Synthesis and Spectral Characterization of 2-Substituted Indole Derivatives

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Twelve 2-substituted indole derivatives were synthesized by the Fischer indole method using polyphosphoric acid (PPA) as cyclodehydrating agent. Uv, ir, and nmr spectral data are reported.

A number of general methods for the synthesis of indole derivatives have been reported *(7)*. Among these, the well-known Fischer synthesis *(1, 2)*, proved to be the most versatile for the synthesis of indole compounds. In the present investigation, 2-substituted indole derivatives are prepared with good yields from phenylhydrazine and a series of methylketones, using polyphosphoric acid (PPA) as cyclodehydrating agent *(3, 4, 6)*. It was found that the use of PPA gives indoles in good yields, which are about as high or higher than those reported *(5)*. It has been found in this method that reaction time and temperature are critical factors *(3, 4)*.

To determine the optimum temperature required for the cyclization of a given compound, a trace of the reactants is mixed with a few drops of PPA. If the mixture turns dark immediately, the reaction should be carried out in the cold; if the color changes gradually, room temperature is preferable; and if only a little color appears, heating is required. Most of the compounds synthesized gave light yellow or light red colors in the beginning, turning to bright red and finally deep red. The structure and physical properties of the synthesized indoles are given in Table I. Uv, ir, and nmr data for the synthesized 2-substituted indoles are given in Tables II and III..

The ir absorption spectra of 2-substituted indoles showed an NH absorption at 3430-3140 cm^{-1}, due to the free NH stretching vibration. Table II shows marked variations in both frequency and intensity of this band in the indoles studied. Both were found to be very sensitive to the surrounding structure.

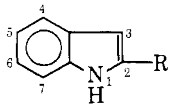
The chemical shift and coupling constants in the nmr spectra of 2-substituted indoles are summarized in Table III. The assignments were as follows: In 5-indolinylindole *(6)*, two triplets were observed at 3.2 and 4.1 δ (J = 7.5 Hz) for the two adjacent methylene groups. The triplet at 4.1 δ was assigned to the methylene group at position 2 next to the nitrogen, and the one at 3.2 δ, to the methylene group at position 3 of the five-membered ring. These triplets are broad due to their coupling with the NH proton. The aromatic protons appeared as a complex pattern at 7.3, 7.5, and 7.8 δ. The signals at 7.5 and 7.8 δ appeared as a group of partially resolved doublets and were assigned to the aromatic protons of the substituent indoline ring. Two other broad signals at 8.2 and 8.3 δ, exchangeable with deuterium, were assigned to the two protons on the nitrogen atoms. The center of these bands was taken as the chemical shift of the corresponding proton. The olefinic proton appeared as a singlet at 7.25 δ.

The NH signal in compound 11, appeared as a doublet at 8.1 δ, (J = 2.5 Hz), due to the coupling with the olefinic proton at C-3. On deuteration, this doublet disappeared and the doublet due to the proton at C-3 collapsed into a singlet, showing that long-range coupling does take place between the protons at positions 1 and 3 of the five-membered ring.

Experimental

Elemental analyses were performed by A. Bernhardt Laboratories, Ruhr, Germany. Melting points were taken

Table I. Characterization of 2-Substituted Indoles[a]



	Molecular formula	R	Mp, °C	Yield, %	Reaction temp, °C	Crystallization solvent
1	$C_{18}H_{13}N$	2-Naphthyl	163–164	85	100	Benzene
2	$C_{21}H_{15}N$	2-Fluorenyl	180–182	80	110	Acetic acid
3	$C_{20}H_{15}N$	4-Biphenyl	167–169	80	110	Benzene
4	$C_{17}H_{15}N$	5-Indanyl	127–129	85	130	Benzene
5	$C_{16}H_{12}N_2$	3-Indolyl	190–191	80	110	Ethanol
6	$C_{16}H_{16}N_2$	5-Indolinyl	173–174	83	120	Ethanol
7	$C_{13}H_{10}N_2$	2-Pyridyl	153–154	85	120	Ethanol
8	$C_{13}H_{10}N_2$	3-Pyridyl	133–134	80	135	Ethanol
9	$C_{13}H_{10}N_2$	4-Pyridyl	241–242	82	130	Ethanol
10	$C_{14}H_{11}N$	2-Phenyl	185–186	75	100	Benzene
11	$C_{14}H_{10}BrN$	2-*p*-Bromophenyl	188–189	80	110	Benzene
12	$C_{14}H_{10}N_2O$	2-*p*-Nitrophenyl	132–133	77	130	Ethanol

