BISINDOLES.

19.* SYNTHESIS OF 2,5'-BIS-1H-INDOLE

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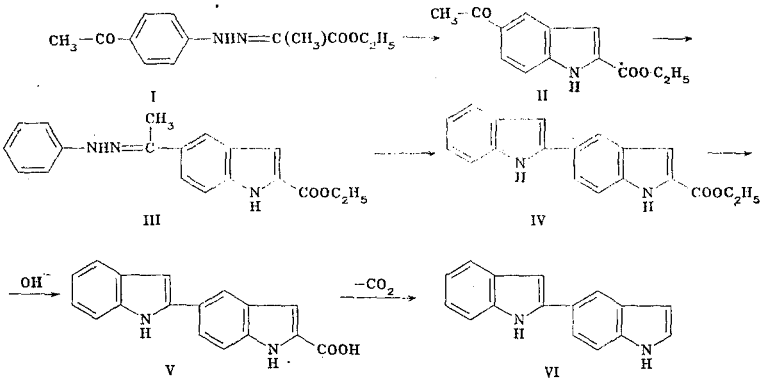
The cyclization of 5-acetyl-2-ethoxycarbonylindole phenylhydrazone gave 2'-ethoxycarbonyl-2,5'-bis-1H-indole, the saponification of which and subsequent decarboxylation of the resulting acid led to the formation of 2,5'-bis-1H-indole — a new unsymmetrical bisindole system.

The present communication is devoted to the synthesis of a new bisindole with an unsymmetrical structure, viz., 2,5'-bis-1H-indole (VI), which contains two pyrrole rings with different reactivities of the β positions.



In contrast to the synthesis of symmetrical bisindoles [2-6], the scheme presented above includes two steps involving Fischer cyclization.

The cyclization of hydrazone I in polyphosphoric acid (PPA) at 110-115°C leads to 5-acetyl-2-ethoxycarbonylindole (II) in 50% yield. Absorption bands of a carbonyl group at 1680 and 1705 cm^{-1} and of an indole NH bond at 3350 and 3475 cm^{-1} are observed in the IR spectrum of II. The PMR spectrum of II contains signals that are characteristic for the protons of the indole ring at 7.26-8.33 ppm, as well as signals for the protons of an acetyl group at 2.57 ppm and an ester group at 4.35 and 1.35 ppm.

The synthesis of 5-acetyl-2-ethoxycarbonylindole phenylhydrazone (III) was realized in ethanol or isopropyl alcohol in the presence of acetic acid. The cyclization of hydrazone III was studied in the presence of various catalysts, but the use of ethyl polyphosphorate at 100-105°C gave the best results (26% yield). Two absorption bands of NH groups at 3330 and 3450 cm^{-1} and an absorption band of an ester group at 1700 cm^{-1} are observed in the IR spectrum of IV. The PMR spectrum of IV confirms its unsymmetrical structure, since it contains two signals that are characteristic for the protons of NH groups in the weak-field region of the spectrum and signals of the protons of two indole rings: the signals of the first ring are observed at 6.9-7.48 ppm, and the signals of the second ring are observed in the form of resolved signals at 7.16-8.09 ppm. The molecular mass of IV determined by mass spectrometry is in agreement with the calculated value, whereas the peaks with masses 258, 230, and 203 are due to the successive splitting out of C_2H_5OH, HCO, and HCN groups, respectively, from the molecular ion.

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*See [1] for Communication 18.

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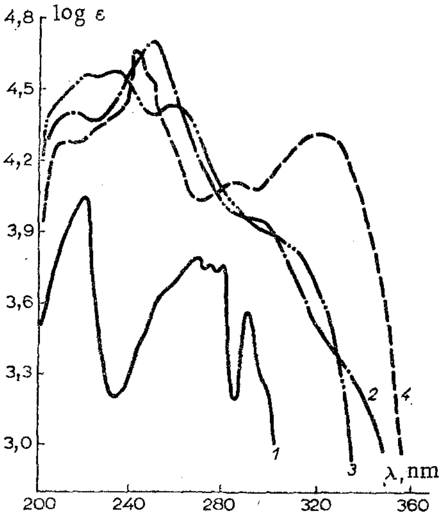

Fig. 1. UV absorption spectra (in ethanol): 1) indole; 2) 5,5'-bis-1H-indole; 3) 3,5'-bis-1H-indole; 4) 2,5'-bis-1H-indole.

