

INDOLE DERIVATIVES.

141. SYNTHESIS AND INVESTIGATION

OF NEW 2-ARYLINDOLES*

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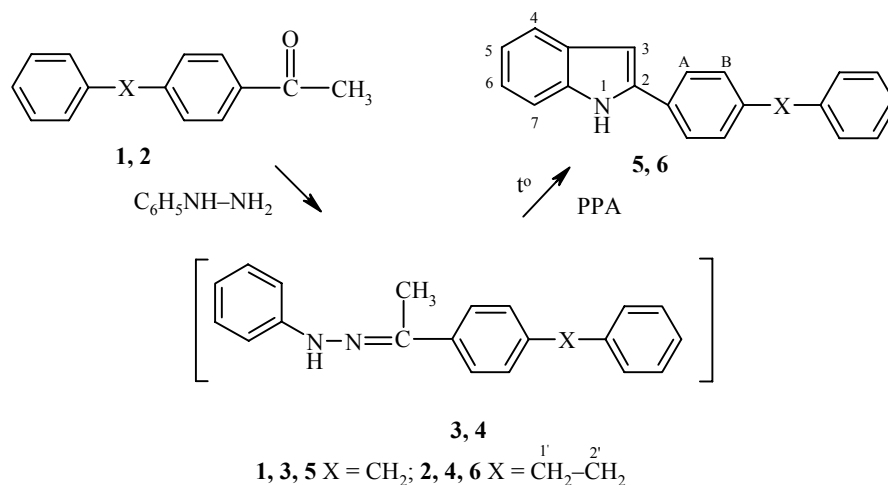
2-(Diphenylmethan-4-yl)- and 2-(dibenzyl-4-yl)indoles have been synthesized by the Fischer reaction. Reactions carried out included azo coupling, formylation, and nitrosation. The corresponding 3-substituted derivatives were obtained.

Keywords: arylindoles, indolization, azo coupling, formylation, nitrosation.

2-Phenylindole and its derivatives, which possess specific properties, constitute an important group of indole compounds of considerable interest from the point of view of various areas of science and technology [2,3], including medicine [4-6].

With the purpose of searching for new indole derivatives with useful properties, we have synthesized 2-(diphenylmethan-4-yl)indole (**5**) and 2-(dibenzyl-4-yl)indole (**6**) from phenylhydrazones **3** and **4** by the Fischer reaction.

The arylindoles **5** and **6** were obtained from the corresponding ketones **1** and **2** and phenylhydrazine in polyphosphoric acid (PPA) at 100 and 110°C without isolation of the intermediate hydrazones **3** and **4**. The yields of these compounds after purification were 25 and 40% respectively.



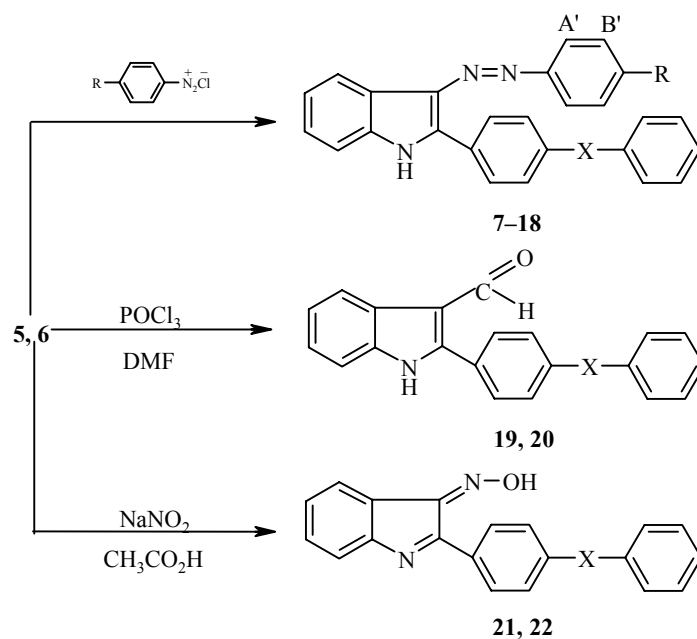
* For part 140 see [1].

