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^{1}H AND ^{13}C NMR SPECTRA OF 9H-PYRIMIDO[4,5-*b*]INDOLES

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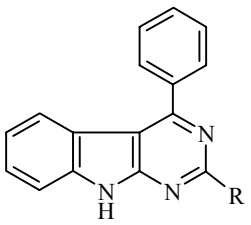
Based on analysis of ^{1}H and ^{13}C NMR spectra of 9H-pyrimido[4,5-b]indole and its 4-phenyl-2-substituted derivatives, we have made assignments for the signals from the ^{1}H and ^{13}C atoms of these compounds.

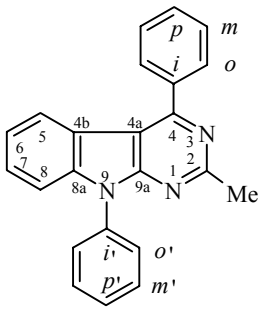
Keywords: 9H-pyrimido[4,5-*b*]indole and its 2,4-substituted derivatives, ^{1}H and ^{13}C NMR spectra.

Derivatives of pyrimido[4,5-*b*]indole are of considerable interest as biologically active compounds [1-4]. A large number of medicinal drugs of the 2,4-diamino-9H-pyrimido[4,5-*b*]indole series have been created based on the products of the reaction of 2-bromocyclohexanone with substituted triaminopyrimidines [3, 4]. Earlier one of us, together with coauthors, proposed a method for synthesis of 2-substituted 4-phenyl-9H-pyrimido[4,5-*b*]indoles from the fluoroborate of (3-arylidene)-2-ethoxyindolenine and amidines, guanidine, urea, and also thiourea [5]. Other routes are also known for obtaining derivatives of the indicated heterocyclic system [6-17]. Despite the use of ^{1}H NMR spectra for confirming the structures of the synthesized compounds (mainly the NH group in the indole moiety), in the overwhelming number of publications a correct assignment of the aromatic proton signals was not made due to their partial or complete overlap. A correct assignment could be made only in the case of 6-substituted 2,4-dioxo-1,2,3,4-tetrahydro-9H-pyrimido[4,5-*b*]indole [13, 14]. The ^{13}C NMR spectra were generally not considered in the indicated papers, despite their considerably greater information content compared with ^{1}H NMR spectra. Such data are only given for some 9-benzyl- and 9-phenyl-substituted pyrimido[4,5-*b*]indoles [18].

In this paper, we give the ^{1}H and ^{13}C NMR spectra for unsubstituted 9H-pyrimido[4,5-*b*]indole (**1**), 2-substituted 4-phenyl-9H-pyrimido[4,5-*b*]indoles **2a-c**, and 2-methyl-4,9-diphenyl-9H-pyrimido[4,5-*b*]indole (**3**).



1, **2a–c**



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1 R = H; **2 a** R = Me, **b** R = Ph, **c** R = NH_2

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In the ^{1}H NMR spectra of the pyrimido[4,5-*b*]indoles **1**, **2a-c** unsubstituted at the 9 position (Table 1), the protons of the NH group appear as somewhat broadened singlets in the 11.5-12.5 ppm region, which is typical of condensed systems including an indole moiety [1, 8, 9, 11, 13, 19-21]. The presence of substituents on the pyrimidine ring of the molecule of pyrimidoindoles does not have a substantial effect on the position of this signal, but the chemical shift is appreciably affected by electronic substituent effects.

The pyrimidine ring protons in the unsubstituted pyrimidoindole **1** appear downfield as two separate singlets. Based on the spectra of its 2-substituted [12] and some 4-substituted [9] derivatives, the singlet furthest downfield at 9.431 ppm should be assigned to the 4-H proton and not to the 2-H proton, as was done earlier in analogy to the spectra of compounds in the pyrimidine series [7]. The resonance of the benzene ring protons in pyrimidoindole is observed further upfield. No difficulties are encountered if we assign the doublet signal at 8.219 ppm to the 5-H proton, and we made this assignment according to the data in [10, 12, 13, 17]. The remaining three benzene ring protons resonate in a rather narrow region (7.3-7.6 ppm) and give an overall multiplet signal, which made its analysis difficult previously. Recording the spectrum of compound **1** on a spectrometer with a frequency of 500 MHz allowed us to separate the signals from the 6-H, 7-H, and 8-H protons. The 8-H signal appears as an asymmetric doublet with fine structure, while the signals from the other two protons are triplets of doublets with spin–spin coupling constants typical of aromatic protons (all the ^3J values are within the range 7.1-8.1 Hz, while $^4J \sim 1.0$ Hz). The assignments of the signals we made were confirmed by recording the spectrum for compound **1** under double resonance conditions with alternating decoupling of these signals.

