New Substituted Indolizines by 1,3-Dipolar Cycloaddition
VII. 7-Benzoyl-indolizine

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*New indolizine derivatives **6** containing a benzoyl group attached to the pyridinic ring are obtained by the reaction of N-phenacylpyridinium bromides **3** with ethyl propiolate as non-symmetrical acetylenic dipolarophile, in 1,2epoxypropane medium. The compounds structure was assigned by elemental analysis, NMR and IR spectroscopy.*

Keywords: pyridinium N-ylide, 1,3-dipolar cycloaddition, acetylenic dipolarophiles, indolizine

Indolizine derivatives are nitrogen containing heterocyclic systems very studied in last years due to their potential mainly in the pharmaceutical field [1]. As an example indolizine derivatives with selective antibacterial activity against Mycobacterium tuberculosis were reported [1c]. Moreover, the high degree of conjugation of their aromatic system generates intense optical properties which make indolizine and azaindolizine systems [2-5] valuable spectral sensitizers or dyes. By attaching different substituents on this aromatic system the fluorescence quantum yield may be improved and also the bioavailability of these derivatives may be modified by controlling the stability of the system. Furthermore, indolizines substituted at the 7 position may be used as highly selective chemosensors when attached to a cyclodextrin moiety [5].

Numerous synthetic routes towards the obtaining of these types of derivatives are known [5a-c]. One of the most versatile methods is the 1,3-dipolar cycloaddition of pyridinium *N*-ylides to activated alkynes or alkenes [6].

The synthesis of the new functionalized indolizines, containing a 7-benzoyl group attached to the pyridine ring, hereby presented, is carried out by 1,3-dipolar cycloaddition reactions of pyridinium *N*-ylides with the acetylenic non-symmetrical dipolarofile ethyl propiolate. By introducing the 7-benzoyl substituent on the pyridine ring and by varying the substituents on the pyrrole moiety, it may be possible to enhance the optical tuning of the spectral properties of indolizine derivatives.

Experimental part

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. Supplementary evidence was given by HETCOR and COSY experiments.

General procedure for synthesis of 4-benzoyl-pyridinium bromides 3

10 Mmol 4-benzoyl-pyridine **1** and 10 mMol 2-bromoacetophenone **2** in 50 mL of methanol were heated at reflux for 8 h and then kept at room temperature until the next day. The pyridinium bromides **3** obtained were collected by filtration and washed with chloroform.

4-Benzoyl-1-(2-phenyl-2-oxoethyl)-pyridinium bromide (**3a**). The product was recrystallized from methanol and pale yellow crystals with mp 200-202°C were obtained; Yield 98 %. Anal. Calcd. $C_{20}H_{16}BrNO_2$: N 3.66. Found N 3.85. FT-IR (cm^{-1}): 1663, 1689, 2930.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.62 (s, 2H, CH_2); 7.53-7.63 (m, 4H, H-3', H-5', H-3", H-5"); 7.70-7.82 (m, 2H, H-4', H-4"); 7.84-7.88 (m, 2H, H-2", H-6"); 8.05-8.08 (m, 2H, H-2', H-3', H-5', H-6'); 8.31 (d, *J* = 6.8 Hz, H-3, H-5); 9.02 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.3 (CH_2); 127.3 (C-3, C-5); 128.7, 129.4, 130.5 (C-2', C-3', C-5', C-6', C-2", C-3", C-5", C-6"); 132.3 (C-1'); 133.4 (C-1"); 135.8 (C-4"); 136.0 (C-4'); 147.2 (C-2, C-6); 152.7 (C-4); 189.4 (COAr); 191.7 (COPh).

4-Benzoyl-1-[2-(4-chlorophenyl)-2-oxoethyl]-pyridinium bromide (**3b**). The product was recrystallized from methanol and beige crystals with mp 270-272°C were obtained; Yield 87 %. Anal. Calcd. $C_{20}H_{15}BrClNO_2$: N 3.36. Found N 3.58.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.62 (s, 2H, CH_2); 7.51 (d, 2H, *J* = 8.6 Hz, H-3', H-5'); 7.57-7.63 (m, 2H, H-3", H-5"); 7.75-7.81 (m, 1H, H-4"); 7.84-7.88 (m, 2H, H-2", H-6"); 8.03 (d, 2H, *J* = 8.6 Hz, H-2', H-6'); 8.31 (d, *J* = 6.8 Hz, H-3, H-5); 9.06 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.3 (CH_2); 127.3 (C-3, C-5); 129.5; 130.1 (C-2", C-3", C-5", C-6"); 129.9, 130.5 (C-2', C-3', C-5', C-6'); 130.8 (C-1'); 133.4 (C-1"); 135.8 (C-4"); 142.4 (C-4'); 147.1 (C-2, C-6); 153.0 (C-4); 188.2 (COAr); 191.6 (COPh).