In the ^1H NMR spectrum of 2-(diphenylmethane-4-yl)indole (**5**) (Table 1) the signals of the 4-H and 7-H protons of the indole fragment were recorded as a doublet of doublets at 7.50 and 7.35 ppm respectively. The signals for the 5-H and 6-H protons (6.97 and 7.07 ppm) were displayed as a triplet of doublets. The signal of the 3-H proton was displayed as a doublet at 6.82 ppm. The low field signal at 11.45 ppm was assigned by us to the NH proton. The protons of the first nucleus of the diphenylmethane give two doublet signals at 7.77 and 7.31 ppm, characteristic of protons of *para*-disubstituted benzenes, the latter partially overlapping the multiplet of protons of the second benzene ring. The singlet for the protons of the bridge methylene group is displayed at 3.97 ppm.

The ^1H NMR spectrum of 2-(dibenzyl-4-yl)indole (**6**) (Table 1) resembled the spectrum of 2-(diphenylmethane-4-yl)indole (**5**). The singlet signal (2.92 ppm) of the bridge group protons $-\text{CH}_2-\text{CH}_2-$ corresponded to four protons in intensity. Identical values for the chemical shifts of these protons and the absence of spin coupling may, in our opinion, be explained by an identical degree of shielding from the side of the aromatic nuclei.

The azo coupling reaction has been studied for arylindoles **5** and **6** with benzenediazonium chloride and its *p*-Cl, *p*-NO₂, *p*-COOH, *p*-COOCH₃, and *p*-SO₂NH₂ derivatives. Best results were achieved when carrying out the reaction in dilute solution at pH 6-7 (Table 2). Formylation of 2-arylamines according to Vilsmeier–Haack was carried out at 40°C in 70-75% yield.

Nitrosation of arylindoles **5** and **6** in acetic acid at 20°C leads to the formation of nitroso compounds **21** and **22** (yellow crystals) in almost quantitative yield.



1, 3, 5, 7-12, 19, 21 X = CH₂; **2, 4, 6, 13-18, 20, 22** X = CH₂-CH₂; **7, 13** R = H;
8, 14 R = Cl; **9, 15** R = NO₂; **10, 16** R = SO₂NH₂; **11, 17** R = COOCH₃; **12, 18** R = COOH

A hypsochromic shift of the long wave maximum of 31 and 20 nm was observed in the electronic spectra of azo compounds **8** and **14** (Figs. 1 and 2) compared with the analogous maximum of the benzeneazo derivatives **7** and **13**. A bathochromic shift of this maximum was observed in the spectra of compounds **9-12** and **15-18**, the value of which grew with an increase in the electron-withdrawing nature of the substituent of the diazo component. It is evident that the character of the absorption in the spectra of compounds **8** and **14** is changed due to the positive mesomeric effect of the chlorine atom.

