SYNTHESIS OF 11,12,12*a*,13-TETRAHYDRO-6H-INDOLO[1,2-*b*]-[2,4]BENZODIAZEPINES

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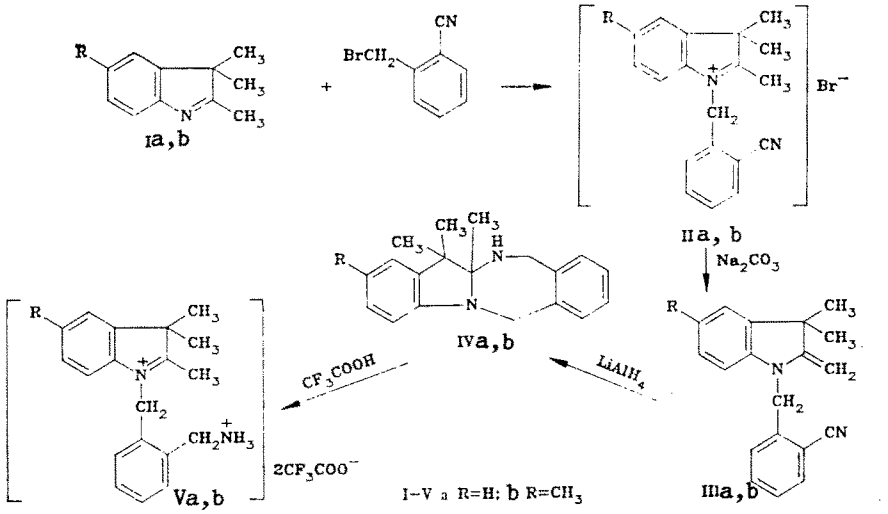
Alkylation of 2,3,3-trimethyl- and 2,3,3,5-tetramethyl-3H-indoles with 2-bromomethylbenzonitrile gave 2-methylene-1-(2-cyanobenzyl)-2,3-dihydro-1H-indoles. When treated with lithium aluminum hydride the latter are cyclized to 11,12,12a,13-tetrahydro-6H-indolo[1,2-b][2,4]benzodiazepines.

We have previously investigated the annelation of the imidazolidine and hexahydropyrimidine rings to indole by reaction of 3H-indoles with α-halogeno- and α, β-unsaturated carboxamides [1, 2]. The present paper concerns the synthesis of condensed heterocycles containing indole and diazepine rings derived from 3H-indoles and 2-bromomethylbenzonitrile. The 4-halogenomethylbenzonitrile alkylation products of 2,3,3-trimethyl-3H-indole have been reported in the patent literature [3].

Heating 2,3,3-trimethyl- and 2,3,3,5-tetramethyl-3H-indoles Ia, b with 2-bromomethylbenzonitrile in toluene of xylene gives 1-(2-cyanobenzyl)-3H-indolium bromides IIa, b. In the presence of base these are converted to the 2-methylene-1-(2-cyanobenzyl)-2,3-dihydro-1H-indoles IIIa, b. They are typified by AB-quadruplet PMR signals (in $CDCl_3$) for the 2-methylene protons in the region 3.76-4.01 ppm (J_{AB} = 2.1 Hz) [4]. The IR spectra show nitrile absorption at 2240 cm^{-1} (C≡N) [5].



It is known that lithium aluminum hydride usually readily reduces nitriles to primary amines [6], but not hydrogenate the enamine group of 2-methylene-2,3-dihydro-1H-indoles [7]. When IIIa, b are treated with this reagent the hydrogenation of the nitrile is accompanied by intramolecular nucleophilic addition of the nitrogen atom of the formed amino group to the α-carbon of the indole ring to produce the 11,12,12*a*,13-tetrahydro-6H-indolo[1,2-b][2,4]benzodiazepines (IVa, b). Their PMR spectra ($CDCl_3$) show two characteristic AB-quadruplets (J_{AB} = 16.0 Hz) in the region 3.41-4.98 ppm for the methylene protons of the diazepine ring.

When recorded in CF_3COOH solvent, compounds IVa, b showed signals for 6-H and 11-H as a singlet at 5.68 ppm and a quadruplet at 4.26-4.62 ppm (J = 5.4 Hz), respectively, and a signal for the 12*a*-CH_3 group which had undergone a 1.40-ppm shift to low field. This showed that the action of strong protonic acids on indolo[1,2-b][2,4]benzodiazepines IVa, b, as in the case of imidazo- and pyrimido[1,2-*a*]indoles [1, 2, 7], causes opening of the ring annelated to the indole to form the 3H-indolium salts Va, b.

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EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer as KBr tablets or as a thin layer. PMR spectra were recorded on a Tesla BS-487C (80 MHz) instrument with HMDS internal standard. Mass spectra were run on a Hitachi M-80A instrument with direct introduction of the sample into the ion source at a temperature of 140°C and ionizing intensity of 20 eV. The reaction course and purity of products were monitored by TLC on Silufol plates in acetone–hexane (3:5) and visualized using iodine vapor.

Elemental analytical data for C, H, N, and Br agreed with that calculated.