4-Benzoyl-1-[2-(4-bromophenyl)-2-oxoethyl]-pyridinium bromide (**3c**). The product was recrystallized from methanol and pale yellow crystals with mp 269 - 271°C were obtained; Yield 88 %. Anal. Calcd. $C_{20}H_{15}Br_2NO_2$: N 3.04. Found N 3.27.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.60 (s, 2H, CH_2); 7.58-7.63 (m, 2H, H-3", H-5"); 7.72, 7.95 (2d, 4H, *J* = 8.6 Hz, H-2', H-3', H-5', H-6'); 7.76-7.82 (m, 1H, H-4"); 7.85-7.88 (m, 2H, H-2", H-6"); 8.32 (d, *J* = 6.8 Hz, H-3, H-5); 9.00 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.2 (CH_2); 127.4 (C-3, C-5); 129.5 130.0 (C-2", C-3", C-5", C-6"); 130.6, 132.9 (C-2', C-3', C-5', C-6'); 131.1, 131.8 (C-1', C-4'); 133.3 (C-1"); 135.9 (C-4"); 147.1 (C-2, C-6); 152.9 (C-4); 188.6 (COAr); 191.9 (COPh).

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4-Benzoyl-1-[2-(3-nitrophenyl)-2-oxoethyl]-pyridinium bromide (**3d**). The product was recrystallized from methanol and colorless crystals with mp 252-4°C were obtained; Yield 73 %. Anal. Calcd. $C_{20}H_{15}BrN_2O_4$: N 6.56. Found N 6.78.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.88 (s, 2H, CH_2); 7.57-7.62 (m, 2H, H-3", H-5"); 7.73-7.81 (m, 2H, H-5', H-4"); 7.85-7.89 (m, 2H, H-2", H-6"); 8.30, 8.35 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 8.34 (d, *J* = 6.8 Hz, H-3, H-5); 8.41-8.48 (m, 2H, H-4', H-6'); 8.92 (t, 1H, *J* = 1.8 Hz, H-2'); 9.14 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.4 CH_2); 123.7 C-2'); 127.4 (C-3, C-5); 129.3, 134.4 (C-4', C-6'); 129.4; 130.4 (C-2", C-3", C-5", C-6"); 130.7 (C-5'); 133.4 (C-1"); 133.9 (C-1'); 135.7 (C-4"); 147.2 (C-2, C-6); 148.7 (C-3'); 152.9 (C-4); 187.7 (COAr); 191.5 (COPh).

4-Benzoyl-1-[2-(4-nitrophenyl)-2-oxoethyl]-pyridinium bromide (**3e**). The product was recrystallized from methanol and colorless crystals with mp 253-5°C were obtained; Yield 86 %. Anal. Calcd. $C_{20}H_{15}BrN_2O_4$: N 6.56. Found N 6.68. FT-IR (cm^{-1}): 1669, 1699, 2848, 2948,.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.81 (s, 2H, CH_2); 7.57-7.63 (m, 2H, H-3", H-5"); 7.75-7.81 (m, 1H, H-4"); 7.84-7.88 (m, 2H, H-2", H-6"); 8.30, 8.35 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 8.32 (d, *J* = 6.8 Hz, H-3, H-5); 9.11 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.6 (CH_2); 124.6 (C-3', C-5'); 127.4 (C-3, C-5); 129.5; 130.1 (C-2", C-3", C-5", C-6"); 130.5 (C-2', C-6'); 133.4 (C-1"); 135.7 (C-4"); 137.7 (C-1'); 147.2 (C-2, C-6); 151.6 C-4'); 153.1 (C-4); 188.2 (COAr); 191.2 (COPh).

