Chemistry of Heterocyclic Compounds, Vol. 33, No. 5, 1997

1,7-MIGRATION OF BENZYL GROUP IN 2-SUBSTITUTED N-BENZYLINDOLES

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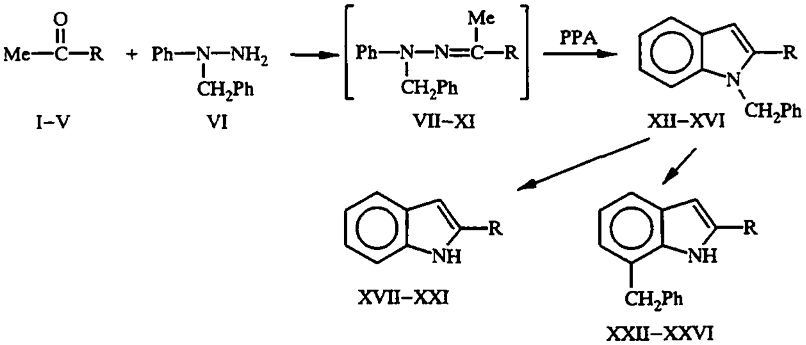
It has been shown that when 2-substituted N-benzylindoles are heated above 100°C in polyphosphoric acid, the benzyl group is split off and undergoes 1,7-migration.

It is known [1] that indole systems typically undergo 1,3-, 2,3-, and 3,2-rearrangements in the pyrrole ring.

We reported in [2] that when a mixture of the hydrochloride of N-benzylphenylhydrazine (VI) and a ketone I-V is heated in polyphosphoric acid (PPA), the products that are formed are not the expected 2-substituted N-benzylindoles XII-XVI, but rather the corresponding N-unsubstituted indoles XVII-XXI and their 7-benzyl derivatives XXII-XXVI.

We established by means of chromatographic monitoring that at relatively low temperatures (50-70°C), all that takes place is partial indolization of the hydrazones VII-XI, with the formation of the N-benzyl derivatives XII-XVI and the N-unsubstituted indoles XVII-XXI. At higher temperatures (100-120°C), the processes of indolization of the hydrazones VII-XI are completed with the formation of a mixture of products of splitting off the benzyl group XVII-XXI and 1,7-migration of this group XXII-XXVI; the reaction products contain traces of the corresponding 2-substituted N-benzylindoles XII-XVI.

Here we must emphasize that the electronic nature of the substituent (R = Ar, Me, COOEt) does not influence the process of rearrangement, and the corresponding 7-benzyl derivatives XXII-XXVI are formed in all cases.



I, VII, XII, XVII, XXII R = p-$C_6H_4NO_2$; II, VIII, XIII, XVIII, XXIII, R = p-C_6H_4Br;
III, IX, XIV, XIX, XXIV R = p-C_6H_4Ph; IV, X, XV, XX, XXV R = Me;
V, XI, XVI, XXI, XXVI R = COOEt

The 2-substituted indoles XVII-XIX and their 7-benzyl derivatives XXII-XXIV were isolated by column chromatography. Compounds XVII-XIX were identified by a comparison of melting points with those reported in the literature [3] and also by IR spectra and elemental analysis of the compounds.

We were able to isolate the target compound, N-benzyl-2-p-nitrophenylindole (XII) only from a mixture of products obtained by partial indolization of the N-benzylphenyl hydrazone of p-nitroacetophenone (VII) in PPA.

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TABLE 1. Characteristics of Compounds VII, XII, XIV, and XXII-XXIV

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	M^+	R_f*	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (and log ε)	Yield, %
		C	H	N						
VII	$C_{21}H_{19}N_3O_2$	73,1 73,0	5,8 5,5	12,0 12,2	90...91	—	0,79[a)]	1700 (C=N), 1530, 1370 (NO_2)	211 (4,25), 260 (4,15)	81
XII	$C_{21}H_{16}N_2O_2$	77,0 76,8	4,9 4,9	8,2 8,5	155...157	—	0,53[b)]	1520, 1360 (NO_2)	208 (4,56), 267 (3,99) sh. 364 (3,90)	4 (A), 44 (B)
XIV	$C_{27}H_{21}N$	90,3 90,2	5,6 5,8	4,0 3,9	147...148	—	0,70[c)]	—	208 (4,27), 261 (3,81), 309 (3,73)	79
XXII	$C_{21}H_{16}N_2O_2$	77,2 76,8	4,7 4,9	8,4 8,5	104...105	328	0,42[d)]	3410 (NH), 1515, 1340 (NO_2)	222 (4,37), 239 (4,33) sh. 270 (4,07) sh. 354 (3,98) sh.	4
XXIII	$C_{21}H_{16}NBr$	70,1 69,6	4,3 4,4	3,7 3,9	133...134	363	0,67[e)]	3470 (NH)	221 (4,65) 230 (4,59) sh. 254 (4,56), 322 (4,66)	3
XXIV	$C_{27}H_{21}N$	90,0 90,2	6,0 5,8	3,8 3,9	190...191	—	0,66[f)]	3450 (NH)	215 (4,54), 263 (4,27), 330 (4,50)	10

