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SHORT COMMUNICATIONS

Transformation of Quaternary 5-Benzyl-2-(2-ethoxy-2-oxoethyl)- and -2-cyanomethyl-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-ium Salts into 1,2,3,4,7,12-Hexahydroazonino[4,5-*b*]indole Derivatives

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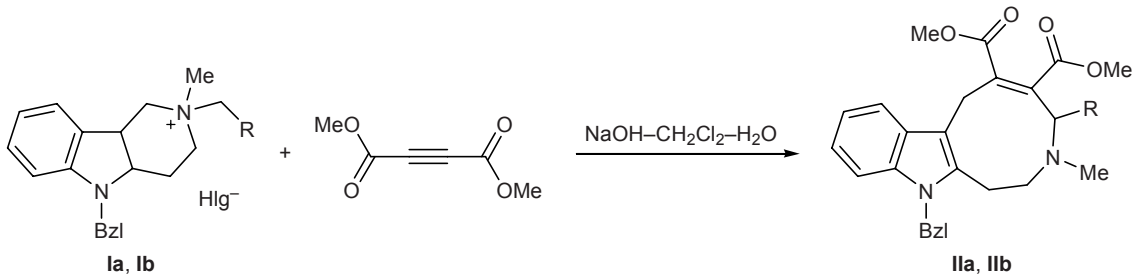
It was recently found that quaternary 1-(2-ethoxy-2-oxoethyl)-1-methyl-1,2,3,6-tetrahydropyridinium salts are capable of undergoing transformation into ethyl 4-vinylpyrrolidine-2-carboxylates by the action of bases [1]. Analogous reactions with structurally related 4-arylpyridinium salts could result in ring expansion with formation of azepine derivatives [2]. In addition, we previously revealed [3] a different recyclization pathway of tetrahydropyridinium ring, which involves ring expansion to nine-membered nitrogen-containing ring. Such transformation occurred on treatment of 2-methoxycarbonylmethyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridinium bromide with triethylamine in the presence of dimethyl acetylenedicarboxylate. Taking the above stated into account, in the present work we examined reactions of 5-benzyl-2-(2-ethoxy-2-oxoethyl)-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-ium bromide (**Ia**) and 5-benzyl-2-cyanomethyl-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-ium chloride (**Ib**) with dimethyl acetylenedicarboxylate in the presence of alkali. The reactions were carried out under conditions of phase-transfer catalysis in the two-phase system methylene chloride–50% aqueous sodium hydroxide at 20°C (reaction time 12 h). After chromatographic separation we isolated the corresponding hexahydrodroazonino-[4,5-*b*]indoles **IIa** and **IIb** in 19 and 37% yield, respectively. Presumably, the transformation sequence includes initial generation of nitrogen ylides which undergo electrophilic attack at the carbanionic center to give intermediate 1,4-zwitterion. Cleavage of the latter at the C–N bond of the allylamine fragment and subsequent recyclization with participation of three carbon atoms in the zwitterion moiety leads to the formation of hexahydroazoninoindole system. The products are structurally related to the base fragments of anticancer (alkaloids Vinblastine and Vincristine [4]) and antileishmanial agents (alkaloid Coronaridine [5]).

5-Benzyl-2-(2-ethoxy-2-oxoethyl)-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-ium bromide (Ia). A solution of 10.9 mmol of 5-benzyl-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido-[4,3-*b*]indole and 10.9 mmol of ethyl bromoacetate in



Ia, **Ib** **IIa**, **IIb**

R = COOEt (**a**), CN (**b**); Hlg = Br (**a**), Cl (**b**).

15 ml of THF was stirred for 48 h at 20°C. The precipitate was filtered off, washed with diethyl ether, and dried. Yield 91%, mp 175–177°C. IR spectrum: ν 1742 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (3H, $CH_2C\mathbf{H}_3$, J = 7.2 Hz), 3.21 m (2H, 1-H), 3.38 s (3H, NCH_3), 4.08 m (2H, 2-H), 4.29 q (2H, OCH_2, J = 7.2 Hz), 4.60 d and 4.63 d (1H each, 4-H, J = 12.8 Hz), 4.92 d and 5.04 d (1H each, CH_2CO, J = 14.8 Hz), 5.42 m (2H, C$\mathbf{H}_2$Ph, *AB* system, J = 14.1 Hz), 7.07–7.35 m (7H, H_{arom}), 7.43 d (1H, 9b-H, J = 8.1 Hz), 7.47 d (1H, 6-H, J = 8.0 Hz). Found, %: Br 17.87; N 6.41. $C_{23}H_{27}BrN_2O_2$. Calculated, %: Br 18.06; N 6.32.