4-Benzoyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-pyridinium bromide (**3f**). The product was recrystallized from methanol and colorless crystals with mp 221-3°C were obtained; Yield 81 %. Anal. Calcd. $C_{21}H_{18}BrNO_3$: N 3.40. Found N 3.66. FT-IR (cm^{-1}): 1660, 1677, 2837, 2934.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 3.87 (s, 3H, MeO); 6.56 (s, 2H, CH_2); 6.97 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.53-7.58 (m, 2H, H-3", H-5"); 7.73-7.76 (m, 1H, H-4"); 7.81-7.84 (m, 2H, H-2", H-6"); 8.02 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 8.24 (d, *J* = 6.8 Hz, H-3, H-5); 9.03 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 56.0 (OMe); 67.6 (CH_2); 114.8 (C-3', C-5'); 127.3 (C-3, C-5); 125.5 (C-1'); 129.4; 130.5 (C-2", C-3", C-5", C-6");131.5 (C-2', C-6'); 133.6 (C-1"); 135.6 (C-4"); 147.3 (C-2, C-6); 152.7 (C-4); 165.8 (C-4'); 187.6 (COAr); 191.5 (COPh).

4-Benzoyl-1-[2-(4-cyanophenyl)-2-oxoethyl]-pyridinium bromide (**3g**). The product was recrystallized from methanol and colorless crystals with mp 259-261°C were obtained; Yield 86 %. Anal. Calcd. $C_{21}H_{15}BrN_2O_2$: N 6.88. Found N 7.04.

4-Benzoyl-1-[2-(2,4-dichlorophenyl)-2-oxoethyl]-pyridinium chloride (**3h**). The product was recrystallized from methanol and colorless crystals with mp 221-3°C were obtained; Yield 72 %. Anal. Calcd. $C_{20}H_{14}Cl_3NO_2$: N 3.44. Found N 3.61. FT-IR (cm^{-1}): 1670, 1692, 2839, 2949.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.49 (s, 2H, CH_2); 7.43 (dd, 1H, *J* = 8.5, 1.9 Hz, H-5'); 7.54 (d, 1H, *J* = 1.9 Hz, H-3'); 7.56-7.61 (m, 2H, H-3", H-5"); 7.74-7.79 (m, 1H, H-4"); 7.82-7.85 (m, 2H, H-2", H-6"); 7.90 (d, 1H, *J* = 8.5 Hz, H-6'); 8.30 (d, *J* = 6.8 Hz, H-3, H-5); 9.00 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 69.1 (CH_2); 127.3 (C-3, C-5); 129.3; 130.3 (C-2", C-3", C-5", C-6"); 128.1, 131.5, 132.3 (C-3', C-5', C-6'); 130.7, 134.0 (C-1', C-3'); 133.3 (C-1"); 135.6 (C-4"); 141.2 (C-4'); 147.0 (C-2, C-6); 152.9 (C-4); 188.6 (COAr); 191.1 (COPh).

General procedure for synthesis of 7-(4-benzoyl)-indolizines 6

5 Mmol of 4-benzoyl-pyridinium salt **3** suspended in 50 mL 1,2epoxypropane, 7 Mmol of ethyl propiolate were added and the mixture was stirred at room temperature for 20 days (with protection against moisture). The solvent was partly removed under reduced pressure, 8-10 mL of methanol were added under stirring, and the mixture was left over night at room temperature. The solid was filtered off, washed with a mixture of methanol-diethyl ether (1:2) and recrystallized from chloroform/diethyl ether.

3,7-Dibenzoyl-1-carboethoxy-indolizine (**6a**). Yellow crystals with mp 130-1°C were obtained; Yield 44 %. Anal. Calc. $C_{25}H_{19}NO_4$: C 75.55; H 4.82; N 3.52. Found C 75.86; H 6.07; N 3.79. FT-IR (cm^{-1}): 1617, 1654, 1704, 2976.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.1 Hz, Me); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 7.51-7.69 (m, 7H, H-6, H-3', H-4', H-5', H-3", H-4", H-5"); 7.83-7.90 (m, 5H, H-2, H-2', H-6', H-2", H-6"); 8.78 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.99 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.4 (CH_2); 109.4 (C-1); 114.5 (C-6); 122.6 (C-8); 123.7 (C-3); 128.5, 128.6, 129.0, 129.9 (C-2', C-3', C-5', C-6', C-2", C-3", C-5", C-6"); 128.8, 129.1 (C-2, C-5); 131.9 (C-4'); 133.0 (C-4"); 134.7, 136.6, 137.8 (C-7, C-8a, C-1"); 139.3 (C-1'); 163.6 (COO); 185.9 (COAr); 194.0 (COPh).