The ^{1}H NMR spectra of 2-substituted 4-phenylpyrimidoindoles **2a-c** are complicated by the presence of signals from aromatic protons of the phenyl substituent. And although the signals from protons of the condensed benzene ring of the pyrimidoindoles are observed further upfield than the multiplets for the phenyl groups, they sometimes partially overlap. The presence of well resolved signals for amino derivative **2c** allowed us to correctly analyze the spin–spin coupling for the 5-H, 6-H, 7-H, and 8-H protons in a 1st order approximation. In this case, we took into account the nature of such coupling in pyrimidoindole **1** and the degree of distortion of the symmetry of the signals. The two doublet signals with spin–spin coupling constants $^3J_{5,6} \sim {}^3J_{8,7} \sim 7.7$ Hz at 7.47 ppm and 7.36 ppm were assigned to the 5-H and 8-H protons, while the two triplet signals with spin–spin coupling constants $^3J_{6,7} \sim {}^3J_{7,8}$ and $^3J_{5,6} \sim {}^3J_{6,7}$ at 7.26 ppm and 6.99 ppm were assigned to the 7-H and 6-H protons respectively. The assignments of the downfield signal to the 5-H proton and the upfield signal to the 6-H proton are consistent with our data for the unsubstituted pyrimidoindole **1**. Furthermore, all four of these signals have fine structure due to long-range spin–spin coupling, and for both triplet signals of 6-H and 7-H the spin–spin coupling constants are $^4J_{5,7} \sim {}^4J_{6,8} \sim 1.1$ Hz.

The spectrum of methyl-substituted **2a** is similar to the spectrum of the amino derivative **2c**, but all the signals from the indole protons (compound **2a**) are shifted downfield by ~0.2 ppm compared with the analogous signals for compound **2c**. This leads to the fact that the furthest downfield signal from the 5-H proton proves to be between the multiplet signals of the phenyl group protons in the position 4. In the spectrum of the 2-phenyl-substituted **2b**, the signals from the 7-H and 8-H protons prove to be completely obscured by one of the multiplets of the phenyl group.

Introducing an N-phenyl group into the molecule of methyl-substituted **2a** (compound **3**) causes a different shift of the resonance signals from the indole protons. Thus signals from the 5-H, 6-H, 7-H protons are shifted downfield by ~0.1 ppm, while the signal from the 8-H proton is shifted upfield by 0.16 ppm (Table 1). The reason for such a shift may be magnetic shielding of this proton under the influence of the ring current induced in the aromatic ring of the N-phenyl group, which because of steric requirements is turned in such a way that the 8-H proton is located above the plane of this ring and falls within the diamagnetic shielding zone. We can also note that both multiplet signals of the aromatic protons of the NPh group itself also are shifted in different directions in the spectrum: the multiplet corresponding to the resonance of the *ortho* protons is shifted more downfield than the multiplets for the 4-phenyl group, while the second multiplet signal is shifted upfield and overlaps the signals from the two indole protons. (The ^{13}C NMR spectra of compounds **1-3** are given in Table 2.)

