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INDOLE DERIVATIVES. 142.* SOME PROPERTIES OF [4-(2-INDOLYL)PHENYL]PHENYLMETHANE AND 1-[4-(2-INDOLYL)PHENYL]-2-PHENYLETHANE

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The reactions of 2-arylindoles with strong electrophiles take place with significant resin formation. It was shown that electrophilic substitution is directed into the indole ring and into the side chain. 1,7-Migration of the substituent is observed in the investigated systems.

Keywords: arylindoles, rearrangement, nitration, N-alkylation.

Earlier [1] we reported on the synthesis of new 2-arylindoles and their reactions with weak electrophiles (azocoupling, formylation, and nitrosation), as a result of which the corresponding 3-substituted derivatives are formed.

In the present communication we describe the nitration, bromination, alkylation, and 1,7-migration of the substituent in these 2-arylindoles.

It is known that the nitration reaction of the simplest indoles is ambiguous on account of complications caused by the strong acids used as components of the usual nitrating mixtures [2, 3].

For the nitration of [4-(2-indolyl)phenyl]phenylmethane (**1**) we used a KNO_3–H_2SO_4 mixture at 0°C and a Ac_2O–50% HNO_3 mixture at 2-7°C. In both cases there was considerable resinification of the reaction mixture. From the each obtained multicomponent mixtures we were able to isolate and characterize two compounds, i.e., **2**, **3** and compounds **4** and **5**, with yields of 18, 31, 19, and 39% respectively (Scheme 1).

In the strongly acidic medium the formation of the product from cleavage of the side chain of compound **2** can be explained by protonation of the nearest 2-phenyl ring, and this probably favors removal of the benzyl or *p*-nitrobenzyl group. In a weakly acidic medium the reaction is characterized by higher selectivity. Substitution in [4-(2-indolyl)phenyl]phenylmethane takes place at the positions of the indole ring that are rich in electron density.

In the ^1H NMR spectra of the three 5-nitro derivatives **2-4** there are signals characteristic of the 4-, 6-, and 7-H protons of 5-substituted indole. We assigned doublets at 8.52 (compound **2**), 8.51 (compound **3**), and 8.27 ppm (compound **4**) with J_m = 2 Hz to the 4-H protons and doublets at 7.41 (compound **2**), 7.53 (compound **3**), and 7.68 ppm (compound **4**) with J_o = 8 Hz to the 7-H protons. The signals of the 6-H protons appear in the form of quadruplets at 8.00 (**2**), 7.98 (**3**), and 7.89 ppm (**4**), while the signals of the 3-H protons appear in the form of singlets at 7.20 (**2**), 7.21 (**3**), and 7.06 ppm (**4**). The analogous signal of the 3-H proton is absent in the spectrum of compound **5**. In the spectrum of compound **3** the presence of two pairs of doublets at 7.55, 8.16 and at 7.40 and 7.84 ppm (J_o = 8 Hz), which we assigned to the protons of the 4,4'-disubstituted diphenylmethane,

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[*] For Communication 141, see [1].