Saponification of ester IV gave acid V, the decarboxylation of which led to bisindole VI. The unsymmetrical structure of the bisindole system that we synthesized was also confirmed by the PMR spectrum of unsubstituted bisindole VI: It contains two signals of protons of NH groups at 10.3 and 10.5 ppm. The signals of the protons in the 3 and 3' positions show up in the form of two multiplets at 6.73 and 6.48 ppm, respectively. The unambiguous assignment of the signals of these protons is possible owing to the spin—spin coupling constant ($J_{2'3'}$ = 3.1 Hz) observed between the protons of the second pyrrole ring. Absorption bands at 210, 242, 284, and 320 nm are noted in the UV spectrum of bisindole VI. A comparison of its spectrum with the spectra of indole, 5,5'-bis-1H-indole, and 3,5'-bis-1H-indole [2] (see Fig. 1, curves 1-3) shows that the spectrum of bisindole VI (curve 4) resembles the spectrum of 5,5'-bis-1H-indole to a greater extent, although at 20 nm bathochromic shift of the long-wave absorption maximum and an increase in intensity are observed in it; in addition, yet another low-intensity maximum at 284 nm appears in the spectrum.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds and the determination of the R_f values were carried out on plates with a fixed layer of Silufol UV-254 silica gel. Silica gel with a particle size of 100-160 μm ws used for column chromatography. The UV spectra of solutions of the compunds in ethanol were recorded with a Specord spectrophotometer. The IR sepctra of mineral oil suspensions were obtained with a UR-20 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer by direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV. The PMR spectra were recorded with a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal standard.

Ethyl pyruvate p-acetylphenylhydrazone (I) was obtained in 54% yield by the method in [7] and had mp 144°C.

5-Acetyl-2-ethoxycarbonylindole (II). A mixture of 25 g of polyphosphoric acid and 2.5 g (10 mmole) of crude hydrazone I was stirred at 110-115°C for 10-15 min, after which it was cooled and poured into 300 ml of cold water. The precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 2.2 g of a crude product, which was purified with a column by elution with benzene—ether (5:1). The fraction with R_f 0.25 [benzene—ether (4:1)] contained 1.15 g (50%) of II with mp 129-130°C. IR spectrum in chloroform): 3350, 3475 (NH); 1680, 1705 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 266 (4.83), 311 (4.04), and 325 nm (3.92). PMR spectrum (in DMSO): 12.0 (s, 1-H), 7.26 (dd, 3-H), 8.33 (d, 4-H), 7.81 (dd, 6-H), 7.48 (dd, 7-H), 4.35 (q, 2-CH_2), 1.35 (t, 2-CH_3), and 2.57 ppm (s, 5-CH); J_{13} = 1.9, J_{37} = 0.6, J_{46} = 1.6, J_{67} = 8.7, and J_{Et} = 7.1 Hz. Mass spectrum, m/z (%): M^+ 231 (61), 216 (74), 188 (43), 185 (46), 170 (100), 142 (56), 114 (59), 88 (50), 87 (47). Found: C 67.3; H 5.8; N 6.2%; M^+ 231. $C_{13}H_{13}NO_3$. Calculated: C 67.5: h 5.6; N 6.1%; M 231.

5-Acetyl-2-ethoxycarbonylindole Phenylhydrazone (III). A 10-ml sample of phenylhydrazine and 2 ml of acetic acid were added to a solution of 2.3 g (10 mmole) of indole II in 50 ml of alcohol, and the mixture was stirred at 50°C for 1.5 h. It was then cooled, and the precipitate was removed by filtration, washed with ether, and dried to give 3 g of product.

The mother liquor was evaporated to give another 0.15 g of hydrazone III for an overall yield of 3.15 g (98%) of a product with mp 176-178°C. IR spectrum: 3280 (NH), 1710 (CO), and 1610 cm^{-1} (C=N). UV spectrum, λ (log ε): 207 (4.38), 252 (4.45), 302 (4.51), and 331 (4.41) sh. Found: C 70.5; H 5.8; N 13.3%. $C_{19}H_{10}N_3O_2$. Calculated: C 71.0; H 5.0; N 13.1%.

