alkyl group in position 7 of compound (XVI) follows from the character of the multiplet structure of the 3-H proton signal in the PMR spectrum, for which no inter-ring coupling with a benzene ring proton was observed. This coupling constant must be 0.8-0.9 Hz [17, 18] and such coupling was noted by us in the PMR spectra of compounds (XV) and (XVII) (see above). Further, it follows from the size of the chemical shift of the signal of the quaternary $C_{(7)}$ carbon atom (116.75) in the ^{13}C NMR spectrum of compound (XVI) that $C_{(7)}$ is linked to a methyl group. In reality methyl and ethyl groups have a large difference in the ipso substitution increments of the benzene ring ($\Delta\delta_{CH_3} = 9.22$ and $\Delta\delta_{C_2H_5} = 15.59$ ppm) [19]. If the ethyl group was in position 7, then relying on the data of [9] the signal for $C_{(7)}$ would be expected to be in the region of 120-122 ppm approximately.

Thus the sole proton on the benzene portion of (XVI) may be in positions 5 or 6 of the indole nucleus only.

It is possible to use the data of the $^{13}C-H$ coupling of carbon $C_{(7)}$ with the aromatic proton to determine its position. For this purpose we recorded the double resonance $^{13}C-H$ spectra with selective irradiation of the CH_3 group protons. On irradiating at a frequency of 244 Hz from TMS with an amplitude of the irradiating field γH_2 36 Hz the signal of the $C_{(7)}$ carbon atom had the shape of a doublet with a splitting of 6.1 Hz (Fig. 3). Such a splitting may only be explained by coupling with a proton located in position 5 [the meta position to $C_{(7)}$] since only intra-ring $^{13}C-H$ coupling through three bonds can

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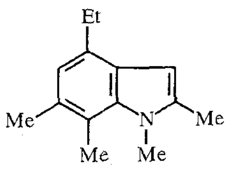
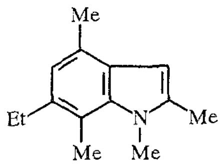
† Assignment of this signal was made on the basis of double resonance $^{13}C\{^1H\}$ NMR spectra with selective decoupling of the CH_3 groups.

have such a large constant (6-8 Hz). The $^{13}C-H$ coupling constant through 2 or 4 bonds [16] in similar structural fragments must not exceed 2 Hz.

Combination of all the data enables discussion to be limited to only two structures for compound (XVI).



XVI



XXVII

A choice between these two structures was made following calculations of the chemical shifts of the ^{13}C nuclei of the benzene ring portion of the molecule using an additivity formula. Calculations were carried out using the formula

$$\delta^{add}_{c-i} = \delta^{o}_{c-i} + \Delta\delta_{c-i}(R_j), \qquad (2)$$

where $\delta_{c-i}{}^{o}$ is the value of the chemical shift of nucleus c-i in 1-methylindole (see Table 2) and $\Delta\delta_{c-i}(R_j)$ is the increment of a substituent R_j on the size of the chemical shift of nucleus c-i.

We used the data of [12] as increments for substitution by methyl groups in positions 2, 4, 6, and 7. The increments for ethyl and n-propyl groups were taken from [19] for the corresponding monosubstituted benzenes. The results of the additivity calculations are represented graphically in Fig. 4. It is clearly seen from the figure that the experimental ^{13}C NMR spectrum of compound (XVI) (Fig. 4a) is in better agreement with that calculated for structure (XVI) (Fig. 4b) than for structure (XXVII) (Fig. 4c).

Based on the combination of all the data presented above we have established the structure of 4-ethyl-1,2,6,7-tetramethylindole (XVI) for the reaction product of 3-nitro-sym-collidinium methiodide with methyl ethyl ketone.

The parameters of the PMR and ^{13}C NMR spectra of compounds (XVII) and (XVIII) are in excellent agreement with the parameters of the spectra of compounds (XV) and (XVI) allowing for the effect of the n-propyl group in position 4 (see Tables 1 and 2). The definitive values of the ^{13}C NMR chemical shifts are given in Table 2.

With the aid of NMR spectra we have established the structure of a large series of polyalkylindoles, previously unstudied in practice, containing various alkyl substituents in different positions of the indole nucleus. Comparison of the structures of the compounds, synthesized from different 3-nitropyridinium salts by varying the actual components, confirms the unique nature of the indolization mechanism [20].

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