2,3,3-Trimethyl-1-(2-cyanobenzyl)-3H-indolium Bromide (IIa, $C_{19}H_{19}BrN_2$). A solution of Ia (4.78 g, 30 mmoles) and 2-bromomethylbenzonitrile (5.88 g, 30 mmoles) in xylene (6 ml) was heated at 95°C for 3 h. The crystalline product was filtered, recrystallized from alcohol, and dried in vacuo to give 3.20 g (30%) with mp 215-216°C. IR spectrum (KBr): 2240 (C≡N), 1635 cm^{-1} (C=N$^+$). PMR spectrum (CF_3COOH): 1.37 (6H, s, 3,3-CH_3); 2.66 (3H, s, 2-CH_3); 5.74 (2H, s, CH_2); 6.97-7.72 ppm (8H, m, Ar).

2,3,3,5-Tetramethyl-1-(2-cyanobenzyl)-3H-indolium Bromide (IIb, $C_{20}H_{21}BrN_2$). A solution of Ib (2.62 g, 15 mmoles) and 2-bromomethylbenzonitrile (2.94 g, 15 mmoles) in toluene (4 ml) was heated at 95°C for 3 h. The product was cooled to 20°C and mixed with acetone (5 ml). The crystalline product was filtered, recrystallized from alcohol, and dried in vacuo to give 1.33 g (24%) with mp 197-198°C. IR spectrum (KBr): 2240 (C≡N), 1640 cm^{-1} (C=N$^+$) PMR spectrum (CF_3COOH): 1.34 (6H, s, 3,3-CH_3); 2.13 (3H, s, 5-CH_3); 2.59 (3H, s, 2-CH_3); 5.67 (2H, s, CH_2); 6.93-7.63 ppm (7H, m, Ar).

3,3-Dimethyl-2-methylene-1-(2-cyanobenzyl)-2,3-dihydro-1H-indole (IIIa, $C_{19}H_{18}N_2$). A solution of IIa (3.55 g, 10 mmoles) in water (30 ml) was treated with sodium carbonate to pH 9 and extracted with ether (2 × 20 ml). The extract was dried with calcium chloride and the solvent distilled to give 2.30 g (84%) of oily product IIIa with R_f 0.85 (Silufol, acetone–hexane, 3:5). PMR spectrum ($CDCl_3$): 1.38 (6H, s, 3,3-CH_3); 3.83, 3.92 (2H, AB-system, J_{AB} = 2.1 Hz, C=CH_2); 4.94 (2H, s, CH_2); 6.39-7.78 ppm (8H, m, Ar).

2-Methylene-3,3,5-trimethyl-1-(2-cyanobenzyl)-2,3-dihydro-1H-indole (IIIb, $C_{20}H_{20}N_2$). A solution of IIb (1.11 g, 3 mmoles) in water (15 ml) was treated with sodium carbonate to pH 9 and extracted with ether (2 × 15 ml). The extract was dried with calcium chloride, the solvent distilled, and the residue crystallized from alcohol to give 0.62 g (72%) with mp 120-121°C. PMR spectrum ($CDCl_3$): 1.38 (6H, s, 3,3-CH_3); 2.28 (3H, s, 5-CH_3); 3.81, 3.90 (2H, AB-system, J_{AB} = 2.1 Hz, C=CH_2); 4.94 (2H, s, CH_2); 6.32-7.78 ppm (7H, m, Ar).

12*a*,13,13-Trimethyl-11,12,12*a*,13-tetrahydro-6H-indolo[1,2-b][2,4]benzodiazepine (IVa, $C_{19}H_{22}N_2$). Lithium aluminum hydride (0.42 g, 12 mmoles) was added to a solution of IIIa (1.37 g, 5 mmoles) in absolute ether (10 ml) and held at 20°C for 16 h. Excess hydride was decomposed using 1 ml of 10% KOH solution. The precipitate was filtered, washed with water (5 ml), and dried ($CaCl_2$). Solvent was distilled and the residue crystallized from hexane to give 0.60 g (43%) with mp 128-129°C. IR spectrum (KBr): 3322 cm^{-1} (N–H). PMR spectrum ($CDCl_3$): 1.09 (3H, s, CH_3); 1.29 (3H, s, CH_3); 1.47 (3H, s, CH_3); 2.11 (1H, br. s, NH); 3.58, 4.13 (2H, AB-system, J_{AB} = 16.0 Hz, C_{11} methylene); 4.44, 4.80 (2H, AB-system, J_{AB} = 16.0 Hz, C_6 methylene); 6.21-7.46 ppm (8H, m, Ar). M^+ 278.

2,12*a*,13,13-Tetramethyl-11,12,12*a*,13-tetrahydro-6H-indolo[1,2-b][2,4]benzodiazepine (IVb, $C_{20}H_{24}N_2$) was obtained from IIIb (0.58 g, 2 mmoles) and lithium aluminum hydride (0.17 g, 4.8 mmoles) similarly to IVa to give 0.28 g (48%) with mp 118-119°C (from alcohol). PMR spectrum ($CDCl_3$): 1.09 (3H, s, CH_3); 1.27 (3H, s, CH_3); 1.47 (3H, s, CH_3); 2.14 (1H, br.s, NH); 2.17 (3H, s, 2-CH_3); 3.61, 4.18 (2H, AB-system, J_{AB} = 16.0 Hz, C_{11} methylene); 4.43, 4.81 (2H, AB-system, J_{AB} = 16.0 Hz, C_6 methylene); 6.18-7.49 ppm (7H, m, Ar). M^+ 292.

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