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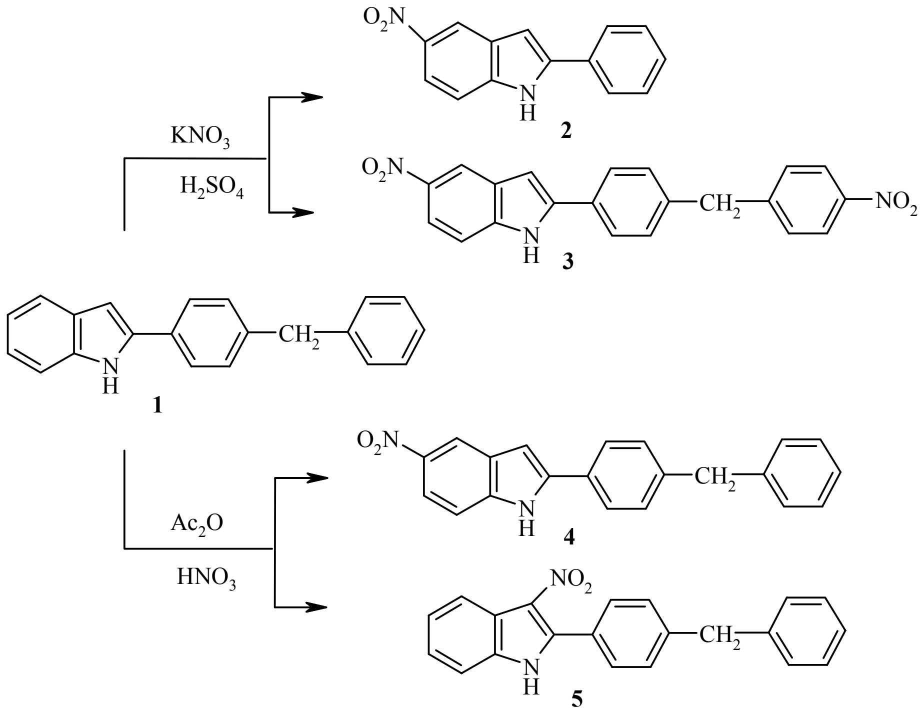
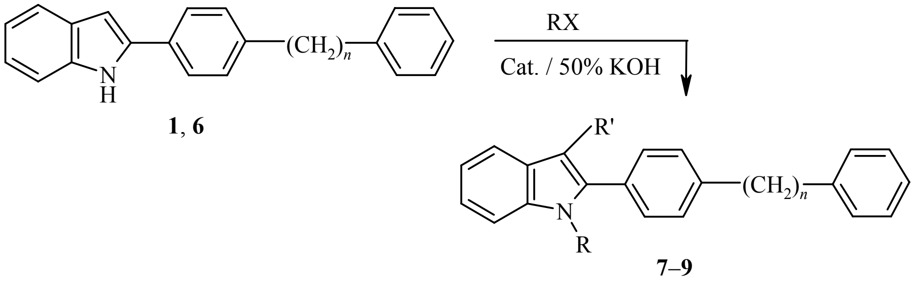
Scheme 1



and also singlet signals for the NH and CH$_2$ groups at 12.22 and 4.16 ppm respectively, confirms conclusively the proposed structure. In the spectra of compounds **2**, **4**, and **5** there are multiplets for the terminal monosubstituted phenyl rings (Table 1).

The alkylation of the indole **1** and 1-[4-(2-indolyl)phenyl]-2-phenylethane **6** was carried out by the method described in [4] under the conditions of phase-transfer catalysis. During benzylation of the indole **1** the 1,3-dibenzylation product **7** was unexpectedly obtained.



7 R = R' = CH$_2$Ph; **8** R = CH$_2$Ph, R' = H; **9** R = CH$_2$CH$_2$Me, R' = H;
1, **7**, **9** n = 1, **6**, **8** n = 2; X = Cl, Br

The ^{1}H NMR spectrum of compound **7** does not contain a signal for the 3-H proton, and the signals for the protons of the N–CH$_2$ and 3-CH$_2$ groups appear in the form of two singlets in the region of 5.23 and 3.99 ppm respectively (Table 1).

In the mass spectrum of compound **7** maximum intensity is observed in the molecular ion peak at 464, the fragmentation of which takes place with successive removal of the two benzyl groups.*

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* The *m*/*z* values are given with the relative intensities at the maximum ion current in parentheses.