2'-Ethoxycarbonyl-2,5'-bis-1H-indole (IV). A mixture of 3.2 g (10 mmole) of hydrazone III and 35 g of ethyl polyphosphorate was heated slowly with stirring to 100-105°C and maintained at this temperature for 50 min, after which it was cooled and poured into cold water. The precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 3 g of crude product, which was purified with a column by elution with chloroform. The fraction with R_f 0.41 [benzene—ether (4:1)] was evaporated to give 0.8 g (26.4%) of a product with mp 260-261°C. IR spectrum: 3330, 3450 (NH); 1700 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 233 (4.41), 253 (4.73), 307 (4.58), 322 (4.34) sh, and 347 nm (4.04). PMR spectrum (in DMSO): 11.4 (s, 1H), 11.9 (s, 1'-H), 6.97 (dd, 3-H), 7.16 (dd, 3'-H), 7.48 (dd, 4-H), 8.09 (d, 4'-H), 6.9-7.0 (m, 5-H, 6-H), 7.76 (dd, 6'-H), 7.37 (dd, 7-H), 7.48 (d, 7'-H), 4.34 (q, 2'-CH_2), and 1.36 ppm (t, 2'-CH_3); J_{13} = 1.6, $J_{1'3'}$ = 2.2, J_{37} = $J_{3'7'}$ = 0.8, J_{46} = $J_{4'6'}$ = 1.2, $J_{6'7'}$ = 9.1, J_{Et} = 6.8 Hz. Mass spectrum, m/z (%): M^+ 304 (100); 258 (96); 230 (87); 203 (70). Found: C 75.6; H 5.5: N 8.8%; M^+ 304. $C_{19}H_{16}N_2O_2$. Calculated: C 75.0; H 5.3; N 9.2%; M 304.

2'-Carboxy-2,5'-bis-1H-indole (V). A suspension of 0.5 g (1.6 mmole) of ester IV in 100 ml of 10% KOH solution and 40 ml of alcohol was refluxed with stirring for 1.5-2 h until a clear solution had formed, after which the solution was cooled and filtered, and the filtrate was acidified to pH 1 with 10% HCl. The yellow precipitate was removed by filtration, washed with water until the wash water was neutral, and dried in a vacuum desiccator over P_2O_5 to give 0.34 g (75%) of a product with mp 256°C. IR spectrum 3330, 3450 (NH), 1700, 1720 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 209 (4.38), 251 (4.52), 298 (4.44), 320 (4.33) sh, and 337 nm (4.18) sh. PMR spectrom (in d_6-acetone) 11.2 (s, 1-H), 11.5 (s, 1'-H), 6.71 (d, 3-H), 7.09 (s, 3'-H), 7.45 (s, 4-H), 8.05 (d, 4'-H), 6.0-7.1 (m, 5-H, 6-H), 7.69 (dd, 6'-H), 7.35 (s, 7=H), and 7.45 ppm (d, 7'-H); J_{13} = 1.2, $J_{4'6'}$ = 1.5, $J_{6'7'}$ = 9.1 Hz. Found: C 73.4; H 4.4; N 9.5%. $C_{17}H_{12}N_2O_2$. Calculated: C 73.9; H 4.3; N 10.0%.

2,5'-Bis-1H-indole (VI). A 0.34-g (1.23 mmole) sample of acid V was heated at 245-257°C for 10-15 min, after which it was cooled and dissolved in acetone, and the solution was purified with a column by elution with benzene to give 0.13 g (46%) of a product with mp 209-210°C and R_f 0.4 [benzene—ether (4:1)]. IR spectrum: 3390 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 209 (4.28), 242 (4.66), 284 (4.13), and 320 nm (4.32). PMR spectrum (in d_6-acetone): 10.5 (s, 1-H), 10.3 (s, 1'-H), 7.3 (d, 2'-H), 6.73 (dd, 3-H), 6.48 (oct, 3'-H), 7.53 (m, 4-H), 8.00 (dd, 4'-H), 6.9-7.04 (m, 5- and 6-H), 7.60 (dd, 6'-H), 7.37 (d, 7-H), and 7.43 ppm (dd, 7'-H); J_{13} = $J_{1'3'}$ = 2.0, $J_{2'3'}$ = 3.1, J_{37} = $J_{3'7'}$ = 0.5, $J_{4'6'}$ = 2.2, $J_{4'7'}$ = 1.0, $J_{6'7'}$ = 8.5 Hz. Mass spectrum, m/z (%): M^+ 232 (100); 204 (16); 116 (19), 89 (12). Found: C 82.4; H 5.4; N 11.7%; M^+ 232. $C_{16}H_{12}N_2$. Calculated: C 82.7; H 5.2: N 12.0%; M 232.

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