[a] Elemental analyses (C, H, N) in agreement with theoretical values were obtained and submitted for review.

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Table II. Characteristic Ir and Uv Absorption of Substituted Indoles[a]

	NH Stretch, cm^{-1}	Aromatic or olefinic stretch, cm^{-1}	Aliphatic CH stretch, cm^{-1}	C=C, C=N, C—N stretch, cm^{-1}	CH deformation, cm^{-1}	$\lambda_{\max}$ mμ log ϵ
1	3360m	3020w 3060w		1605s, 1570s, 1510s, 1490s, 1440m, 1380m, 1340m, 1300s, 1260s	1150s, 1080m, 960m, 945m, 900s, 870s, 830s, 755s, 700s	208(4.49) 235(4.63) 342(4.45)
2	3360m	3050w	2940m	1610s, 1595s, 1500s, 1460m, 1430m, 1400m, 1340m, 1300m, 1260s	1240m, 1150m, 1080m, 1100m, 900m, 850m, 780s, 760s, 750s, 700s	209(3.55) 269(3.44) 350(3.35)
3	3330m	3020w 3040w		1670s, 1595m, 1570s, 1540m, 1480s, 1440m, 1420m, 1400s, 1320s, 1290m	1245s, 1140s, 1060s, 1000m, 990m, 950m, 880m, 835s, 760s, 745m, 720s, 680s	210(4.35) 276(4.32)
4	3380m	3020w 3060w 3080s	2920s 2840s	1650s, 1590s, 1540s, 1490s, 1445s, 1370s, 1300s	1235s, 1170m, 1150s, 1070m, 1040m, 990s, 965s, 880s, 855s, 750s, 705s, 680s, 650s	206(4.00) 235(4.18) 288(3.45)
5		3020w 3040w 3050w		1600s, 1570s, 1515s, 1485s, 1430s, 1410s, 1375s, 1320m, 1310s	1230s, 1170s, 1130s, 1100s, 1020s, 1000s, 930s, 870m, 800s, 750s, 670m, 630m	207(4.11) 229(4.16) 290(3.81)
6	3240m	3010w	2940w	1660s, 1630s, 1590s, 1480s, 1435s, 1390s, 1350m, 1320s, 1250s	1100m, 1020m, 920w, 890w, 810m, 735m, 680m	209(4.02) 306(3.86) 347(3.87)
7	3280m	3020w		1600s, 1570s, 1550m, 1480s, 1440m, 1410s, 1370s, 1330s, 1290s, 1250s	1150s, 1080s, 1030s, 965s, 890s, 810s, 750s, 700s, 620s	206(3.09) 255(2.89) 348(2.85)
8	3180m 3140m	3010w 3070w		1590s, 1550s, 1480s, 1460s, 1420s, 1350m, 1330m, 1280s	1240s, 1140s, 1070m, 1040m, 990s, 880m, 775s, 740s, 685s	207(4.13) 225(4.09) 300(3.94) 342(4.31)
9	3420m 3380m	3030w 3080m		1625s, 1590s, 1540s, 1470s, 1370m, 1330w, 1280m	1230s, 1190s, 1160m, 1070s, 805s, 750s, 685s	206(4.00) 230(3.88) 330(4.22)
10	3430m	3030m 3090w		1600m, 1520m, 1480s, 1450m, 1400m, 1350s, 1300s	1240m, 1220m, 1185m, 1070m, 1045m, 930m, 900m, 790s, 755s, 735m, 680s	
11	3400m	3020w		1530m, 1470s, 1445s, 1415s, 1340s, 1290s	1235m, 1180m, 1110m, 1070s, 1000s, 825s, 790s, 745s, 700m, 650m	
12	3330m			1600s, 1590s, 1540s, 1490s, 1320s, 1250s	1185s, 1165s, 880m, 850s, 750s, 680s	

[a] s = strong, m = medium, w = weak.