TABLE 1. Spectral Characteristics for Compounds 5-22

Compound	IR spectrum, ν , cm^{-1}	UV spectrum, λ_{max} , nm (log ϵ)	^1H NMR spectrum, ppm*	J , Hz
1	2	3	4	5
5	3425 (NH)	214 (4.48); 247 (4.28); 315(4.42)	11.45 (1H, s, NH); 6.82 (1H, d, 3-H); 7.50 (1H, d, 4-H); 6.97 (1H, dt, 5-H); 7.07 (1H, d, 6-H); 7.35 (1H, d, 7-H); 7.77 (2H, d, AH); 7.31 (2H, d, BH); 7.20-7.32 (5H, m, C_6H_5); 3.97 (2H, s, CH_2)	$J_{13} = 1.73$; $J_{46} = J_{57} = 1.16$; $J_{45} = J_{67} = 8.11$; $J_{AB} = 8.11$
6	3452 (NH)	210 (4.40); 247 (4.18); 315 (4.30)	11.45 (1H, s, NH); 6.84 (1H, d, 3-H); 7.50 (1H, d, 4-H); 6.98 (1H, dt, 5-H); 7.06 (1H, dt, 6-H); 7.38 (1H, d, 7-H); 7.76 (1H, d, AH); 7.30 (2H, d, BH); 7.18-7.28 (5H, m, C_6H_5); 2.92 (4H, s, CH_2CH_2)	$J_{13} = 1.36$; $J_{46} = J_{56} = 1.14$; $J_{45} = J_{67} = 8.0$; $J_{AB} = 7.96$
7	3455 (NH); 1460 (N=N)	209 (4.43); 253 (4.27); 300 (4.35); 406 (4.44)	12.30 (1H, s, NH); 8.48 (1H, d, 4-H); 7.20-7.56 (11H, 5-H+7-H, B'H, C'H, C_6H_5); 7.80 (2H, d, AH); 7.47 (2H, d, BH); 8.10 (2H, d, A'H); 4.05 (2H, s, CH_2)	$J_{AB} = 7.52$; $J_{A'B'} = 7.96$ $J_{45} = 7.52$
8	3420 (NH); 1425 (N=N)	211 (4.56); 254 (4.40); 302 (4.50); 375 (4.26)	8.62 (1H, s, NH); 7.92 (1H, d, 4-H); 7.20-7.39 (12H, m, 5-H+7-H, AH, BH, C_6H_5); 7.44 (2H, d, A'H); 7.81 (2H, d, B'H); 4.06 (2H, s, CH_2)	$J_{A'B'} = 8.40$
9	3345 (NH); 1420 (N=N); 1330 (NO_2)	209 (4.34); 289 (4.24); 465 (4.21)	12.61 (1H, s, NH); 8.60 (1H, d, 4-H); 7.21-7.49 (7H, m, 5-H, 6-H, C_6H_5); 7.63 (1H, d, 7-H); 8.21 (2H, d, AH); 7.58 (2H, d, BH); 8.03 (2H, d, A'H); 8.44 (2H, d, B'H); 4.05 (2H, s, CH_2)	$J_{AB} = 8.0$; $J_{67} = J_{45} = 8.0$ $J_{A'B'} = 8.11$
10	3325 (NH); 1450 (N=N); 1360 (SO_2)	210 (4.57); 254 (4.44); 299 (4.56); 416.6 (4.52)	12.47 (1H, s, NH); 8.48 (1H, d, 4-H); 7.20-7.34 (7H, m, 5-H, 6-H, C_6H_5); 7.51 (1H, d, 7-H); 7.91 (2H, d, AH); 7.89 (2H, d, BH); 8.10 (2H, d, A'H); 7.48 (2H, d, B'H); 7.41 (2H, s, NH_2); 4.06 (2H, s, CH_2)	$J_{AB} = 7.96$; $J_{A'B'} = 8.4$ $J_{45} = 7.08$
11	3340 (NH); 1700 (CO); 1420 (N=N)	211 (4.49); 250 (4.31); 308 (4.41); 426 (4.13)	12.47 (1H, s, NH); 8.48 (1H, d, 4H); 7.20-7.34 (7H, m, 5-H, 6-H, C_6H_5); 7.51 (1H, d, 7-H); 8.10 (2H, d, AH); 7.48 (2H, d, BH); 8.10 (2H, d, A'H); 7.88 (2H, d, B'H); 3.88 (3H, s, CH_3); 4.06 (2H, s, CH_2)	$J_{A'B'} = 8.4$; $J_{AB} = 7.96$ $J_{45} = 7.08$
12	3400 (NH); 1680 (CO); 1410 (N=N)	211 (4.51); 255 (4.31); 303 (4.40); 416.6 (4.35)	12.46 (1H, s, NH); 8.49 (1H, d, 4-H); 7.20-7.34 (7H, m, 5-H, 6-H, C_6H_5); 7.51 (1H, d, 7-H); 8.07 (2H, d, AH); 7.49 (2H, d, BH); 8.10 (2H, d, A'H); 7.87 (2H, d, B'H); 12.99 (1H, s, OH); 4.06 (2H, s, CH_2)	$J_{AB} = 8.4$; $J_{A'B'} = 8.84$
13	3400 (NH); 1455 (N=N)	208 (4.67); 250 (4.48); 298 (4.57); 400 (4.39)	12.32 (1H, s, NH); 8.48 (1H, d, 4-H); 7.20-7.34 (11H, 5H+7-H, B'H, C'H, C_6H_5); 7.81 (2H, d, AH); 7.48 (2H, d, BH); 8.08 (2H, d, A'H); 2.98 (4H, s, CH_2CH_2)	$J_{AB} = 7.52$; $J_{A'B'} = 8.40$ $J_{45} = 7.96$

