

^{13}C NMR spectra of some indole derivatives

A. A. Panasenکو, A. F. Caprosh, O. M. Radul,* and M. A. Rekhier

*Institute of Chemistry of the Academy of Sciences of Moldova,
3 ul. Akademicheskaya, 277028 Kishinev, Moldova.
Fax: +7 (042) 273 9954*

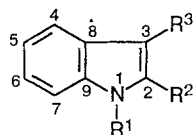
The effect of acyl and carboxyl groups in position 2 or 3 of the indole ring on the ^{13}C chemical shifts of the ring was studied. α -, β -, and γ -Increments of the indole and isatin rings for ^{13}C chemical shifts of the substituents at the ring N-atom were determined.

Key words: indole, ^{13}C NMR, chemical shift, increments of chemical shifts.

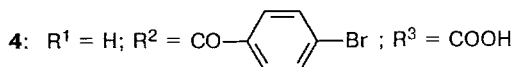
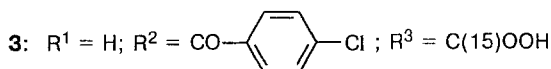
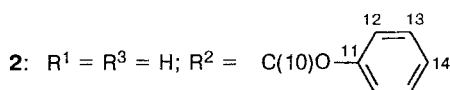
Derivatives of indole are widely used as drugs, pesticides, and growth stimulants for plants.^{1–3} There are many works on the study of the ^{13}C NMR spectra of various natural and synthetic derivatives of indole.^{3–8}

2-Acylindoles are the starting compounds for the synthesis of sedative preparations of a novel type.⁹ The presence of the carboxyl group at the C(3) atom enhances the biological activity of these compounds.¹⁰ These compounds can be prepared most readily from indoline-2,3-diones (isatins) containing a 2-oxoalkyl group at the N-atom.

In this work we have studied the ^{13}C NMR spectra of a number of novel derivatives of indole and isatin and the effects of various substituents on the chemical shifts of the carbon nuclei of indole and isatin, and determined the contributions of the indole and isatin rings to the chemical shifts of the substituents at the N atom. The following compounds have been studied.



1: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$



5: $\text{R}^1 = \text{C}(16)\text{H}_2-\text{C}(17)\text{H}_3$; $\text{R}^2 = \text{CO}-\text{Ph}$; $\text{R}^3 = \text{COOH}$

6: $\text{R}^1 = \text{C}(16)\text{H}_2-\text{C}(17)\text{H}_2-\text{C}(18)\text{H}_3$; $\text{R}^2 = \text{COPh}$; $\text{R}^3 = \text{COOH}$

7: $\text{R}^1 = \text{C}(16)\text{H}_2-\text{C}(17)\text{H}_2-\text{C}(18)\text{H}_2-\text{C}(19)\text{H}_3$; $\text{R}^2 = \text{COPh}$; $\text{R}^3 = \text{COOH}$

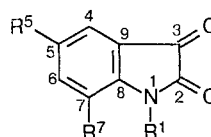
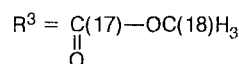
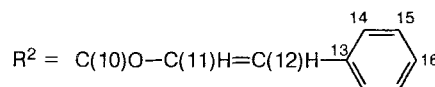
8: $\text{R}^1 = \text{C}(16)\text{H}_2-\text{C}(17)\text{H}=\text{C}(18)\text{H}_2$; $\text{R}^2 = \text{COPh}$; $\text{R}^3 = \text{COOH}$

9: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{C}(10)\text{OC}(11)\text{H}_2-\text{C}(12)\text{H}(\text{C}(13,14)\text{H}_3)_2$; $\text{R}^3 = \text{C}(15)\text{OOH}$

10: $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{C}(10)\text{OC}(11)\text{H}(\text{C}(14)\text{H}_3)\text{C}(12)\text{H}_2-\text{C}(13)\text{H}_3$; $\text{R}^3 = \text{C}(15)\text{OOH}$

11: $\text{R}^1 = \text{C}(16)\text{H}_2-\text{C}(17)\text{H}_2-\text{C}(18)\text{H}_3$; $\text{R}^2 = \text{COPh}$; $\text{R}^3 = \text{C}(15)\text{OC}(19)\text{H}_2\text{C}(20)\text{H}_2\text{C}(21)\text{H}_3$