5-Benzyl-2-cyanomethyl-2-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-ium chloride (Ib) was synthesized in a similar way. Yield 92%, mp 150–152°C. IR spectrum: ν 2253 cm^{-1} (C≡N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.25 br.s (2H, 1-H), 3.38 s (3H, NCH_3), 4.12 m (2H, 2-H), 5.03 d and 5.07 d (1H each, 4-H, J = 11.0 Hz), 5.43 m (4H, CH_2CN, C$\mathbf{H}_2$Ph), 7.07–7.35 m (7H, H_{arom}), 7.47 d (1H, 8-H, J = 7.7 Hz), 7.54 d (1H, 5-H, J = 7.6 Hz). Found, %: Cl 10.24; N 12.03. $C_{21}H_{22}ClN_3$. Calculated, %: Cl 10.10; N 11.95.

4-Ethyl 5,6-dimethyl 12-benzyl-3-methyl-1,2,3,4,7,12-hexahydroazonino[4,5-*b*]indole-4,5,6-tricarboxylate (IIa). Yield 19%, mp 165–167°C. IR spectrum, ν, cm^{-1}: 1736, 1732 (C=O), 1638 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 t (3H, $CH_2C\mathbf{H}_3$, J = 7.3 Hz), 2.50 s (3H, NCH_3), 2.93 m (2H, 1-H), 3.35 s (3H, OCH_3), 3.62 s (3H, OCH_3), 3.83 q (2H, OCH_2, J = 7.3 Hz), 3.87 s (2H, 7-H), 4.17 m (2H, 2-H), 5.32 s (2H, C$\mathbf{H}_2$Ph), 6.18 s (1H, 4-H), 6.93 d (2H, H_{arom}, J = 7.8 Hz), 7.07–7.35 m (6H, H_{arom}), 7.56 d.d (1H, 8-H, J = 7.3, 1.3 Hz). Mass spectrum: m/z 505 $[M + 1]^+$. Found, %: C 69.35; H 6.47; N 5.35. $C_{29}H_{32}N_2O_6$. Calculated, %: C 69.03; H 6.39; N 5.55.

Dimethyl 12-benzyl-4-cyano-3-methyl-1,2,3,4,-7,12-hexahydroazonino[4,5-*b*]indole-5,6-dicarboxylate (IIb). Yield 37%, mp 120–122°C. IR spectrum, ν, cm^{-1}: 2207 (CN), 1736 (C=O), 1624 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.45 s (3H, NCH_3), 2.85 m (2H, 1-H), 3.05 m (1H, 2-H), 3.35 s (6H, OCH_3), 3.65 s (2H, 7-H), 3.68 s (1H, 4-H), 4.46 t (1H, 2-H), 5.44 s (2H, C$\mathbf{H}_2$Ph), 6.94 d (2H, H_{arom}, J = 7.8 Hz), 7.01–7.32 m (7H, H_{arom}), 7.48 d.d (1H, 8-H, J = 7.4, 1.4 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 23.3 (C^7), 24.4 (C^1), 42.7 (NCH_3), 45.6 (C^4), 52.3 (OCH_3), 54.9 ($\mathbf{C}H_2Ph$), 109.7 (C^{7a}), 117.7 (CN), 118.9–135.4 (C_{arom}), 136.1 and 138.4 (C^5, C^6), 164.4 and 171.6 (C=O). Mass spectrum: m/z 458 $[M + 1]^+$. Found, %: C 70.76; H 6.08; N 9.03. $C_{27}H_{27}N_3O_4$. Calculated, %: C 70.88; H 5.95; N 9.18.

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker WM-400 instrument at 400 and 100 MHz, respectively. The mass spectra (ionization by protons) were obtained on a PE SCIEX API 165 (150) LC–MS system (Shimadzu HPLC SCL10Avp, Gilson 215 autosampler, ELSD Sedex 75).

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