TABLE 1 (continued)

1	2	3	4	5
14	3460 (NH); 1430 (N=N)	209 (4.58); 252 (4.39); 300 (4.44); 380 (4.36)	—	—
15	3360 (NH); 1420 (N=N); 1320 (NO ₂)	207 (4.43); 286 (4.21); 265 (4.14)	8.76 (1H, s, NH); 8.63 (1H, d, 4-H); 7.18-7.48 (8H, m, 5-H+7-H, C ₆ H ₅); 7.96 (2H, d, AH); 7.32 (2H, d, BH); 7.93 (2H, d, A'H); 8.35 (2H, d, B'H); 3.70 (4H, s, CH ₂ -CH ₂)	$J_{A'B'} = 8.88$
16	3300 (NH); 1430 (N=N); 1370 (SO ₂)	210 (4.54); 252 (4.36); 303 (4.41); 416.6 (4.35)	12.49 (1H, s, NH); 8.49 (2H, d, 4-H); 7.20-7.32 (7H, m, 5-H, 6-H, C ₆ H ₅); 7.51 (1H, d, 7-H); 7.96 (2H, d, AH); 7.91 (2H, d, BH); 8.08 (2H, d, A'H); 7.48 (2H, d, B'H); 7.43 (2H, s, NH ₂); 2.99 (4H, s, CH ₂ CH ₂)	$J_{A'B'} = 8.4$; $J_{AB} = 8.84$ $J_{45} = 7.96$
17	3300 (NH); 1690 (CO); 1410 (N=N)	210 (4.73); 254 (4.58); 303 (4.63); 426 (4.60)	12.51 (1H, s, NH); 8.62 (1H, d, 4H); 7.27-7.45 (7H, m, 5-H, 6-H, C ₆ H ₅); 7.62 (1H, d, 7-H); 8.17 (2H, d, AH); 7.59 (2H, d, BH); 8.22 (2H, d, A'H); 7.98 (2H, d, B'H); 4.00 (3H, s, CH ₃); 3.15 (4H, s, CH ₂ CH ₂)	$J_{A'B'} = 8.0$; $J_{45} = 7.52$
18	3450 (NH); 1670 (CO); 1420 (N=N)	210 (4.55); 252 (4.36); 303 (4.41); 416.6 (4.36)	12.48 (1H, s, NH); 8.50 (1H, d, 4-H); 7.51 (1H, d, 7-H); 7.19-7.32 (7H, m, 5-H, 6-H, C ₆ H ₅); 8.09 (2H, d, AH); 7.49 (2H, d, BH); 8.09 (2H, d, A'H); 7.86 (2H, d, B'H); 12.99 (1H, s, OH); 2.98 (4H, s, CH ₂ CH ₂)	$J_{AB} = 8.4$; $J_{45} = 7.96$
19	3140 (NH); 1620 (CO)	212 (4.41); 225 (4.32); 261 (4.54); 318 (4.22)	10.01 (1H, s, NH); 8.34 (1H, d, 4-H); 7.05-7.41 (8H, m, 5-H+7-H, C ₆ H ₅); 7.49 (2H, d, AH); 7.28 (2H, d, BH); 8.78 (1H, s, CHO); 4.04 (2H, s, CH ₂)	$J_{AB} = 8.4$
20	3150 (NH); 1630 (CO)	211 (4.46); 226 (4.41); 260 (4.40); 317 (4.06)	10.10 (1H, s, NH); 8.44 (1H, d, 4-H); 7.40 (1H, t, 5-H); 7.21-7.37 (7H, m, 6-H, 7-H, C ₆ H ₅); 7.58 (2H, d, AH); 7.20 (2H, d, BH); 8.62 (1H, s, CHO); 3.01 (2H, t, 2'-CH ₂); 3.03 (2H, t, 1'-CH ₂)	$J_{AB} = 7.6$; $J_{1'2'} = 11.0$
21	3300-3600; br. p (OH)	209 (4.31); 225 (3.97); 268 (4.42)	13.81 (1H, s, OH); 8.20 (1H, d, 4-H); 7.25-7.58 (7H, m, 5-H, 6-H, C ₆ H ₅); 7.48 (1H, d, 7-H); 8.31 (2H, d, AH); 7.64 (2H, d, BH); 4.21 (2H, s, CH ₂)	$J_{AB} = 8.0$; $J_{45} = 8.0$
22	3300-3600; br. p (OH)	210 (4.33); 225 (3.99); 269 (4.53)	13.76 (1H, s, OH); 8.10 (1H, d, 4-H); 7.15-7.33 (6H, m, 5-H, C ₆ H ₅); 7.46 (1H, t, 6-H); 7.53 (1H, d, 7-H); 8.18 (2H, d, AH); 7.38 (2H, d, BH); 2.96 (2H, t, 2'-CH ₂); 2.94 (2H, t, 1'-CH ₂)	$J_{AB} = 7.96$; $J_{1'2'} = 12.0$