12: $\text{R}^1 = \text{C}(19)\text{H}_3$;



13: $\text{R}^1 = \text{R}^5 = \text{R}^7 = \text{H}$

14: $\text{R}^5 = \text{R}^7 = \text{H}$; $\text{R}^1 = \text{CH}_2-\text{CH}_3$

15: $\text{R}^5 = \text{R}^7 = \text{H}$; $\text{R}^1 = \text{CH}_2-\text{CH}_2-\text{CH}_3$

16: $\text{R}^5 = \text{R}^7 = \text{H}$; $\text{R}^1 = \text{CH}_2-\text{CH}=\text{CH}_2$

17: $\text{R}^5 = \text{R}^7 = \text{H}$; $\text{R}^1 = \text{CH}_2\text{COCH}_3$

18: $\text{R}^5 = \text{R}^7 = \text{H}$; $\text{R}^1 = \text{CH}_2-\text{C}\equiv\text{CH}_3$

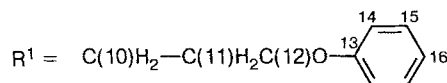
19: $\text{R}^5 = \text{R}^7 = \text{H}$;

$\text{R}^1 = -\text{C}(10)(\text{C}(14)\text{H}_3)-(\text{C}11)\text{H}_2-\text{C}(12)\text{OC}(13)\text{H}_3$

20: $\text{R}^5 = \text{R}^7 = \text{H}$;

$\text{R}^1 = \text{C}(10)\text{H}_2-\text{C}(11)\text{H}_2\text{C}(12)\text{O}-\text{C}(13)(\text{C}(14)\text{H}_3)$

21: $\text{R}^5 = \text{R}^7 = \text{H}$;

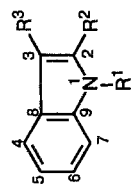


22: $\text{R}^5 = \text{R}^7 = \text{H}$;

$\text{R}^1 = \text{C}(10)\text{H}_2-\text{C}(11)\text{HBr}-\text{C}(12)\text{H}_2\text{OH}$

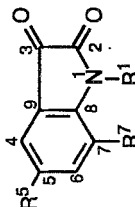
23: $\text{R}^5 = \text{CH}_3$; $\text{R}^1 = \text{R}^7 = \text{H}$

24: $\text{R}^7 = \text{CH}_3$; $\text{R}^1 = \text{R}^5 = \text{H}$

Table 1. The ¹³C chemical shifts of indole and its derivatives

Compo- und	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(15)	C(16)	C(17)	C(18)	C(19)	C(20)	C(21)
1*	123.1	100.9	119.9	118.7	120.8	111.3	127.6	135.8	186.5	138.1	128.9	128.5	132.5							
2	134.4	112.8	122.9	120.1	125.7	112.3	127.1	138.2	189.2	135.9	129.0	131.0	138.7	165.0						
3	135.7	108.6	122.2	121.6	124.2	112.7	125.7	138.7	189.3	136.2	131.0	131.8	127.8	165.0						
4	135.7	108.7	122.1	121.5	124.1	112.6	125.6	139.0	190.3	136.3	128.3	128.5	133.5	164.1	38.9	14.6				
5	135.2	106.8	121.7	121.0	123.0	110.4	124.8	140.1	190.3	136.3	129.1	129.2	134.3	164.9	46.0	23.3	11.0			
6	136.5	107.7	122.4	121.7	123.6	111.5	125.3	140.9	191.0	137.0	129.1	129.2	134.3	164.7	44.1	31.9	19.2	13.3		
7	136.3	107.6	122.3	121.6	123.9	111.2	125.2	140.7	190.8	136.9	129.0	129.1	134.2	164.8	46.6	134.1	117.8			
8	136.4	108.2	122.5	121.2	123.9	111.5	125.4	140.9	190.7	137.1	128.1	129.3	132.9	164.8						
9	135.5	107.5	122.5	122.1	125.1	112.9	126.6	137.7	197.1	49.9	25.0	22.3	22.3	165.3						
10	135.6	109.1	122.3	122.1	124.8	112.8	126.5	138.4	201.5	45.2	26.1	11.2	15.8	165.5						
11	135.6	106.1	121.7	120.7	123.3	110.4	124.5	140.1	189.8	136.2	128.3	128.4	133.5	162.6	45.3	22.5	9.5	65.0	20.7	10.1
12	136.7	106.0	122.5	121.5	123.9	111.2	124.9	142.2	189.5	128.1	134.1	145.4	128.86	128.93	131.1	163.9	51.0	31.1		

* See Ref. 5.