TABLE 1. The Spectral Data of the Compounds

Compound	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	^{1}H NMR spectrum, δ, ppm	*J*, Hz
2	3400 (NH), 1520, 1335 (NO_2)	207 (4.30), 230 (4.09) sh, 297 (4.40)	7.20 (1H, d, 3-H); 7.41 (1H, d, 7-H); 7.48-7.58 (3H, m, H_{Ph}); 7.98 (2H, d, A-H); 8.00 (1H, dd, 6-H); 8.52 (1H, d, 4-H); 12.21 (1H, s, NH)	J_{46} = 2.00; J_{13} = 1.35; J_{67} = 7.20
3	3390 (NH), 1510, 1340 (NO_2)	207 (4.50), 220 (4.00) sh, 300 (4.54)	4.16 (2H, s, CH_2); 7.12 (1H, d, 3-H); 7.40 (2H, d, B-H); 7.53 (1H, d, 7-H); 7.55 (2H, d, A'-H); 7.84 (2H, d, A-H); 7.98 (1H, dd, 6-H); 8.16 (2H, d, B'-H); 8.51 (1H, d, 4-H); 12.22 (1H, s, NH)	J_{46} = 2.20; J_{13} = 1.37; J_{AB} = 7.84; $J_{A,B'}$ = 8.72
4	3395 (NH), 1525, 1345 (NO_2)	210 (4.61), 257 (4.41), 377 (4.21)	4.01 (2H, s, CH_2); 7.06 (1H, d, 3-H); 7.24-7.31 (5H, m, $H_{Ph'}$); 7.38 (1H, d, B-H); 7.68 (1H, d, 7-H); 7.84 (1H, d, A-H); 7.89 (1H, d, 6-H); 8.27 (1H, d, 4-H); 12.21 (1H, s, NH)	J_{46} = 1.90; J_{67} = 8.80; J_{AB} = 8.22; J_{13} = 1.48
5	3400 (NH), 1515, 1337 (NO_2)	209 (4.95), 261 (4.61), 333 (4.47)	12.66 (1H, s, NH); 8.21 (1H, d, 4-H); 4.05 (2H, s, CH_2); 7.30-7.43 (10H, m, 5-, 7-, 13-H, $H_{Ph'}$); 7.67 (2H, d, A-H); 8.21 (1H, d, 4-H); 12.66 (1H, s, NH)	J_{AB} = 8.20
7	—	213 (4.51), 227 (4.52), 301 (4.16)	7.36 (1H, d, 4-H); 6.96 (1H, dt, 5-H); 7.07 (1H, dt, 6-H); 7.32 (1H, d, 7-H); 7.17 (2H, d, A-H); 6.83 (2H, d, B-H); 5.29 (2H, s, N–CH_2); 7.08-7.33 (15H, m, $H_{Ph'}$, $H_{Ph''}$, $H_{Ph'''}$); 3.99 (2H, s, $C_{(3)}$–CH_2); 3.98 (2H, s, CH_2)	J_o = 7.96; J_m = 0.88; J_{AB} = 7.92
8	—	214 (4.55), 218 (4.52) sh, 227 (4.64), 241 (4.51) sh, 300 (4.44)	3.05 (4H, s, CH_2CH_2), 5.47 (2H, s, N–CH_2); 6.74 (1H, s, 3-H); 7.14 (2H, d, B-H); 7.22-7.41 (13H, m, 5-, 7-H, $H_{Ph'}$, $H_{Ph''}$); 7.46 (2H, d, A-H); 7.77 (1H, dd, 4-H)	J_{AB} = 8.40; J_{45} = 8.40; J_{46} = 2.0
9	—	209 (4.58), 222 (4.53) sh, 238 (4.37) sh, 297 (4.26)	0.64 (3H, t, CH_3); 1.56 (2H, sextet, CH_2); 4.02 (2H, s, CH_2); 4.13 (2H, t, N–CH_2); 6.46 (1H, s, 3-H); 7.03 (1H, t, 5-H); 7.14 (1H, t, 6-H); 7.17-7.53 (5H, m, $H_{Ph'}$); 7.36 (2H, d, B-H); 7.45 (2H, d, A-H); 7.50 (1H, d, 7-H); 7.53 (1H, d, 4-H)	J_{67} = 7.92; J_{AB} = 7.96; J_{45} = 1.32
14	3410 (NH)	210 (4.61), 249 (4.33), 311 (4.39)	2.93 (4H, s, CH_2CH_2); 4.32 (2H, s, $C_{(7)}$–CH_2); 6.80 (1H, d, 6-H); 6.84 (1H, d, 3-H); 6.91 (1H, t, 5-H); 7.15-7.33 (12H, m, B-H, $H_{Ph'}$, $H_{Ph''}$); 7.36 (1H, d, 4-H); 7.83 (2H, d, A-H); 11.09 (1H, s, NH)	J_{45} = 7.52; J_{13} = 2.24; J_{56} = 7.08; J_{AB} = 8.40