7-Benzoyl-1-carboethoxy-3-(4-chlorobenzoyl)-indolizine (**6b**). Yellow crystals with mp 207-8°C were obtained; Yield 57 %. Anal. Calcd. $C_{25}H_{18}ClNO_4$: C 69.53; H 4.20; Cl 8.21; N 3.24. Found C 69.87; H 4.61; Cl 8.52; N 3.51. FT-IR (cm^{-1}): 1628, 1660, 1701, 2985.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, *J* = 7.1 Hz, Me); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 7.51-7.59 (m, 5H, H-6, H-3', H-5', H-3", H-5"); 7.64-7.70 (m, 1H, H-4"); 7.81 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 7.85 (s, 1H, H-2); 7.87-7.90 (m, 2H, H-2", H-6"); 8.78 (dd, 1H, *J* = 2.0, 1.0, Hz, H-8); 9.96 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.5 (CH_2); 109.5 (C-1); 114.7 (C-6); 122.6 (C-8); 123.3 (C-3); 128.6, 128.7, 128.8 (C-2, C-5, C-2", C-3", C-5", C-6"); 128.9; 130.5 (C-2', C-3', C-5', C-6'); 133.0 (C-4"); 135.0, 136.5, 137.8 (C-7, C-8a, C-1"); 137.6, 138.0 (C-1', C-4"); 163.4 (COO); 184.5 (COAr); 194.0 (COPh).

7-Benzoyl-1-carboethoxy-3-(4-bromobenzoyl)-indolizine (**6c**).Yellow crystals with mp 211-2°C were obtained; Yield 55 %. Anal. Calcd. $C_{25}H_{18}BrNO_4$: C 63.04; H 3.81; Br 16.77; N 2.94. Found C 63.41; H 4.03; Br 17.04; N 3.25. FT-IR (cm^{-1}): 1627, 1660, 1701, 2984.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, *J* = 7.1 Hz, Me); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 7.52-7.59 (m, 3H, H-6, H-3", H-5"); 7.63-7.75 (m, 5H, H-4", H-2', H-3', H-5', H-6'); 7.85 (s, 1H, H-2); 7.86-7.90 (m, 2H, H-2", H-6"); 8.79 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.95 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.5 (CH_2); 109.6 (C-1); 114.7 (C-6); 122.6 (C-8); 123.3 (C-3); 126.8 (C-4'); 128.6, 129.9 (C-2", C-3", C-5", C-6"); 128.8, 128.9 (C-2, C-5); 130.6; 131.6 (C-2', C-3', C-5', C-6'); 133.1 (C-4"); 135.0, 136.5, 138.0 138.1 (C-7, C-8a, C-1', C-1"); 163.5 (COO); 184.6 (COAr); 194.0 (COPh).

7-Benzoyl-1-carbethoxy-(3-nitrobenzoyl)-indolizine (**6d**). Yellow crystals with mp 204-5°C were obtained; Yield 58 %. Anal. Calcd. $C_{25}H_{18}N_2O_6$: C 67.87; H 4.10; N 6.33. Found C 68.03; H 4.43; N 6.59. FT-IR (cm^{-1}): 1633, 1658, 1703, 2980.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.33 (t, 3H, *J* = 7.1 Hz, Me); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 7.54-7.59 (m, 2H, H-3", H-5"); 7.62 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.65-7.70 (m, 1H, H-4"); 7.76 (t, 1H, *J* = 7.9 Hz, H-5'); 7.84 (s, 1H, H-2); 7.88-7.93

(m, 2H, H-2", H-6"); 8.15-8.19 (m, 1H, H-6'); 8.45-8.49 (m, 2H, H-8, H-4'); 8.68 (t, 1H, *J* = 1.9 Hz, H-2'); 8.80 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.99 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.6 (CH_2); 110.0 (C-1); 114.7 (C-6); 122.6 (C-8); 123.5 (C-3); 123.7 (C-2'); 125.6 (C-4'); 128.6, 128.9 129.6, 129.9 (C-2, C-5, C-5', C-2", C-3", C-5", C-6"); 129.7 (C-5); 131.7 (C-2); 134.4 134.5 (C-6', C-4"); 135.3, 136.3, 139.4 (C-7, C-8a, C-1"); 140.8 (C-1'); 148.2 (C-3'); 163.2 (COO); 182.9 (COAr); 193.8 (COPh).

