N-ALLYLATION AND N-BENZYLATION OF 2-PHENYLINDOLE AND ITS CONDENSATION WITH CARBONYL COMPOUNDS

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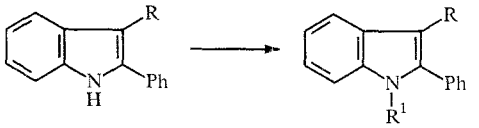
By allylation and benzylation of 2-phenyl- and 2-phenyl-3-formylindole, N-allyl- and benzyl-substituted indoles have been obtained. By condensation of 2-phenylindole with 2-formylfluorene, and also with 4-aza- or 3-methyl-2-azafluorenone, compounds containing fragments of the indole, fluorene, and azafluorenone systems have been synthesized. In the interaction of 2-phenylindole or indole with formaldehyde and 2,5-dimethylpiperidin-4-one, depending on the temperature, bis(2-phenylindol-3-yl)methane, (2',5'-dimethyl-4'-oxopiperidino)-(1-indolyl)methane, and bis(indol-3-yl)methane are formed.

For the synthesis of 2-phenylindole (I), the Fisher method [1] may be used, or the substance may be prepared by the dehydrocyclization of N-benzylidene-o-toluidine over K-16 catalyst [2]. In this article we will describe the preparation of N-allyl-2-phenylindole (II) and N-benzyl-2-phenylindole (III), and also N-allyl-2-phenyl-3-formylindole (IV), compounds that may be useful as the starting materials in the synthesis of condensed heterocyclic compounds containing the indole fragment.

We obtained compounds II and III in high yields (74% and 85%, respectively) by allylation and benzylation of 2-phenylindole (Scheme 1). The allylation was performed by the use of allyl bromide, the benzylation by the use of benzyl bromide in the presence of sodium hydroxide in DMSO at room temperature. Under analogous conditions, the allylation of 2-phenyl-3-formylindole (V) gave the product IV with a yield greater than 86%.

Scheme 1



I, V II–IV

I—III R = H; IV, V R = CHO; II, IV $R^1 = CH_2CH=CH_2$; III R = $CH_2C_6H_5$

We also investigated the reaction of 2-phenylindole with certain carbonyl compounds in the presence of hydrochloric acid at room temperature (Scheme 2). In the condensation of the indole I with 2-formylfluorene, we obtained a quantitative yield of a crystalline substance with a violet color. On the basis of elemental analyses and spectral data, this compound was assigned the structure (2-phenylindol-3-yl)-(fluoren-2-yl)methane (VI).

Upon condensation of the indole I with 4-azafluorenone or 3-methyl-2-azafluorenone, in both cases we obtained colored, high-melting crystalline substances — 9-(2-phenylindol-3-yl)-4-azafluorenylium chloride (VII) and 9-(2-phenylindol-3-yl)-3-methyl-2-azafluorenylium chloride (VIII), respectively.

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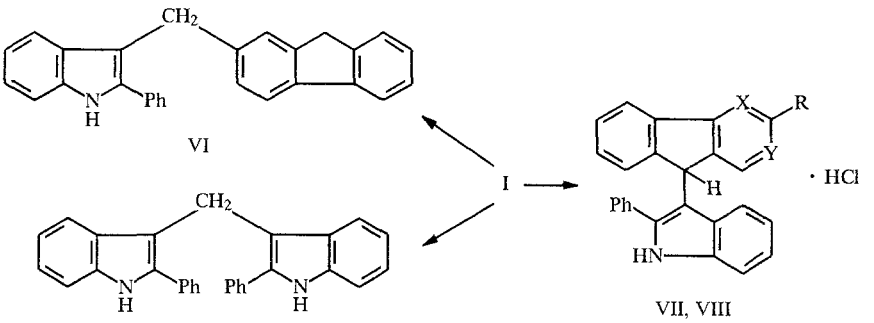
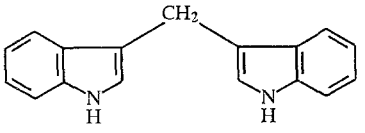
Scheme 2

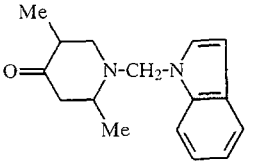


VII X = N, Y = CH; VIII X = CH, Y = N

We also attempted to carry out an analogous reaction of 2-phenylindole and also indole with formaldehyde and 2,5-dimethylpiperidin-4-one. In the first case, the product of the Mannich condensation was not obtained; all that we recovered was a 10% yield of bis(2-phenylindol-3-yl)methane (IX) [3]. In the case of indole itself, at a temperature of 50-60° we obtained (2′,5′-dimethyl-4-oxopiperidino)-(1-indolyl)methane (X); but at 100°, the reaction product was bis(indol-3-yl)methane (XI) [4]



XI



X

EXPERIMENTAL

In monitoring the course of the reaction and the purity of the products, as well as the separation of the products, we used TLC on Silufol UV-254 plates. Mass spectra were obtained in a MKh-1303 mass spectrometer. PMR spectra were taken in a Bruker WP-80 instrument, and for compound X in a Bruker WM-400 as well. IR spectra were taken in a UR-20 instrument, in KBr tablets; UV spectra were taken in a Specord UV-Vis spectrophotometer, in ethanol.