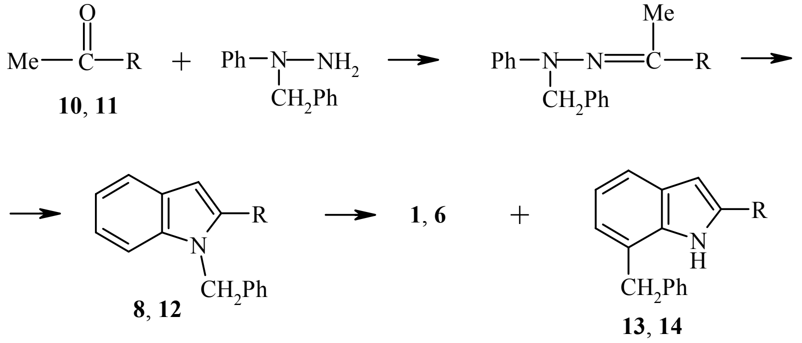
$$\begin{tikzcd}
M^{+}\,464\ (34) \arrow[r, "-PhMe", "-92"'] & 372\ (4.05) \arrow[r, "-PhCH_2Ph", "-168"'] & 204\ (3.85) \arrow[r, "-CH_2Ph", "-91"'] \arrow[dr, "-CN", "-26"'] & 113\ (2.32) \\
 & & & 178\ (4.89)
\end{tikzcd}$$

During propylation of the same arylindole **1** with propyl bromide under analogous conditions a single reaction product, [4-(1-propyl-2-indolyl)phenyl]phenylmethane (**9**), was obtained.

Alkylation of the 2-arylindoles **1** and **6** with benzyl chloride under Friedel–Crafts conditions led to complete resinification of the reaction mixture.

In both cases bromination with dioxane dibromide in dioxane gave complex mixtures of products.

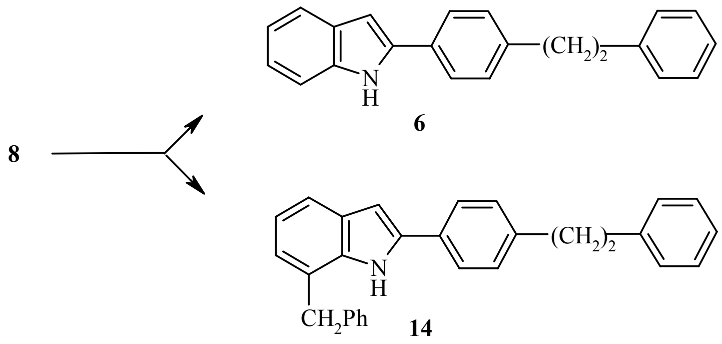
Earlier we reported that when a mixture of N-benzylphenylhydrazine and certain ketones was heated in polyphosphoric acid the corresponding N-unsubstituted indoles and their 7-benzyl derivatives were formed instead of the expected 2-substituted N-benzylindoles [5, 6]. We obtained a similar result during the synthesis of the N-benzyl derivatives **8** and **12**.



10, **12**, **13** R = $C_6H_4CH_2Ph$; **8**, **11**, **14** R = $C_6H_4(CH_2)_2Ph$

Compounds **6** and **14** were likewise obtained when 1-[4-(N-benzyl-2-indolyl)phenyl]-2-phenylethane was treated in polyphosphoric acid at 125°C, indicating 1,7-migration of the substituent.