7-Benzoyl-1-carbethoxy-(4-nitrobenzoyl)-indolizine (**6e**). Yellow crystals with mp 233-5 °C were obtained; Yield 60 %. Anal. Calcd. $C_{25}H_{18}N_2O_6$: C 67.87; H 4.10; N 6.33. Found C 68.03; H 4.44; N 6.61. FT-IR (cm^{-1}): 1629, 1658, 1707, 2991.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.33 (t, 3H, *J* = 7.1 Hz, Me); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 7.58-7.63 (m, 2H, H-3", H-5"); 7.71 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.73-7.78 (m, 1H, H-4"); 7.89-7.92 (m, 2H, H-2", H-6"); 7.96 (s, 1H, H-2); 7.99 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 8.44 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 8.80 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 10.06 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 14.0 (Me); 62.2 (CH_2); 110.2 (C-1); 115.9 (C-6); 122.9 (C-8); 123.2 (C-3); 124.0 (C-3', C-5'); 128.9 (C-3", C-5"); 129.7 (C-5); 129.9 (C-2", C-6"); 131.7 (C-2); 130.3 (C-2', C-6'); 134.4 (C-4"); 135.3, 136.3, 139.1 (C-7, C-8a, C-1"); 143.4 (C-1'); 149.8 (C-4'); 165.0 (COO); 185.1 (COAr); 196.5 (COPh).

7-Benzoyl-1-carboethoxy-(4-methoxybenzoyl)-indolizine (**6f**). Yellow crystals with mp 137-9°C were obtained; Yield 46 %. Anal. Calcd. $C_{26}H_{21}NO_5$: C 73.06; H 4.95; N 3.28. Found C 73.34; H 5.26; N 3.44. FT-IR (cm^{-1}): 1625, 1655, 1700, 2984.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, *J* = 7.1 Hz, Me); 3.92 (s, 3H, MeO); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 7.04 (d, 2H, , *J* = 8.8, H-3', H-5'); 7.52-7.57 (m, 2H, H-3", H-5"); 7.62 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.63-7.68 (m, 1H, H-4"); 7.78-7.90 (m, 6H, H-2, H-6, H-2', H-6', H-2", H-6"); 8.76 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.89 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

7-Benzoyl-1-carboethoxy-(4-cyanobenzoyl)-indolizine (**6g**). Yellow crystals with mp 251-2°C were obtained; Yield 41 %. Anal. Calcd. $C_{26}H_{18}N_2O_4$: C 73.92; H 4.29; N 6.63. Found C 74.22; H 4.61; N 6.97.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.1 Hz, Me); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 7.53-7.59 (m, 2H, H-3", H-5"); 7.62 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.64-7.70 (m, 1H, H-4"); 7.82 (s, 1H, H-2); 7.88-7.93 (m, 6H, H-2', H-3', H-5', H-6', H-2", H-6");); 8.80 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 10.00 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.6 (CH_2); 110.0 (C-1); 115.1 (C-6); 115.3, 118.0 (CN, C-4'); 122.5 (C-8); 122.9 (C-3); 128.7 (C-3", C-5"), 128.9 (C-5);, 129.1 (C-2); 129.4, 132.4 (C-2', C-3', C-5', C-6'); 129.9 (C-2", C-6"); 133.2 (C-4"); 135.5, 136.4, 138.4 (C-7, C-8a, C-1"); 143.0 (C-1'); 163.3 (COO); 183.7 (COAr); 193.8 (COPh)

7-Benzoyl)-1-carboethoxy-3-(2,4-dichlorobenzoyl)-indolizine (**6h**).Yellow crystals with mp 182-4°C were obtained; Yield 45 %. Anal. Calcd. $C_{25}H_{17}Cl_2NO_4$: C 64.39; H 3.67; Cl 15.21; N 3.00. Found C 64.65; H 4.88; Cl 15.49; N 3.26. FT-IR (cm^{-1}): 1616, 1663, 1697, 2988.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.1 Hz, Me); 4.36 (q, 2H, *J* = 7.1 Hz, CH_2); 7.39-742 (m, 2H, H-H-3', H-5'); 7.52-7.56 (m, 3H, H-6', H-3", H-5"); 7.58 (s, 1H, H-2); 7.61 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.64-7.69 (m, 1H, H-4") 7.86-7.90 (m, 2H, H-2", H-6"); 8.78 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 10.03 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