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*System for chromatography:

a) benzene;

b) hexane–ether, 7:1;

c) hexane;

d) benzene–hexane, 2:1;

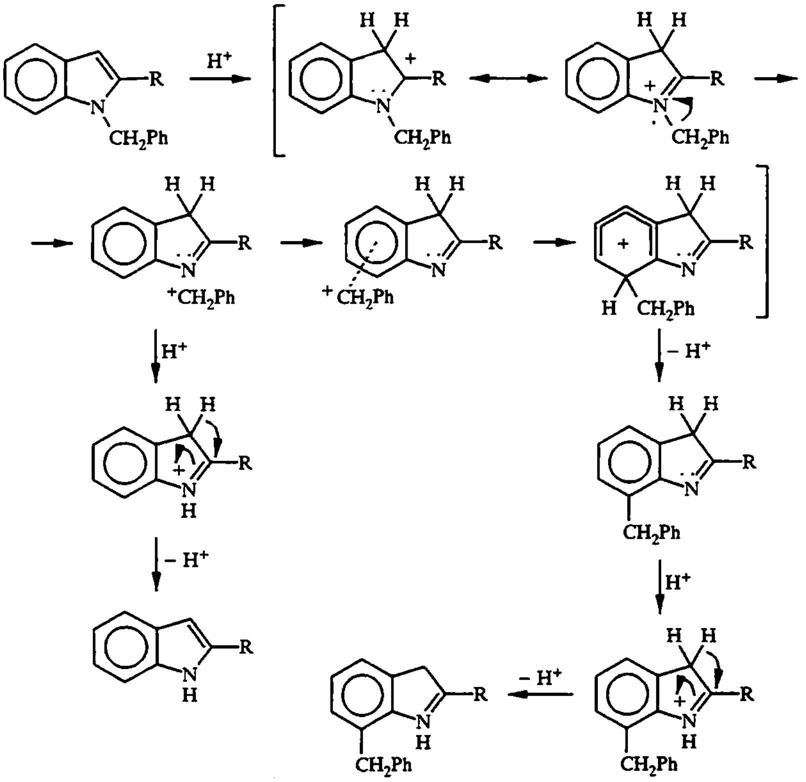
e) benzene–hexane, 1:1;

f) hexane–ether, 10:1.

With the aim of studying the process of migration of the benzyl group, we investigated conversions of certain N-benzylindoles XII and XIV that had been synthesized by N-benzylation of the corresponding 2-substituted indoles XVII and XIX under conditions of phase-transfer catalysis, following a procedure given in [4]. When the N-benzyl derivatives XII and XIV are heated above 100°C in PPA, they are almost completely converted to products of splitting off the benzyl group (XVII, XIX) and 1,7-migration (XXII, XXIV), with the formation of complex mixtures that we found impossible to separate; however, the compounds XVII, XIX and their 7-benzyl derivatives XXII, XXIV were identified in these mixtures by a comparison of R_f values with those of chromatographically pure samples.

We also investigated the possibility of migration of the N-phenyl group under analogous conditions. We found that heating of the hydrochloride of N,N-diphenylhydrazine and the ketones I-III in PPA results in the formation of the corresponding 2-substituted N-phenylindoles, which, when the temperature is raised to 100-120°C, form a tarry mass without any splitting or migration of the N-phenyl group. This finding apparently indicates that 1,7-migration can be attributed to the electronic features of the benzyl group, in particular the higher stability of the benzyl cation.

In our opinion, the detachment and 1,7-migration of the benzyl group take place in a β-protonated N-benzylindole, probably through the following mechanism:



In the IR spectra of the 7-benzyl derivatives XXII-XXIV, there are absorption bands that are characteristic for the indole NH group in the 3410-3470 cm^{-1} region; there are no such bands in the spectra of the corresponding N-benzyl derivatives XII and XIV (Table 1).