In the IR spectrum of the 7-benzyl derivative **14** there is a band characteristic of the indole NH group in the region of 3410-3430 cm^{-1}, which is absent in the spectrum of the corresponding N-benzyl derivative **8**.



The position to which the benzyl group migrates was established by comparing the ^1H NMR spectra of the N-benzyl derivative **8** and the product from migration of the benzyl group **14** (Table 1). In particular, the spectrum of 1-[4-(1-benzyl-2-indolyl)phenyl]-2-phenylethane (**8**) does not contain a signal for the 1-H proton. A signal in the form of a doublet of doublets at 7.77 ppm can be assigned to the 4-H proton, while the signals for the 5-, 6-, and 7-H protons are included in the multiplet at 7.22-7.41 ppm.

In the ^1H NMR spectrum of 1-[4-(7-benzyl-2-indolyl)phenyl]-2-phenylethane (**14**) a signal for 1-H appears at 11.09 ppm, while the signal of the 7-H proton disappears. The signal for 6-H appears at 6.80 ppm in the form of a doublet, the signal for 5-H appears at 6.91 ppm in the form of a triplet, and the signal for 4-H appears at 7.36 ppm in the form of a doublet. In addition, for compounds **8** and **14** there are signals in the form of two doublets characteristic of the A-H and B-H protons of *p*-disubstituted benzenes, singlets for the bridging group (CH_2CH_2), and signals for the protons of the benzyl group. In the mass spectrum of compound **14** maximum intensity is observed in the peak of the molecular ion at 387.

TABLE 2. The Characteristics of the Compounds

Compound	Empirical formula	Found, % / Calculated, % C	H	N	M, Found, % / Calculated, %	R_f*	mp, °C	Yield, %
2	$C_{14}H_{10}N_2O_2$	70.71 70.59	4.38 4.20	11.61 11.76	238 238	0.46	194-195	19
3	$C_{21}H_{15}N_3O_4$	67.68 67.56	4.21 4.02	11.22 11.26	373 373	0.41	218-219	31
4	$C_{21}H_{16}N_2O_2$	76.91 76.83	4.72 4.88	8.32 8.54	328 328	0.64	157-158	19
5	$C_{21}H_{16}N_2O_2$	76.95 76.83	4.69 4.88	8.65 8.54	328 328	0.35	167-168	39
7	$C_{35}H_{29}N$	90.08 90.71	6.12 6.26	3.18 3.02	463 463	0.58	129-130	45
8	$C_{29}H_{25}N$	89.72 89.92	6.22 6.46	3.45 3.62	387 387	0.50	114-115	47
9	$C_{24}H_{23}N$	88.41 88.62	7.23 7.08	4.22 4.31	— 325	0.50	97-98	49
14	$C_{29}H_{25}N$	89.95 89.92	6.37 6.46	3.48 3.62	387 387	0.56	139-140	*[2]

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* System for chromatography: hexane–ether, 1:1 (compounds **2**-**5**); benzene–hexane, 1:3 (compounds **7** and **8**); heptane (compound **9**); hexane–ether, 6:1 (compound **14**).

*[2] Yield 6% (by method B) and 18% (by method A).

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a UR-20 instrument. The UV spectra were obtained in ethanol on a Specord spectrometer. The ^{1}H NMR spectra were obtained on a Bruker AM-400 spectrometer at 400 MHz with TMS as internal standard. The mass spectra were obtained on an MS-Varian, Mat-311, EL-MS spectrometer at 70 eV.

The reactions and the purity of the compounds were monitored and the R_f values were determined on Silufol UV-254 plates.