* The spectra of compounds **5-7**, **9-13**, **16-18**, **21**, and **22** were taken in DMSO-d₆, and of **8**, **15**, **19**, and **20** in CHCl₃.

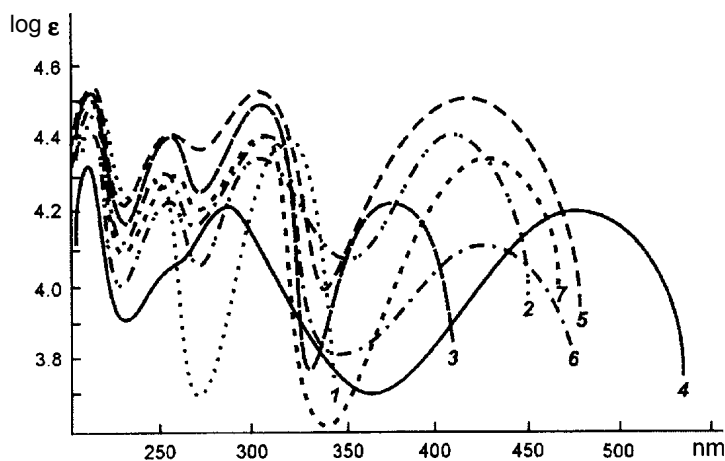


Fig. 1. Electronic spectra of compounds **5** (1), and **7-12** (2-7).

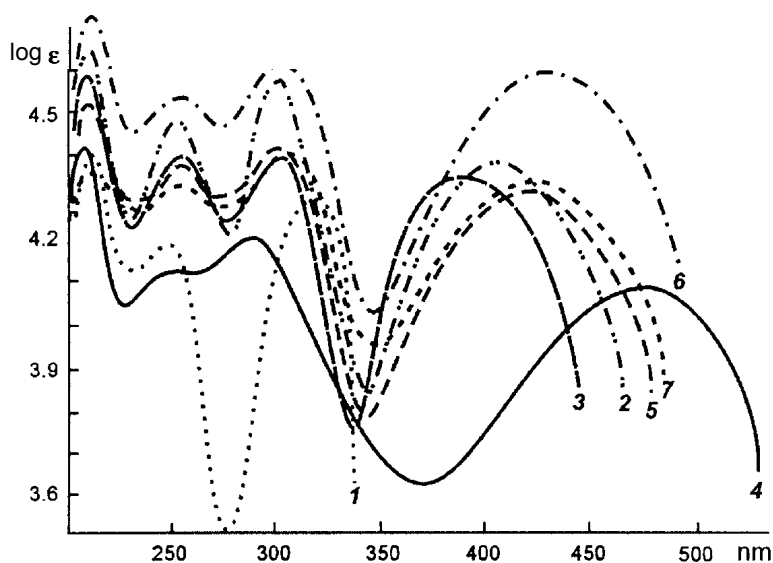


Fig. 2. Electronic spectra of compounds **6** (1) and **13-18** (2-7).

In the IR spectra of compounds **12-18** (Table 1) there were characteristic absorption bands for the N=N group at 1410-1460 cm^{-1} .