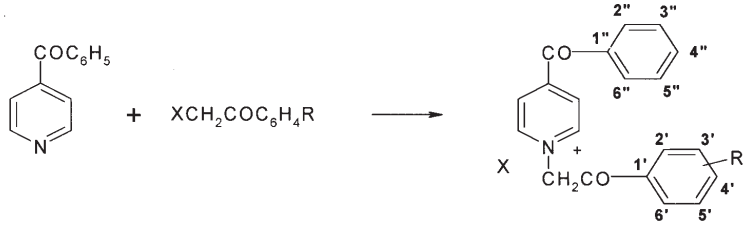
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3 (Me); 60.5 (CH_2); 110.1 (C-1); 115.2 (C-6); 122.5 (C-8); 123.5 (C-3); 126.8 (C-4'); 127.1; 130.0 130.3 (C-3', C-5', C-6'); 128.3 (C-6'); 128.7, 129.9 (C-2", C-3", C-5", C-6"); 129.0, 129.5 (C-2, C-5); 132.5 (C-2'); 133.1 (C-4"); 135.7, 136.5, 136.7, 137.2, 138.5 (C-7, C-8a, C-1', C-4', C-1"); 163.5 (COO); 184.6 (COAr); 194.0 (COPh).

Results and discussion

The indolizines **6** were obtained by 1,3-dipolar cycloaddition reactions between pyridinium *N*-ylides (generated *in situ* from the corresponding pyridinium salts **3**) and ethyl propiolate as electron deficient alkyne. The pyridinium salts **3** were prepared by *N*-alkylation of 4-benzoylpyridine **1** with the corresponding 2-bromoacetophenones **2** or 2-chloroacetophenone in the case of compound **3h** in methanol at reflux (scheme1).

The structure of the bromides **3** was confirmed by IR and NMR spectroscopy.

The IR spectra of the salts present the bands of the main functional groups as could be predicted. The two carbonyl groups are slightly shifted due to conjugation within aromatic system. The carbonyl group in the benzoyl radical



1 2 3

3a: R = H, X = Br; **3b**: R = 4-Cl, X = Br;; **3c**: R = 4-Br, X = Br; **3d**: R = 3-NO_2, X = Br; **3e**: R= 4-NO_2, X = Br; **3f**: R= 4-OMe, X = Br; **3g**: R = 4-CN, X = Br; **3h**: R = 2,4-Cl_2, X = Cl.

Scheme 1

Table 1

REPRESENTATIVE ^{1}H-NMR DATA FOR BROMIDES OF TYPE **3**

Compound	H-2	H-3	CH2N
1-(2-Phenyl-2-oxoethyl)-4-benzoyl-pyridinium bromide	9.02	8.31	6.62
1-(2-Phenyl-2-oxoethyl)-4-cyano-pyridinium bromide	9.07	8.39	6.57
1-(2-Phenyl-2-oxoethyl)-4-(4-nitrobenzyl)-pyridinium bromide	8.71	7.88	6.39
1-(2-Phenyl-2-oxoethyl)-4-benzyl-pyridinium bromide	8.58	7.80	6.35

Table 2
REPRESENTATIVE ^{13}C-NMR DATA FOR BROMIDES OF TYPE **3**

Compound	C-2	C-3	C-4	CH_2N
1-(2-Phenyl-2-oxoethyl)-4-benzoyl-pyridinium bromide	**147.2**	**127.3**	**152.7**	**67.3**
1-(2-Phenyl-2-oxoethyl)-4-(4-nitrobenzyl)-pyridinium bromide	145.7	128.0	161.0	66.1
1-(2-Phenyl-2-oxoethyl)-4-benzyl-pyridinium bromide	145.4	128.1	163.4	66.2
1-(2-Phenyl-2-oxoethyl)-4-*tert*-butyl-pyridinium bromide	145.6	125.5	173.4	66.3

attached to pyridine (PhCOPy) ring presents a strong band at about 1660-1670 cm^{-1}. The band of the carbonyl group in the aroyl moiety (CH_2COAr radical) appears between 1677 cm^{-1} and 1699 cm^{-1} due to various substituent influences. The two methylene strech bands could be observed at about 2840 cm^{-1} and 2950 cm^{-1}. The presence of the two bands together or only one of them might be influenced by the substituents in the aroyl moiety. In the case of *para*-substituted aroyl moieties the bands at 2840 cm^{-1} present higher absorbances. The IR spectra of the salts are similar down the series.

