Dedicated to Prof. P.T. Frangopol on the occasion of his 75th anniversary

New Substituted Indolizines by 1,3-Dipolar Cycloaddition
VI. 7-(4-Nitrobenzyl)indolizines

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*New indolizine derivatives **6** and **7** containing a 4-nitrobenzyl group attached to the pyridinic ring are obtained by the reaction of N-phenacylpyridinium bromides **3** with 3-butyn-2-one, methyl and ethyl propiolate in 1,2 epoxypropane 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 quite common in nature, mainly as alkaloids, and benefit from considerable attention due to their potential applications as pharmaceuticals. Moreover, the high degree of cojugation of their aromatic system generates intense optical properties, that make indolizine and azaindolizine systems [1-4] valuable spectral sensitizers or even dyes. By attaching different substituents on this relatively simple system the fluorescence quantum yield may be variated and, on the other side the bioavailability of the therapeutic agents based on such type of derivatives may be increased.

Furthermore, indolizines substituted at the 7 position may be used as highly selective chemosensors when attached to a cyclodextrin moiety [4].

The molecular construction of such substituted indolizines can be achieved by numerous synthetic routes. One of the simplest, yet most versatile method is the 1,3-dipolar cycloaddition of pyridinium *N*-ylides to activated alkynes or alkenes [5].

The synthesis of new functionalized indolizines, containing a 4-nitrobenzyl group attached to the pyridine ring, hereby presented, is carried out by 1,3-dipolar cycloaddition reactions of pyridinium *N*-ylides to acetylenic non-symmetrical dipolarofiles: 3-butyn-2-one, methyl and ethyl propiolate. By introducing the 4-nitrobenzyl substituent on the pyridine ring and by varying the substituents on the pyrrole moiety, it may be possible to obtain a finer tuning of the optical 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 and 75 MHz for ^{13}C. Supplementary evidence was given by HETCOR and COSY experiments.

General procedure for synthesis of 4-(4-nitrobenzyl)-pyridinium bromides 3

10 Mmol 4-(4-nitrobenzyl)-pyridine and 10 mmol phenacyl bromide 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.

1-(2-Phenyl-2-oxoethyl)-4-*(4*-nitrobenzyl)-pyridinium bromide (**3a**). The product was recrystallized from methanol and light yellow crystals with mp 233-5°C were obtained; Yield 98 %. Anal. Calcd. $C_{20}H_{17}BrN_2O_3$: N 6.78. Found N 7.03.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.44 (s, 2H, CH_2Ph); 6.39 (s, 2H, NCH_2); 7.44 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.48-7.53 (m, 2H, H-3', H-5'); 7.65-7.70 (m, 1H, H-4'); 7.88 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 7.99-8.01 (m, 2H, H-2', H-6'); 8.19 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.71 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 41.0 (CH_2Ph); 66.1 (NCH_2); 124.5 (C-3", C-5"); 128.0 (C-3, C-5); 128.4, 129.2 (C-2', C-3', C-5', C-6'); 130.4 (C-2", C-6"); 132.6 (C-1'); 135.5 (C-4'); 142.8 (C-1"); 145.7 (C-2, C-6); 147.4 (C-4"); 161.0 (C-4); 189.4 (COAr).