In the ^1H NMR spectra of compounds **7-22** (Table 1) there were no signals for the 3-H protons of the initial arylindoles. The values of the chemical shifts and the multiplicity of the remaining protons were in accordance with the proposed structures of **7-22**. In the ^1H NMR spectra of the 3-formyl and 3-nitroso derivatives **20** and **22** (Table 1) the signals of the bridge ethylene group were displayed as two triplets at 3.03, 3.01 and 2.96, 2.94 ppm respectively. In our opinion this is caused by the strong electron-withdrawing influence of the formyl and nitroso groups leading to a reduction in the degree of shielding of the 1- CH_2 group. A similar picture was not observed in the remaining derivatives of this arylindole **7-18**, **19**, and **21**, probably due to the lower influence of the substituent in position 3.

TABLE 2. Characteristics of the Synthesized Compounds 5-22

Compound	Empirical formula	Found, %			mp, °C,	R_f	Yield, % (color)
		Calculated, %					
		C	H	N			
5	C ₂₁ H ₁₇ N	$\frac{89.1}{89.00}$	$\frac{6.10}{6.00}$	$\frac{4.80}{4.90}$	151-152	0.38 ^a	25 (colorless)
6	C ₂₂ H ₁₉ N	$\frac{88.8}{88.9}$	$\frac{6.40}{6.40}$	$\frac{4.80}{4.70}$	204-205	0.31 ^a	38 (colorless)
7	C ₂₇ H ₂₁ N ₃	$\frac{83.10}{83.70}$	$\frac{5.50}{5.45}$	$\frac{10.81}{10.85}$	132-133	0.59 ^b	95 (orange)
8	C ₂₇ H ₂₀ ClN ₃	$\frac{76.10}{76.80}$	$\frac{4.76}{4.74}$	$\frac{9.89}{9.96}$	82-83	0.61 ^c	95 (orange)
9	C ₂₇ H ₂₀ N ₄ O ₂	$\frac{74.90}{75.00}$	$\frac{4.60}{4.62}$	$\frac{13.10}{12.96}$	249-250	0.54 ^c	95 (red)
10	C ₂₇ H ₂₂ N ₄ O ₂ S	$\frac{69.48}{69.53}$	$\frac{4.80}{4.74}$	$\frac{11.97}{12.01}$	171-172	0.75 ^d	90 (red)
11	C ₂₉ H ₂₃ N ₃ O ₂	$\frac{77.90}{78.20}$	$\frac{5.38}{5.16}$	$\frac{9.41}{9.43}$	190-191	0.55 ^c	85 (red)
12	C ₂₈ H ₂₁ N ₃ O ₂	$\frac{78.00}{77.96}$	$\frac{4.84}{4.87}$	$\frac{9.80}{9.74}$	241-242	0.71 ^c	89 (red)
13	C ₂₈ H ₂₃ N ₃	$\frac{83.81}{83.79}$	$\frac{5.68}{5.70}$	$\frac{10.39}{10.47}$	131-132	0.58 ^f	95 (orange)
14	C ₂₈ H ₂₂ ClN ₃	$\frac{77.20}{77.15}$	$\frac{5.01}{5.05}$	$\frac{9.59}{9.64}$	124-125	0.71 ^b	95 (orange)
15	C ₂₈ H ₂₂ N ₄ O ₂	$\frac{75.12}{75.33}$	$\frac{4.97}{4.93}$	$\frac{10.72}{10.76}$	261-262	0.74 ^f	95 (red)
16	C ₂₈ H ₂₄ N ₄ O ₂ S	$\frac{69.90}{70.00}$	$\frac{5.01}{5.00}$	$\frac{9.95}{10.00}$	200-201	0.74 ^d	90 (red)
17	C ₃₀ H ₂₅ N ₃ O ₂	$\frac{78.61}{78.43}$	$\frac{5.25}{5.41}$	$\frac{9.21}{9.15}$	180-181	0.51 ^c	89 (red)
18	C ₂₉ H ₂₃ N ₃ O ₂	$\frac{78.40}{78.20}$	$\frac{5.11}{5.16}$	$\frac{8.12}{8.09}$	248-249	0.78 ^d	85 (red)
19	C ₂₂ H ₁₇ NO	$\frac{88.89}{88.88}$	$\frac{5.71}{5.72}$	$\frac{4.70}{4.72}$	179-180	0.85 ^g	70 (colorless)
20	C ₂₃ H ₁₉ NO	$\frac{88.73}{88.74}$	$\frac{6.12}{6.11}$	$\frac{4.50}{4.52}$	211-212	0.83 ^g	75 (colorless)
21	C ₂₁ H ₁₆ N ₂ O	$\frac{80.77}{80.76}$	$\frac{5.13}{5.11}$	$\frac{8.97}{8.98}$	220-221	0.73 ^h	95 (yellow)
22	C ₂₂ H ₁₈ N ₂ O	$\frac{80.98}{80.97}$	$\frac{5.52}{5.53}$	$\frac{8.58}{8.57}$	259-260	0.72 ^h	96 (yellow)