From the ^{1}H-NMR spectra of the bromides can be depicted that the methylene protons neighbouring the quaternary nitrogen atom appear as a singlet (δ = 6.35-6.53 ppm). The signals of these protons appear deshielded due to the contribution of both quaternary nitrogen atom and the carbonyl group. The pyridine protons ring appears as doublet of doublets H-3, H-5 ($\delta \approx 8.31$ ppm) and H-2, H-6 ($\delta \approx 9.02$ ppm) with a coupling of $^3J_{H2H3}$ = 6.8 Hz. The chemical shifts of these protons as compared with previously reported pyridinium bromides make these compounds more similar to the 4-cyano substituted bromides [6b]. Some differences can be noted in previous literature data, where both 4-benzyl and 4-nitrobenzyl group, respectively, have a opposite influence on the ^{1}H-NMR signals [6]. In these compounds the methylene group linked to the quaternary nitrogen atom is more shielded (δ = 6.35-6.39 ppm), and also the protons from the pyridinium ring appear shielded by about 0.5 ppm (table 1).

The protons from the two benzene moieties appear in aromatic region and were assigned by COSY and HETCOR experiments. These signals appear in normal limits for these types of compounds.

The ^{13}C-NMR spectra present all the expected signals. Due to the influence of the quaternary nitrogen atom, both α and γ carbons from the pyridinic ring are more deshielded ($\delta \approx$ 147.2 ppm) than the β carbons ($\delta \approx$127.3 ppm). The C-4 carbon appears much shielded as compared with previously described pyridinium bromides with about 10-20 ppm, fact which might have as explanation the influence of the keto group. The methylene carbon attached to the quaternary nitrogen atom is slightly deshielded with about 1.3 ppm but this is insignificant as compared with similar compounds described previously [6].

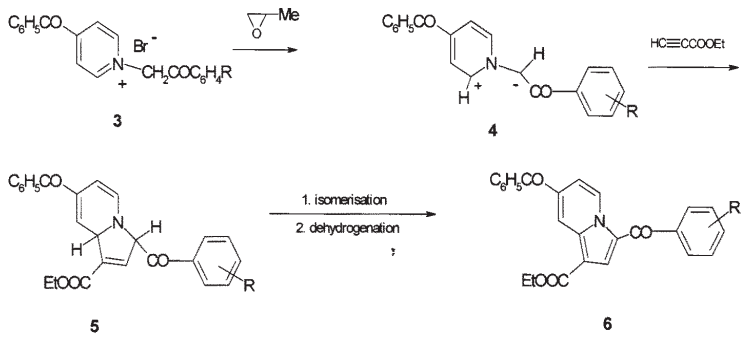
The aliphatic methylene carbon appears at ca. 67 ppm while the two carbons in the keto groups appear at 191.7 ppm (COPh) and 189.4 ppm (COAr) this being more shielded due to various electronic effects. The carbon atoms in the aromatic moieties are assigned by 2D experiments such as HETCOR.

Carbanion monosubstituted pyridinium *N*-ylides are usually unstable compounds, and therefore, are generated *in situ* by various methods, such as the treatment of the pyridinium salts with triethylamine in organic solvents or with an aqueous solution of an inorganic base. A different method for the *in situ* generation of *N*-ylides consists in the use of epoxides as reaction medium [6]. While in the first case the *N*-ylide generation mechanism is direct, consisting of the deprotonation of the pyridinium salt by the base, the reaction performed in epoxides has an indirect mechanism including as a first step the formation of the alkoxide due to the attack of the bromide ion onto the oxirane ring, subsequently followed by the ring opening. The second step consists in the actual deprotonation of the pyridinium salts by the alkoxide, thus, generating the *N*-ylides. The indirect epoxide method is very practical because all the reaction sequences (generation of *N*-ylide, cycloaddition, rearrangement and aromatization) take place one pot to the indolizines formation.

By treatment of the pyridinium bromides **3** with ethyl propiolate as dipolarophile, in an epoxide medium, the compounds **6** were obtained in moderate yields (scheme 2).

The structure of cycloadducts **6** was assigned by elemental analysis, FT-IR and NMR spectroscopy.

The IR spectra of the cycloadducts are interesting mainly because *via* the 1,3-dipolar cycloaddition reaction in presence of ethyl propiolate another carbonyl group is inserted to the aromatic system by means of an ester group.