The results of elemental analyses of the synthesized compounds were in agreement with the calculated values.

1-Allyl-2-phenylindole (II). A suspension of 11.4 g (0.2 mole) of KOH in 120 ml of DMSO and 9.65 g (0.05 mole) of 2-phenylindole was stirred for 1 h, after which 12 g (0.1 mole) of allyl bromide was added, and stirring was continued for another 1.5 h. Next, 100 ml of water was added, the reaction products were extracted with ether, and the extract was dried over magnesium sulfate. Distillation of the residue from the ether extract gave 8.6 g (74.4%) of compound II, a viscous, colorless liquid, bp 182-185°C/3 mm Hg, n_D^{20} 1.6410. PMR spectrum ($CDCl_3$): 7.9...7.4 (9H, m, arom.); 6.82 (1H, s, 3-H); 6.17 (2H, d.d.m., J_1 = 18.0, J_2 = 11.0, J_3 = 5.0, N−CH_2); 5.39 (1H, d.m., J = 11.0, CH-cis); 5.18 (1H, d.m., J = 18.0, CH-trans); 4.89 ppm (2H, d.t., J_1 = 5.0, J_2 = 2.5, CH_2). Found: M^+ 233. $C_{17}H_{15}N$. Calculated: M 233.

1-Benzyl-2-phenylindole (III). Analogously, from 2.24 g (0.04 mole) of KOH in 25 ml of DMSO, 1.93 g (0.01 mole) of 2-phenylindole, and 3.42 g (0.02 mole) of benzyl bromide, we obtained 2.42 g (85.5%) of compound III, light-green crystals, mp 120-122°C (from hexane). PMR spectrum ($CDCl_3$): 7.6-6.9 (15H, m, arom); 4.05 ppm (2H, s, CH_2). Found: M^+ 283. $C_{21}H_{17}N$. Calculated: M 283.

1-Allyl-2-phenyl-3-formylindole (IV). From 2.21 g (0.01 mole) of compound V and 2.24 g (0.04 mole) of KOH in 25 ml of DMSO and 2.4 g (0.02 mole) of allyl bromide, obtained 2.25 g (86.2%) of compound IV, light-yellow crystals, mp 117-119°C (from heptane). PMR spectrum ($CDCl_3$): 9.75 (1H, s, -C); 8.45 (1H, m, 4-H); 5.95 (1H, d.d.t., J_1 = 18.0, J_2 = 11.0, J_3 = 5.0, CH=CH_2); 5.20 (1H, d.m., J = 11.0, CH=CH_2); 5.15 (1H, d.m., J = 18.0, CH=CH_2); 5.15 (1H, d.m.,

J = 18.0, CH=CH_2); 4.6 (2H, d.t., -CH_2-); 3.7...3.5 m.d. (8H, m, arom.). Found: M^+ 261. $C_{18}H_{15}NO$. Calculated: M 261.

(2-Phenylindol-3-yl)-(fluoren-2-yl)methane (VI). To a solution of 0.3 g (1.55 mmoles) of 2-phenylindole and 0.3 g (1.55 mmoles) of 2-formylfluorene in 20 ml of ethanol, 10 ml of hydrochloric acid was added dropwise with stirring. The precipitated product was filtered off and crystallized from ethanol. Obtained 0.41 g (72%) of compound VI, violet-colored crystals, mp 86-89°C. IR spectrum: 3072 cm^{-1} (=CH). UV spectrum [λ_{max} (log ε)]: 296 nm (4.6), 360 nm (3.58). PMR spectrum (acetone-d_6): 7.9-6.9 (17H, m, arom.); 3.9 ppm (2H, s, CH_2). Found: M^+ 369. $C_{28}H_{19}N$. Calculated: M 369.