TABLE 1. [1]H NMR Spectra of 9H-Pyrimido[4,5-*b*]indoles

Com-pound	Chemical shift, δ, ppm (spin–spin coupling constant, *J*, Hz)						
	5-H, d	6-H	7-H	8-H, d	C_6H_5, m	2-R	NH, s
1*	8.219*[2] (*J* = 7.8)	7.310 (td, *J* = 7.8, 7.1, 1.1)	7.525 (td, *J* = 8.1, 7.1, 1.2)	7.577*[2] (*J* = 8.1)			12.317
2a	7.73 (*J* = 8.0)	7.14 (td, *J* = 8.0, 7.2, 1.2)	7.46 (td, *J* = 8.0, 7.2, 1.0)	7.56 (*J* = 8.0)	7.65-7.70 (3H), 7.85-8.00 (2H)	2.73 (s)	12.22
2b	7.82 (*J* = 8.0)	7.19 (t, *J* = 8.0)	—*[3]	—*[3]	7.65-7.75 (3H), 8.00-8.10 (2H)	7.45-7.65 (m, 3H), 8.50-8.65 (m, 2H)	12.51
2c	7.47 (*J* = 7.7)	6.99 (t, *J* = 7.7, 7.3)	7.26 (t, *J* = 7.7, 7.3)	7.36 (*J* = 7.7)	7.53-7.67 (3H), 7.75-7.90 (2H)	6.67 (br. s)	11.66
3	7.81 (*J* = 8.0)	7.26 (td, *J* = 8.0, 6.9, 1.2)	7.51 (td, *J* = 7.7, 6.9, 1.0)	7.39 (*J* = 7.7)	7.56-7.75 (3H), 7.85-7.97 (2H)	2.69 (s)	

* Compound **1**: 8.936 ppm (2-H, s); 9.431 ppm (4-H, s).

*[2] Doublet has fine structure.

*[3] Signal in the region of the multiplet for the 2-phenyl group (7.45-7.65 ppm).

TABLE 2. ^{13}C NMR Spectra of 9H-Pyrimido[4,5-*b*]indoles

Com-poun	Chemical shifts, δ, ppm*													
	$C_{(2)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(4b)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(8a)}$	$C_{(9a)}$	C_i/C_i'	C_o/C_o'	C_m/C_m'	C_p/C_p'
1	154.44	148.51	113.86	118.80	121.67	120.93	127.71	111.87	138.44	155.11	—	—	—	—
2a*[2]	163.09 [163.1]	158.90 [156.7]	107.41 [108.9]	118.75	121.53	120.36	126.97	111.74	138.41	156.97 [156.4]	138.41	128.59	128.46	129.67
2b	159.10 [159.6]	159.37 [157.3]	108.89 [111.0]	118.80	121.81	120.67	127.43	111.88	138.55	157.19 [156.6]	138.06, 138.09	128.78, 128.64	128.47, 127.61	130.16, 129.95
2c	161.59	160.37	102.54	120.31	119.82	119.90	124.76	111.02	138.61	159.07	137.75	128.38	128.34	129.50
3*[3]	163.62	159.53	108.14	118.72	121.73; 121.65		128.30	110.53	139.49	156.59	138.14 / 134.80	128.62 / 129.64	128.62 / 127.58	129.91 / 127.58

* In square brackets we give the values calculated according to an additive scheme.

*[2] Signal from the CH_3 group, 25.79 ppm.

*[3] Signal from the CH_3 group, 25.92 ppm.

TABLE 3. $J_{C–H}$ Constants for 9H-Pyrimido[4,5-*b*]indole (**1**)

Constant	Spin-spin coupling constants, $J_{C–H}$, Hz									
	$C_{(2)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(4b)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(8a)}$	$C_{(9a)}$
$^1J_{C–H}$	201.8	181.6	—	—	161.6	160.5	159.8	162.8	—	—
$^2J_{C–H}$	—	—	—	—	~1	1.9	2.3	~2	3.4	2.1
$^3J_{C–H}$	10.7	10.3	br. 7.8	br. 5.5, 5.5	8.0	7.2	7.8	8.2	8.9, 8.9	5.8, 9.8

We studied in detail the unsubstituted pyrimidoindole **1** and its aminophenyl-substituted **2c**, and we recorded their single resonance spectra and their spectra with complete proton decoupling under *J*-modulation conditions. Furthermore, the correctness of the assignment of the signals for compound **1** was confirmed by recording the two-dimensional heteronuclear COSY [^{13}C][^{1}H] spectrum (the spin–spin coupling constants for it are given in Table 3). In compound **1**, the most deshielded nuclei prove to be the carbon atoms bonded to the two heterocyclic (pyrimidine and indole) nitrogen atoms (the $C_{(9a)}$ atom) and to the two pyrimidine nitrogens (the $C_{(2)}$ atom). The signals from these atoms are significantly shifted downfield (to 155 ppm), while the signal from the $C_{(4)}$ atom, which is bonded to only one pyrimidine nitrogen atom, is shifted to the 148 ppm region. The signals from the carbon atoms of the benzene ring of the indole moiety are located further upfield (111-127 ppm or more); the chemical shifts of the $C_{(5)}$, $C_{(6)}$, and $C_{(8)}$ atoms are quite consistent with the shifts of the carbon atoms in the corresponding positions of indole [22]. Thus it becomes possible to predict the changes in the ^{13}C NMR spectra under the influence of substituents in the 9H-pyrimido[4,5-*b*]indole molecule independently for the pyrimidine and indole moieties. We used this conclusion to test the assignments in the spectra of the pyrimidinoindole derivatives.