5-Nitro-2-phenylindole (2) and [4-(5-Nitro-2-indolyl)phenyl](4-nitrophenyl)methane (3). A solution of potassium nitrate (0.44 g, 5.2 mmol) in sulfuric acid (5 ml) was slowly added dropwise to a suspension of [4-(2-indolyl)phenyl]phenylmethane (0.2 g, 0.7 mmol) in sulfuric acid (10 ml), cooled to -2°C, while keeping the temperature at 0°C. The reaction mixture was stirred for 5 min and poured onto crushed ice (100 g). The product was extracted with ethyl acetate, and the extract was washed with an aqueous solution of sodium carbonate and with water and dried with sodium sulfate. The mixture was separated on a column of silica gel with 6:1 hexane–ether as eluent. We isolated 0.03 g of compound **2** and 0.082 g of compound **3** in the form of yellow crystals.

[4-(5-Nitro-2-indolyl)phenyl]phenylmethane (4) and [4-(3-Nitro-2-indolyl)phenyl]phenylmethane (5). 50% Nitric acid (0.07 ml, 1.4 mmol) and then a solution of [4-(2-indolyl)phenyl]phenylmethane (**1**) (0.19 g, 0.67 mmol) in acetic anhydride (5-7 ml) were added dropwise to acetic anhydride (25 ml), cooled to 0°C, while keeping the temperature at 0°C. The reaction mixture was stirred at 5-7°C for 30 min, poured onto ice (100 g), and extracted with ether. The extract was washed with an aqueous solution of sodium carbonate and with water and dried with sodium sulfate. The mixture was separated on a column of silica gel (hexane–ether, 4:1). We isolated 0.04 g of compound **4** and 0.85 g of compound **5** in the form of yellow crystals.

[4-(1,3-Dibenzyl-2-indolyl)phenyl]phenylmethane (7). To a solution of the indole **1** (0.28 g, 1 mmol) in benzene (30 ml) we added a 50% aqueous solution of potassium hydroxide (5 ml), tetrabutylammonium bromide (0.035 g), and benzyl chloride (0.63 g, 5 mmol). The mixture was stirred at 60°C for 4 h, cooled, diluted with water, and extracted with benzene. The extract was washed with water and dried with sodium sulfate. The mixture was separated on a column of silica gel (heptane). We isolated 0.21 g of compound **7** in the form of colorless crystals.

1-[4-(1-Benzyl-2-indolyl)phenyl]-2-phenylethane (8). This compound was obtained by the method described for compound **7** from 1-[4-(2-indolyl)phenyl]-2-phenylethane (**6**) (0.30 g, 1 mmol) and benzyl chloride (0.63 g, 5 mmol). We isolated 0.18 g of compound **8** as colorless crystals.

[4-(1-Propyl-2-indolyl)phenyl]phenylmethane (9). This compound was obtained by the method described for compound **7** from the indole **1** (0.28 g, 1 mmol) and propyl bromide (0.62 g, 5 mmol). We isolated 0.16 g of compound **9** in the form of colorless crystals.

1-[4-(2-Indolyl)phenyl]-2-phenylethane (6) and 1-[4-(7-Benzyl-2-indolyl)phenyl]-2-phenylethane (14). A. A mixture of 4-acetyldiphenylmethane (**11**) (2.24 g, 10 mmol), N-benzylphenylhydrazine hydrochloride (2.57 g, 10 mmol), and polyphosphoric acid (50 g) was stirred at 100-110°C for 45 min. The mixture was cooled and poured as a thin stream into water (200 ml). The product was extracted with ether, and the extract was washed with water and dried. The mixture was separated on a column of silica gel (heptane–ether, 50:1). We isolated 0.7 g (18%) of compound **14** and 1.18 g (40%) of compound **6** in the form of colorless crystals.

B. A mixture of compound **8** (0.15 g, 0.3 mmol) and polyphosphoric acid (7 ml) was stirred at 125°C for 30 min. The mixture was cooled and poured into water (30 ml). The precipitate was filtered off, washed with water, and dried. The mixture was separated on a column of silica gel (heptane–ether, 20:1). We isolated 0.16 g (6%) of compound **14** in the form of colorless crystals.

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