9-(2-Phenylindol-3-yl)-4-azafluorenylium Chloride (VII). To a solution of 0.4 g (2.07 mmoles) of 2-phenylindole and 0.4 g (2.2 mmoles) of 4-azafluorenone in 20 ml of ethanol, 0.5 ml of hydrochloric acid was added gradually. The resulting mixture was held for 72 h at room temperature. Then the precipitate that had formed was filtered off, washed with alcohol, and dried. Obtained 0.67 g of compound VII, yellow crystals, mp 234-236°C (from 5:1 alcohol–acetone mixture). IR spectrum: 3414 cm^{-1} (NH). UV spectrum [λ_{max} (log ε)]: 285 nm (4.89), 360 nm (3.7). PMR spectrum (DMF-d_6): 11.1 (1H, brs, NH); 8.65 (1H, d.m., J = 7.5; 5-H azafluorenylium); 8.45 (1H, br., J = 5.0, 3-H azafluorenylium); 8.15 (1H, brd, J = 8.0, 1-H azafluorenylium); 7.8-6.6 ppm (14H, m, arom., and H-9).

9-(2-Phenylindol-3-yl)-3-methyl-2-azafluorenylium chloride (VIII). Analogously, from 0.3 g (1.55 mmoles) of 2-phenylindole 0.3 g (1.5 mmoles) of 3-methyl-2-azafluorenone, and 0.5 ml of hydrochloric acid, obtained 0.57 g (90%) of compound VIII, light-brown crystals, mp 300-302°C (from acetone). IR spectrum: 3412 cm^{-1} (NH). PMR spectrum (DMF-d_6): 11.0 (1H, br., NH); 8.7 (1H, br., 1-H azafluorenylium); 8.9-7.7 (15H, m, arom., and H-9); 3.0 ppm (3H, br.s, CH_3).

Bis-(2-phenylindol-3-yl)methane (IX). A mixture of 5.7 g (0.029 mole) of 2-phenylindole (I), 3.6 g (0.029 mole) of 2,5-dimethylpiperidin-4-one, and 4 ml of formalin was held for 5 min at 190°C, obtaining 9.1 g of a glassy mass with a dark cherry color. Upon chromatographing 5 g of this mass on silica gel (column 30 × 3.5 cm, eluent 1:4 ether–heptane), recovered 0.6 g (10.2%) of compound IX, light-yellow crystals, mp 181-183°C (from heptane). PMR spectrum ($CDCl_3$): 7.9 (2H, b.s, 2NH); 6.7-7.7 (18H, m, arom.); 4.45 ppm (2H, s, CH_2). Found: M^+ 398. $C_{29}H_{22}N_2$. Calculated: M 398.

As a result of holding a mixture of indole, 2,5-dimethylpiperidin-4-one, and formalin at 100°C for 5 h, obtained **bis(indol-3-yl)methane (XI)** with a 22.6% yield.

(2′,5′-Dimethyl-4′-oxopiperidino)-(1-indolyl)methane (X). A mixture of 3.28 g (0.023 mole) of indole, 3.5 g (0.028 mole) of 2,5-dimethylpiperidin-4-one, and 3 ml of formalin was held for 1 h at 50-60°C. Obtained 6.74 g of a mixture with a dark amber color. Upon chromatographing 3 g of this mixture under the conditions indicated for compound IX, 0.4 g of indole and 0.33 g (10.3%) of compound X were recovered successively. Colorless crystals, mp 87-89°C (from heptane). IR spectrum: 1710 cm^{-1} (CO). PMR spectrum (CD_2Cl_2): Indole ring — 7.22 (1H, d, J 3.2, 2-H); 6.03 (1H, dd, J_1 = 3.2, J_2 = 0.9, 3-H); 6.0 (1H, ddd, J_1 = 7.9, J_2 = 1.2, J_3 = 0.7, 4-H); 7.09 (1H, ddd, J_1 = 7.9, J_2 = 7.1, J_3 = 0.9, 5-H); 7.20 (1H, dddd, J_1 = 8.3, J_2 = 7.1, J_3 = 1.2, J_4 = 0.4, 6-H); 7.51 (1H, ddt, J_1 = 8.3, J_2 = 0.7, J_3 = 0.9, 7-H); piperidine ring — 0.87 (3H, d, J = 6.8, 5-CH_3); 1.39 (3H, d, J = 6.0, 2-CH_3); 2.14 (1H, t, J = 11.5, 6a-H); 2.35 (2H, d, J = 6.8, 3a, 3e-2H); 2.55 (1H, d. quint., J_1 = 11.5, J_2 = 6.0, 5a-H); 2.90 (1H, sext, J = 6.8, 2-H); 3.07 (1H, dd, J_1 = 11.5, J_2 = 6.0, 6e-H); CH_2; 4.78 and 5.23, ppm, two d, J = 13.1. Found: M^+ 256. $C_{16}H_{20}N_2O$. Calculated: M 256.

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