6a: R = H; **6b**: R = 4-Cl; **6c**: R = 4-Br; **6d**: R = 3-NO_2; **6e**: R = 4-NO_2; **6f**: R = 4-**OMe; 6g**: R = 4-CN; **6h**: R = 2,4-Cl_2

Scheme 2

The carbonyl group in the benzoyl moiety presents its strong band at approximately 1660 cm^{-1} while the carbonyl group of the ester moiety is observed as a strong band at around 1700 cm^{-1} The interesting fact to be observed is that the carbonyl group in the aroyl moiety is found to be at a low wavenumber than in the salts, 1628-1633 cm^{-1}. This might be explained by observation that in the bromine (**3a-g**) or chlorine (**3h**) salts the keto group is directly bonded to an aliphatic radical while in the indolizines **6** is directly bonded to the aromatic system which implies a certain degree of conjugation. The aliphatic C-H stretch band can be observed at about 2985 cm^{-1}. The IR region between the fingerprint region and 1600 cm^{-1} is similar along the series with differences given by the various substitutions on the aroyl benzene ring.

The NMR chemical shifts for hydrogen and carbon atoms were established based on multiplicity and magnitude of the coupling constants, as well as by HH-COSY and HETCOR experiments.

The three protons attached to the pyridinic ring appear as doublet of doublets having the coupling constants $^3J_{5,6}$ = 7.2 Hz, $^4J_{6,8}$ = 1.9 Hz and $^5J_{5,8}$ = 1.0 Hz. The H-5 proton appears to be the most deshielded (δ = 9.95-10.06 ppm) in all the cycloadducts, due to its proximity to the nitrogen atom and to the spatial influence with the carbonyl group from the phenacyl moiety. The H-8 proton (δ = 8.78-8.80 ppm) appears also deshielded due to the vicinity of the groups 7-benzoyl and carboethoxy. The chemical shifts for proton H-6 is in the range δ = 6.62-6.71 ppm. Based on this assessment for the chemical shifts of the pyridine ring protons in the new synthesized indolizines one can conclude that the spectra of presented compounds are in agreement with already presented indolizines, the only differences being due to various substitutions [6]. The proton H-2 ($\delta \approx$ 7.98 ppm) appears as a sharp singlet, deshielded due to the contribution of both phenacyl and the carboethoxy group attached at C-1. The protons in the carboethoxy group linked to the carbon C-1 appear in normal limits and multiplicity.

The ^{13}C-NMR presents all the predicted signals. At a first look it can be observed that by using the ethyl propiolate as dipolarophile a new keto group is added to the system and this is very easily noticed. The three carbons in the keto groups are assigned as follows:$\delta \approx$ 163.5 (COO); $\delta \approx$ 184.6 (COAr); $\delta \approx$ 194.0 (COPh). The carbonyl group in the benzoyl moiety attached at the carbon C-7 appears slightly deshielded than in bromides. The deshielding is not significant but might induce the supposition that the quaternary nitrogen atom had some influence on this group. The methyl and methylene groups appear in normal limits at about 14.3 ppm and 60.5 ppm respectively.

The pyridinic carbon atoms present known chemical shifts as compared with previously presented 7-substituted indolizines [6]. The C-1 chemical shifts present the expected values for such compounds (about 109.0-110.0 ppm). The atoms C-6 and C-8 appear slightly shielded due to β position in respect with the nitrogen atom. The C-8 carbon is more deshielded than C-6 because of the spatial influence of the neighbouring keto group. The C-7 carbon atom appears deshielded due to the influence of the benzoyl group and also C-8a appears in a similar range due to its α position in respect with the pyridine nitrogen. The C-2 carbon atom in the pyrrole ring appears at δ = 128.4-131.1 ppm, normal values for such type of compounds. The chemical shifts of the carbon atoms in the two benzoyl moieties appear in the expected ranges, in accordance with the various substitutions.

Conclusions

Eight new 7-substituted indolizines **6a-h** were obtained by 1,3-dipolar cycloadditions of pyridinium *N*-ylides to the non-symmetrical acetylenic dipolarophile, ethyl propiolate. The title compounds were obtained in epoxypropane, used both as reaction media and as an agent for ylide generation from pyridium salts **3**. The new indolizine based compounds were purified by recrystallization from methanol/chloroform and characterized by elemental analysis and IR and NMR spectroscopy.

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