The ^{13}C NMR spectrum of aminophenyl-substituted **2c** has a more complex pattern than the spectrum of the heterocyclic system itself, which is more likely explained not by the presence of signals from the phenyl substituent but rather by the proximity of the signals from the $C_{(9a)}$, $C_{(2)}$, and $C_{(4)}$ atoms and also the $C_{(6)}$ and $C_{(5)}$ atoms. Therefore for this compound, we additionally recorded the ^{13}C NMR spectrum while applying the frequency at 8.3 ppm (^{1}H) for selective proton decoupling. The characteristic multiplicity of the signals, the values of the spin–spin coupling constants $^1J_{CH}$, and the observed changes in the signals with such proton decoupling allowed us to identify the signals from atoms of the indole moiety and the phenyl group. Assigning (Table 2) the two signals at 119.8-119.9 ppm to the $C_{(5)}$ and $C_{(6)}$ atoms is based on the larger Overhauser effect for the first one. Assignment of the group of signals to carbon atoms of the phenyl substituent that are bonded to protons is based on their relative intensity (C*o* ~ C*m* > C*p*) and the larger Overhauser effect for *ortho* carbon atoms than for *meta* atoms.

The two signals at 138.6 ppm and 137.8 ppm in the spectrum of compound **2c** of approximately equal intensity, belonging to C atoms not bonded to protons, are respectively assigned to the junction $C_{(8a)}$ atom of the heterocycle and the *ipso* atom of the phenyl group, since the second signal, in contrast to the first, is symmetric and is a doublet of triplets with typical long-range spin–spin coupling constants ($^2J_{CH}$ = 3.7 Hz, $^3J_{CH}$ = 8.9 Hz). Assignments of the two low-intensity signals (the doublet at 102.5 ppm ($^3J_{CH}$ = 8.9 Hz) and the doublet of triplets at 120.3 ppm ($^2J_{CH}$ = 3.7, $^3J_{CH}$ = 8.9 Hz)) to the junction $C_{(4a)}$ and $C_{(4b)}$ atoms respectively are consistent with the data for analogous junction atoms in the spectra of the above-indicated 9-phenylpyrimido[4,5-*b*]indoles [18].

The three downfield signals in the spectrum of compound **2c** do not belong to C atoms of the pyrimidine ring that are bonded with protons. The furthest downfield signal at 161.6 ppm is a singlet and we assigned it to the $C_{(2)}$ atom, and we assigned the adjacent triplet at 160.4 ppm ($^3J_{CH}$ = 8.9 Hz) and doublet at 159.1 ppm ($^2J_{CH}$ = 3.0 Hz) to the $C_{(4)}$ and $C_{(9a)}$ atoms respectively. A direct comparison of the spectral data for compound **2c**

and 4-amino-9-phenyl-substituted isomer [18] is apparently not valid due to the different effect of the 2- and 4-amino groups on the chemical shifts of the C atoms of the heterocycle.

For the other two 2-substituted pyrimido[4,5-*b*]indoles (compounds **2a** and **2b**), the assignments of the resonance signals from the carbon atoms of the phenyl group and the benzene ring of the indole moiety (Table 2) are made based on the data for compound **1**, taking into account the substituent effect. In this case, we used an additive scheme for calculating the chemical shifts for the $C_{(2)}$, $C_{(4)}$, $C_{(4a)}$, and $C_{(9a)}$ atoms, introducing increments for the methyl and phenyl groups according to the ^{13}C NMR data for the corresponding derivatives of pyrimidine [23] and quinazoline [24, 25]. In the case of compound **3**, the presence of the 9-phenyl group has practically no effect on the position of all the resonance signals of the heterocyclic system, while the signals for this group itself are consistent with the data for 4-amino-9-phenylpyrimidoindole [18].