Table III. Nmr Data For 2-Substituted Indoles[a]

	Solvent	Aliphatic-H δ, ppm	Aromatic-H δ, ppm	H-1 δ, ppm	H-3 δ, ppm	J, Hz
1	$CDCl_3$		7.55m, 7.9m, 8.22dd	6.97b	7.25s	$J_{13} = 2.5$
2	$CDCl_3$	4.0s, CH_2	7.3m, 7.85m, 8.05m	7.50b	7.28s	
3	$CDCl_3$		7.5m, 7.7s, 7.85s, 7.95s	6.95	7.22	
4	$CDCl_3$	2.0s, 2.08s	6.78d, 6.9d, 7.3m, 7.38d	7.7bs	5.7bs	
	DMSO	1.86s, 1.9s	6.9m, 7.2m	5.8b	7.0s	
5	DMSO		7.0m, 7.4m, 7.8m	8.05b	7.01s	
6	DMSO	3.1t, 4.01t	6.8m, 7.27m	8.0b 7.68b	6.95s	$J_{23} = 7$
	$CDCl_3$	3.2t, 4.1t	7.3m, 7.5m, 7.8m	8.2b 8.3b	7.25s	$J_{23} = 7.5$
7	DMSO		7.0m, 7.52s, 7.67d, 8.3t, 8.42t, 8.73dd, 9.25d	9.66s	7.4d	$J_{13} = 2$
8	DMSO		7.1m, 7.3d, 7.43d, 7.6s, 7.85d, 8.0d, 8.15d, 8.4m, 8.82dd	9.77d	6.1bs	$J_{13} = 2$
9	DMSO		7.63m, 8.45d, 8.97d	10.85b	7.49bs	$J_{AB} = 7$
	$CDCl_3$		7.18d, 7.33d, 7.53m, 8.1m, 8.58m	9.08b	7.28s	$J_{AB} = 7.5$
10	$CDCl_3$		7.32m, 7.83m, 8.02m	6.95b	7.22s	
11	DMSO		7.2d, 7.32d, 7.23m, 7.53m, 7.7m, 7.9d	8.1d	7.08d	$J_{13} = 2.5$
12	DMSO		7.0m, 7.3m, 8.1d, 8.4d	9.85s	7.5s	$J_{AB} = 8$

[a] s = singlet, d = doublet, t = triplet, m = multiplet, b = broad, bs = broad singlet, J_{AB} = coupling constant in AB systems.

on a Kofler melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR 18A spectrometer. All compounds were examined in a potassium bromide matrix. Uv absorption spectra were obtained with a Unicam SP800B spectrophotometer on solutions in ethanol. Nmr spectra were measured on a Varian A60A spectrometer with tetramethylsilane (TMS) as the internal reference.

Preparation of 2-Substituted Indoles

A mixture of phenylhydrazine (0.01 mole) and the ketone (0.01 mole), were added to polyphosphoric acid (30 grams) in a flask protected from moisture. The viscous mass was mixed thoroughly and kept at the required temperature (Table I). The reaction mixture was stirred every few minutes and stopped as soon as a deep yellow, purple, or blue color was observed. The contents of the flask were poured into ice water (100 ml), and the product which separated was collected by filtration. Recrystallization of the crude product gave pure 2-substituted indole. Physical properties, yields, reaction conditions, and solvents of recrystallizations are given in Table I.

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