Table 2. The ¹³C chemical shifts of isatin and its derivatives

Compo- und	C(2)	C(3)	C(4)*	C(5)	C(6)*	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(15)	C(16)
13	159.5	184.5	138.5	122.9	124.7	117.4	117.9	150.9							
14	157.6	183.4	138.4	123.0	124.5	110.6	117.4	150.4	34.4	12.2					
15	158.5	184.1	138.7	123.6	124.8	111.0	118.2	151.9	41.9	20.9	11.1				
16	157.9	183.2	138.2	123.3	124.5	111.1	117.6	150.6	41.8	131.3	117.6				
17	158.1	183.9	138.4	123.5	124.4	111.1	117.3	150.8	49.3	201.6	27.1				
18	157.3	182.5	138.2	123.6	124.6	111.2	117.6	149.5	29.1	77.3	74.9				
19	158.4	184.1	138.6	123.4	123.9	111.8	118.4	151.7	45.3	46.5	205.4	29.6	17.5		
20	158.2	183.6	138.4	123.3	124.7	111.0	117.9	151.3	35.6	33.9	212.9	43.9	25.9		
21	157.8	183.1	137.9	122.8	124.0	110.8	117.3	150.4	34.5	35.3	197.5	136.1	128.4	127.6	132.9
22	158.1	182.7	138.1	123.2	124.3	110.9	117.2	150.4	43.5	52.2	63.5				
23**	159.4	184.5	138.8	132.1	124.7	112.1	117.6	148.6							
24***	159.9	184.7	139.4	121.9	122.6	121.6	117.4	150.0							

* Interchanging of the chemical shift values is possible. ** ₈CH₃ = 20.3. *** ₈CH₃ = 15.4.

Experimental

The ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer (20 MHz) for 10–20 % solutions in $\text{DMSO}-d_6$ under the conditions of complete proton decoupling. To determine the degree of protonation of the C atoms, the spectra were recorded in multipulse JMODXH and INERTRD type successions with inversion of the C signals in the positive or negative direction (relative to the y scale) depending on the degree of their protonation, or under conditions in which the signals only from methine C atoms were recorded (the average value for $^1J_{\text{CH}} = 140\div 170$ Hz was taken). The delay time between the pulses was 10–25 s in the JMODXH mode and 1–2 s in the INERTRD mode. The chemical shifts are given in the δ scale and referred to TMS; $\text{DMSO}-d_6$ was the internal standard.

The compounds were synthesized according to the known procedures.²

Results and Discussion

A comparison of the chemical shifts (Table 1) of indole and 2-benzoylindole (compound **2**) made it possible to determine the contributions of the PhCO group to the chemical shifts of the C atoms of indole: $\Delta\text{C}(2) = 9.3$ ppm (α -effect), $\Delta\text{C}(3) = 11.9$ ppm (β -effect); $\Delta\text{C}(4) = 3.0$ ppm; $\Delta\text{C}(5) = 1.4$ ppm; $\Delta\text{C}(6) = 4.9$ ppm; $\Delta\text{C}(7) = 1.0$ ppm; $\Delta\text{C}(8) = 0.5$ ppm; $\Delta\text{C}(9) = 2.4$ ppm; and a comparison of the chemical shifts of compounds **2**, **3**, and **4** enabled the determination of the contribution of the COOH group at C(3): $\Delta\text{C}(2) = 1.3$ ppm (β -effect); $\Delta\text{C}(3) = -4.1$ ppm (α -effect), $\Delta\text{C}(4) = -0.8$ ppm; $\Delta\text{C}(5) = -1.5$ ppm; $\Delta\text{C}(6) = 1.6$ ppm; $\Delta\text{C}(7) = 0.4$ ppm; $\Delta\text{C}(8) = -1.5$ ppm (β -effect); $\Delta\text{C}(9) = 0.8$ ppm. Interestingly, when there is no substituent at the C(2) atom, the α -contribution of the COOH group attached to C(3) is 7.6 ppm (the chemical shift was taken from Ref. 3).