The site of migration of the benzyl group was established by comparing PMR spectra of the N-benzyl derivatives and the products of migration of the benzyl group (Table 2). In particular, we found that in the spectrum of N-benzyl-2-p-nitrophenylindole (XII), there is no signal of the 1-H proton, and the signal of the 7-H proton is manifested in the form of a doublet of doublets at 7.40 ppm. The signal in the form of a doublet of doublets at 7.61 ppm can be assigned to the 4-H proton, and the triplet of doublets at 7.06 ppm can be assigned to the 6-H proton.

In the spectrum of the 7-benzyl derivatives XXII, the 1-H signal is manifested at 11.54 ppm, while the signal of the 7-H proton disappears. There is also a change in the multiplicity of the signal of the 6-H proton, which is manifested at 6.84 ppm in the form of a doublet of doublets. The signal of the 5-H proton is manifested at 6.93 ppm in the form of a triplet, and that of the 4-H proton at 7.40 ppm in the form of a doublet of doublets. It would also be possible to reverse this assignment of signals of the 4-H and 7-H protons; however, judging from the electronic nature of indole, 1,4-migration of the benzyl group is very improbable.

TABLE 2. PMR Spectra of Compounds XII and XXII-XXIV

Compound	Chemical shifts δ, ppm	SSCC, Hz
XII	6,84 (1H, s, 3-H); 7,61 (1H, dd,. 4-H); 7,14 (1H, m, 5-H); 7,06 (1H, td,. 6-H); 7,40 (1H, dd, 7-H); 7,75 (2H, d, A-H); 8,24 (2H, d, 5-H); 7,11...7,18 (5H, m, $CH_2\underline{C_6H_5}$); 5,50 (2H, s, $\underline{CH_2}C_6H_5$)	$J_{45} = 7,90$, $J_{46} = 1,40$, $J_{67} = 8,20$, $J_{AB} = 9,00$
XXII	11,54 (1H, s, 1-H); 7,40 (1H, dd, 4-H); 6,93 (1H, t, 5-H); 6,84 (1H, dd, 6-H); 8,16 (2H, d, A-H); 8,28 (2H, d, B-H); 7,09...7,31 (6H, m, 3H, $CH_2\underline{C_6H_5}$); 4,29 (2H, s, $\underline{CH_2}C_6H_5$)	$J_{45} = 7,60$, $J_{46} = 1,20$, $J_{56} = 7,20$, $J_{A\bar{B}} = 9,20$
XXIII	10,90 (1H, s, 1-H); 6,90 (1H, d, 3-H); 7,34 (1H, dd, 4-H); 6,89 (1H, t, 5-H); 6,78 (1H, dd, 6-H); 7,61 (2H, d, A-H); 7,85 (2H, d, B-H); 7,11...7,26 (5H, m, $CH_2\underline{C_6H_5}$); 4,26 (2H, s, $\underline{CH_2}C_6H_5$)	$J_{13} = 2,20$, $J_{45} = 7,80$, $J_{46} = 1,10$, $J_{56} = 7,30$, $J_{AB} = 8,70$
XXIV	10,25 (1H, s, 1-H); 6,98 (1H, d, 3-H); 7,35 (1H, dd, 4-H); 6,94 (1H, t, 5-H); 6,84 (1H, dd, 6-H); 8,05 (2H, d, A-H); 7,80 (2H, d, B-H); 7,34...7,75 (5H, m, $C_6H_4\underline{C_6H_5}$); 7,18...7,39 (5H, m, $CH_2\underline{C_6H_5}$); 4,34 (2H, s, $\underline{CH_2}C_6H_5$)	$J_{13} = 1,71$, $J_{56} = 7,68$, $J_{AB} = 7,54$

In the PMR spectra of the compounds that we synthesized, namely XII and XXII-XXIV, signals are observed in the form of two doublets that are characteristic for A-H and B-H protons of p-disubstituted benzenes; also observed are signals of the benzyl-group protons.