* Systems for chromatography: a) hexane–ether, 12 : 1; b) hexane–ether, 3 : 2; c) benzene; d) benzene–ether, 1 : 1; e) benzene–ether, 1 : 3; f) benzene–hexane, 1 : 3; g) benzene–acetone, 5 : 1; h) benzene–ether, 6 : 1.

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument in nujol, the UV spectra on a Specord spectrophotometer in ethanol, and the ¹H NMR spectra on a Bruker AM 400 spectrometer, internal standard was TMS. A check on the progress of reactions and the purity of compounds with determination of R_f values was carried out on Silufol UV 254 plates.

2-(Diphenylmethan-4-yl)indole (5). A mixture of ketone **1** (2.12 g, 10 mmol), phenylhydrazine hydrochloride (1.59 g, 11 mmol), and polyphosphoric acid (PPA) (40 g) was heated to 100°C and stirred for 30 min. The mixture was cooled and poured into water (150 ml). The solid was filtered off, washed with water to pH 7, and dried. The product was recrystallized from heptane.

2-(Dibenzyl-4-yl)indole (6) was obtained analogously to compound **5** from ketone **2** (2.24 g, 10 mmol) at 110°C.

General Method of Synthesis of 3-Arylazo Derivatives of 2-(Diphenylmethan-4-yl)indole and 2-(Dibenzyl-4-yl)indole (7-18). A solution of indole derivative **5** or **6** (1 mmol) in a mixture of isopropyl alcohol (160 ml) and dioxane (60 ml) was cooled to 0°C and a solution obtained by diazotizing the aniline derivative (4 mmol) was added dropwise, maintaining pH 6-7 by adding sodium acetate. The reaction mixture was stirred at 0-5°C for 30 min and diluted with water (600 ml). The precipitated solid was filtered off, washed with water, and dried.

2-(Diphenylmethan-4-yl)-3-formylindole (19). Phosphorus oxychloride (0.35 ml, 4 mmol) was added dropwise during 30 min with stirring to cold freshly distilled dimethylformamide (2.3 ml, 30 mmol). The solution obtained was stirred for 10 min at 20-25°C, cooled to 0°C, and a solution of 2-(diphenylmethan-4-yl)indole **5** (0.28 g, 1 mmol) in DMF (1 ml) was slowly introduced maintaining the temperature at 0-5°C. The reaction mixture was stirred for 1 h at 40°C, crushed ice (4 g) was added, and then a 20% solution of sodium hydroxide (15 ml) with vigorous stirring. The mixture was carefully heated to boiling and slowly cooled. The precipitated solid was filtered off, washed with water to pH 7, and dried. The solid was recrystallized from alcohol.

2-(Dibenzyl-4-yl)-3-formylindole (20) was obtained analogously to compound **19** from 2-(dibenzyl-4-yl)indole **6** (0.32 g, 1 mmol).

2-(Diphenylmethan-4-yl)-3-nitrosoindole (21). Sodium nitrite (0.43 g, 5 mmol) was added to a solution of indole **5** (0.28 g, 1 mmol) in glacial acetic acid (25 ml). The mixture was stirred at room temperature for 30 min and poured into water (200 ml). The precipitated solid was filtered off, washed with water to pH 7, and dried. The product was recrystallized from ethyl acetate.

2-(Dibenzyl-4-yl)-3-nitrosoindole (22) was obtained analogously to compound **21** from 2-(dibenzyl-4-yl)indole **6** (0.32 g, 1 mmol).

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