The introduction of an alkyl or allyl substituent to the N atom (compounds **5**–**8**, **11**, and **12**) results in only a minor downfield shift, of 1.1–1.2 ppm, of the signal of C(9) (cf. compounds **4** and **5**) (β -effect) and an upfield shift (0.4–2.6 ppm) of the signal of C(3) (γ -effect).

A comparison of the chemical shifts (Table 2) of the corresponding C atoms of isatin (compound **13**) and its 1-substituted derivatives (compounds **14**–**22**) shows that in this case, unlike the 1-substituted compounds **5**–**8**, **11**, and **12**, the introduction of a substituent in position 1 leads to a substantial diamagnetic shift (5.6–6.8 ppm) of the C(7) signal. The chemical shifts of the remaining C atoms change insignificantly.

The dissimilar behavior of the chemical shifts of the C(7) atom in 1-substituted isatins and 1-substituted 2-acylindolyl-3-carboxylic acids is probably due to the differences between the structures of isatin and indole molecules. According to Ref. 11, isatin molecules form dimers in the crystalline state by means of two $\text{N}-\text{H}\cdots\text{O}(\text{C}(2))$ H-bonds.

In concentrated (10–20 %) solutions the dimeric state of isatin is apparently retained, whereas 1-alkylisatins are monomeric. It is quite probable that the local fields near the C(7) atom in dimeric isatin and its 1-substituted derivatives are essentially different; and this is the reason for the diamagnetic shift of the C(7) signal in the latter. In the case of indole, which is monomeric, the chemical shift for C(7) does not markedly differ from that in 1-substituted indoles and isatins.

Introducing CH_3 groups to positions 5 and 7 causes the following changes (cf. compounds **13**, **23**, and **24**): in the former case (compound **23**) the signals for C(7) and C(9) are displaced upfield (γ - and δ -effects) by 5.3 and 2.3 ppm, respectively, and the signal for C(5) shifts downfield by 9.2 ppm (α -effect); in the latter case (compound **24**) the signal for C(7) shifts downfield by 4.2 ppm (α -effect) and the C(6) (β -effect) and C(5) (γ -effect) signals are displaced upfield by 2.1 and 1.0 ppm, respectively.

A comparison of the chemical shifts of the carbon atoms of the substituents with those for their hydrocarbon analogs allowed us to determine the α -, β -, and γ -contribution of the isatin ring for saturated hydrocarbons (CH_3CH_3 , $\text{CH}_3\text{CH}_2\text{CH}_3$) as well as for $\text{CH}_3\text{CH}_2\text{COPh}$, $\text{CH}_3-\text{CH}=\text{CH}_2$, CH_3COCH_3 , and $\text{CH}_3-\text{C}\equiv\text{CH}$. The values for the chemical shifts for the model compounds were taken from Ref. 12. For alkanes, the following values for the contributions were obtained: $\Delta\text{C}_\alpha = 26.8$ ppm; $\Delta\text{C}_\beta = -4.9$ ppm, and $\Delta\text{C}_\gamma = -3.8$ ppm. For those compounds whose CH_3 groups are bonded with sp^2 - or sp -hybridized carbon atoms, the contributions for propene are $\Delta\text{C}_\alpha = 24.6$ ppm, $\Delta\text{C}_\beta = -4.9$ ppm, and $\Delta\text{C}_\gamma = 1.6$ ppm; for propyne: $\Delta\text{C}_\alpha = 11.9$ ppm, $\Delta\text{C}_\beta = -3.1$ ppm, and $\Delta\text{C}_\gamma = 6.6$ ppm; for acetone: $\Delta\text{C}_\alpha = 18.6$ ppm, $\Delta\text{C}_\beta = -5.1$ ppm, and $\Delta\text{C}_\gamma = -3.6$ ppm.

Similar contributions of the 2-acyl-3-carboxyindole ring were determined for normal hydrocarbons and for unsaturated hydrocarbons of the series $\text{CH}_3-\text{CH}=\text{CHR}$. In the former case $\Delta\text{C}_\alpha = 31.1$ ppm, $\Delta\text{C}_\beta = 7.3$ ppm, and $\Delta\text{C}_\gamma = -5.0$ ppm; in the latter case $\Delta\text{C}_\alpha = 29.4$ ppm, $\Delta\text{C}_\beta = -2.1$ ppm, and $\Delta\text{C}_\gamma = 1.9$ ppm.

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