$$\begin{tikzcd}
\text{XXII } M^{+}328^{*}\ (59) \arrow[r, "-NO_2"] & 282\ (3) \arrow[r, "-CH_2Ph"] & 191\ (4) \arrow[r, "-HCN"] & 164\ (10) \arrow[r, "-C_6H_4"] & 88\ (2)
\end{tikzcd}$$

$$\begin{tikzcd}
\text{XXIII } M^{+}363\ (^{81}Br)\ (96) \arrow[r, "-HBr"] & 281\ (10) \arrow[r, "-CH_2Ph"] \arrow[d, "-C_6H_4"] & 190\ (0{,}6) \arrow[d, "-HCN"] \\
& 205\ (6) \arrow[d, "-HCN"] & 163\ (0{,}1) \arrow[d, "-C_6H_4"] \\
& 178\ (2) \arrow[r, "-CH_2Ph"] & 87\ (0{,}4)
\end{tikzcd}$$

*Values of m/z and (in parentheses) intensities relative to maximum ion current.

In the mass spectra of compound XXII and XXIII, maximum intensity is observed for the peaks of the molecular ions with mass 328 and 363, respectively, the fragmentation of which passes through a stage of 2,3-migration of the phenyl group that is characteristic for 2-phenylindoles [5], either before or after the obligatory detachment of the benzyl group.

EXPERIMENTAL

The IR spectra were registered on a UR-20 instrument in white mineral oil, the UV spectra on a Specord spectrophotometer in ethanol, and the PMR spectra on a Varian-300 spectrometer in DMSO-d_6, internal standard TMS. The mass spectra were registered in a Ribermag 10-10-B spectrometer, with a 70-eV ionizing electron energy. The course of the reactions and the purity of the compounds were monitored on Silufol 254 plates, and the R_f values were determined. The sorbent used in the column chromatography was silica gel with particle size 100-250 or 100-160 μm.

N-Benzylphenylhydrazone of p-Nitroacetophenone (VII). To a solution of 2.35 g (10 mmoles) of the hydrochloride of N-benzylphenylhydrazine (VI) in 200 ml of warm water, a solution of 1.65 g (10 mmoles) of p-nitroacetophenone (I) in 100 ml of 2-propanol was added, and the mixture was stirred for 2 h at room temperature. The resulting precipitate was filtered off, washed with a 1:3 mixture of 2-propanol and water, and dried. This product was purified in a column with a 15:1 mixture of hexane and ether as the eluent. Obtained red crystals, yield 2.8 g.

N-Benzyl-2-p-nitrophenylindole (XII). *A.* A mixture of 1 g (3 mmoles) of the N-benzylphenylhydrazone of p-nitroacetophenone (VII) and 10 g of PPA was stirred for 20 min at 80-90°C. After cooling to 30°C, the mixture was poured as a thin stream into 100 ml of water. This solution was extracted with 200 ml of ether, and the extracts were dried with anhydrous $CaCl_2$. The product was purified in a column with a 15:1 mixture of hexane and ether as the eluent. Obtained yellow crystals, yield 0.035 g.

B. To a solution of 2.38 g (10 mmoles) of 2-p-nitrophenylindole (XVII) in 150 ml of benzene, 40 ml of a 50% aqueous KOH solution, 0.32 g of $[CH_3(CH_2)_3]_4NBr$, and 6.32 g (50 mmoles) of benzyl chloride was added. This mixture was stirred for 2 h at 60°C, after which it was diluted with water and extracted with benzene. The extract was washed with water and dried with anhydrous Na_2SO_4. The solvent was evaporated, and the residue was recrystallized from heptane, obtaining yellow crystals, yield 1.45 g.

N-Benzyl-2-diphenylindole (XIV). This compound was obtained in the same manner as XII, from 1 g (4 mmoles) of 2-diphenylindole (XIX), 0.13 g of $[CH_3(CH_2)_3]_4NBr$, and 2.53 g (20 mmoles) of benzyl chloride, at 75-80°C. The oily product that was obtained was diluted with hexane, and the resulting precipitate was filtered off and dried. Obtained colorless crystals, yield 1.14 g.

2-Substituted Indoles XVII-XIX and Their 7-Benzyl Derivatives XXII-XXIV. A mixture of 20 mmoles of a ketone I-III, 20 mmoles of the hydrochloride of N-benzylphenylhydrazine (VI), and 100 g of PPA was stirred for 1 h at 100-120°C. After cooling, the mixture was poured as a thin stream into 100 ml of water. The resulting precipitate was filtered off, washed with water, and dried. The resulting mixture was separated in a column, using as the eluent either CCl_4 (compounds XVII, XXII and XIX, XXIV) or hexane (compounds XVIII, XXIII).

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