EXPERIMENTAL

The NMR spectra of compound **1** were recorded on a DRX-500 spectrometer (500 MHz for ^1H nuclei and 125 MHz for ^{13}C nuclei), the spectra for compounds **2a-c** and **3** were recorded on a Bruker AC 200 spectrometer (200 MHz and 50 MHz), solvent DMSO-d_6 (concentration of solutions, 1-2%). As the internal standards, we used the signals from the solvent at 2.50 ppm (^1H) and 39.50 ppm (^{13}C). The ^{13}C NMR spectra were recorded with complete proton decoupling and under conditions with *J*-modulation of induction decay. Compound **1** was obtained as described in [26]; its derivatives **2** and **3** were obtained by the familiar procedure in [5].

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REFERENCES

1. B. Venugopalan, P. D. Desai, and N. J. de Souza, *J. Heterocycl. Chem.*, **25**, 1633 (1988).
2. C. E. Müller, I. Hide, J. W. Daly, K. Rothenhäusler, and K. Eger, *J. Med. Chem.*, **33**, 2822 (1990).
3. G. L. Bundy, J. R. Palmer, and G. L. Weber, WO Pat. 9626941; *Chem. Abstr.* **125**:275901 (1996).
4. G. L. Bundy and J. R. Palmer, US Pat. 5795986; *Chem. Abstr.*, **129**:175648 (1998).
5. V. P. Borovik, L. S. Filatova, and V. P. Mamaev, *Izv. Siber. Otdel. Akad. Nauk SSSR, Ser. Khim. Nauk*, No. 3, 137 (1975).
6. S. Senda, K. Hirota, and M. Takahashi, *J. Chem. Soc., Perkin Trans. 1*, 503 (1975).
7. J. A. Hyatt and J. S. Swenton, *J. Heterocycl. Chem.*, **9**, 409 (1972).
8. J. A. Hyatt and J. S. Swenton, *J. Org. Chem.*, **37**, 3216 (1972).
9. T. Higashino, E. Hayashi, H. Matsuda, and T. Katori, *Heterocycles*, **15**, 483 (1981).
10. J. Bratt, B. Iddon, A. G. Mack, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 648 (1980).
11. Y. Kondo, R. Watanabe, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **37**, 2933 (1989).
12. M. Tielemans, V. Areschka, J. Colomer, R. Promel, W. Langenaeker, and P. Geerlings, *Tetrahedron*, **48**, 10575 (1992).
13. G. E. Wright, *J. Heterocycl. Chem.*, **13**, 539 (1976).
14. J.-L. Bernier and J.-P. Henichart, *J. Org. Chem.*, **46**, 4197 (1981).
15. V. V. Lapachev, W. Stadlbauer, and T. Kapper, *Monatsh. Chem.*, **119**, 97 (1988).
16. Yu. N. Portnov, S. N. Bulaga, V. G. Zabrodnyaya, and L. D. Smirnov, *Khim. Geterotsikl. Soedin.*, 400 (1991).
17. N. Ple, A. Turck, A. Heynderickx, and G. Queguiner, *J. Heterocycl. Chem.*, **31**, 1311 (1994).

18. K. Eger, W. Lanzner, and K. Rothenhäusler, *Liebigs Ann. Chem.*, 465 (1993).
19. Sadtler Standard NMR Spectra, Sadtler Research Lab., Philadelphia (1986), **78**, 43935.
20. V. F. Sedova, V. P. Krivopalov, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, 986 (1979).
21. E. Arzel, P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *J. Heterocycl. Chem.*, **34**, 1205 (1997).
22. P. Joseph-Nathan, R. E. del Rio, and M. S. Morales-Rios, *Heterocycles*, **27**, 377 (1988).
23. J. Riand, M.-T. Chenon, and N. Lumbroso-Bader, *Tetrahedron Lett.*, 3123 (1974).
24. S. G. Baram, O. P. Shkurko, and V. P. Mamaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 686 (1991).
25. U. Ewers, H. Günter, and L. Jaenicke, *Angew. Chem. Int. Ed.,* **14**, 354 (1975).
26. K. E. Schulte, J. Reisch, and U. Stoess, *Arch. Pharm.*, **305**, 523 (1972).