1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3b**). The product was recrystallized from methanol and light yellow crystals with mp 263-5°C were obtained; Yield 87 %. Anal. Calcd. $C_{20}H_{16}BrFN_2O_3$: N 6.50. Found N 6.77.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.45 (s, 2H, CH_2Ph); 6.37 (s, 2H, NCH_2); 7.21 (t, 2H, *J* = 8.6 Hz, H-3', H-5'); 7.45 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.87 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.08 (dd, 2H, *J* = 8.6, 5.2 Hz, H-2', H-6'); 8.23 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.67 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3c**). The product was recrystallized from methanol and yellow crystals with mp 276-7°C were obtained; Yield 89 %. Anal. Calcd. $C_{20}H_{16}BrClN_2O_3$: N 6.26. Found N 6.43.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.45 (s, 2H, CH_2Ph); 6.37 (s, 2H, NCH_2); 7.45 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.51 (d, 2H, *J* = 8.7 Hz, H-3', H-5'); 7.87 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 7.98 (d, 2H, *J* = 8.7 Hz, H-2', H-6'); 8.23 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.68 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3d**). The product was recrystallized from methanol and light yellow crystals with mp 282-4°C were obtained; Yield 93 %. Anal. Calcd. $C_{20}H_{16}Br_2N_2O_3$: N 5.69. Found N 5.87.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.76 (s, 2H, CH_2Ph); 6.35 (s, 2H, NCH_2); 7.45 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.72, 7.85 (2d, 4H, *J* = 8.5 Hz, H-2', H-3', H-5', H-6'); 7.88 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.27 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.64 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

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1-[2-(3-Nitrophenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3e**). The product was recrystallized from methanol and light yellow crystals with mp 216-8°C were obtained; Yield 88 %. Anal. Calcd. $C_{20}H_{16}BrN_3O_5$: N 9.17. Found N 9.35.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.49 (s, 2H, CH_2Ph); 6.54 (s, 2H, NCH_2); 7.53 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.80 (t, 1H, *J* = 8.1 Hz, H-5'); 7.95 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.28 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.40-8.43, 8.51-8.55 (2m, 2H, H-4', H-6'); 8.71 (d, 2H, *J* = 6.7 Hz, H-2, H-6). 8.87 (t, 1H, *J* = 1.8 Hz, H-2').

1-[2-(4-Nitrophenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3f**). The product was recrystallized from methanol and yellow crystals with mp 264-6°C were obtained; Yield 92 %. Anal. Calcd. $C_{20}H_{16}BrN_3O_5$: N 9.17. Found N 9.32.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.53 (s, 2H, CH_2Ph); 6.49 (s, 2H, NCH_2); 7.53 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.95 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.29, 8.32 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 8.41 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.72 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-4-(4-nitrobenzyl)-pyridinium bromide (**3g**). The product was recrystallized from methanol/diethylether and colorless crystals with mp 250-252°C were obtained; Yield 90 %. Anal. Calcd. $C_{21}H_{19}BrN_2O_4$: N 6.32. Found N 6.51.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 3.93 (s, 3H, MeO); 4.45 (s, 2H, CH_2Ph); 6.35 (s, 2H, NCH_2); 7.04 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 7.46 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.83 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.03 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 8.28 (d, 2H, *J* = 8.8 Hz, H-3", H 5"); 8.63 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

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

5 Mmol of 4-(4-nitrobenzyl)-pyridinium bromide **3** were suspended in 50 mL 1,2 epoxypropane, 7 Mmol of acetylenic dipolarophyle (1-butyn-3-one or methyl or 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.

1-Acetyl-3-benzoyl-7-(4-nitrobenzyl)-indolizine (**6a**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 198-9°C were obtained; Yield 35 %. Anal. Calcd. $C_{24}H_{18}N_2O_4$: C 72.35; H 4.55; N 7.03. Found 72.67; H 4.79; N 7.24. IR (cm^{-1}) : 1710; 1615; 1521; 1477; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, MeCO); 4.22 (s, 2H, CH_2Ph); 6.93 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.52-7.61 (m, 3H, H-3', H-4', H-5'); 7.69 (s, 1H, H-2); 7.80-7.83 (m, 1H, H-2', H-6'); 8.18 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.55 (d d, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.88 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

1-Acetyl-3-(4-fluorobenzoyl)-7-(4-nitrobenzyl)-indolizine (**6b**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 197-9°C were obtained; Yield 38 %. Anal. Calcd. $C_{24}H_{17}FN_2O_4$: N 6.73. Found N 6.95. IR (cm^{-1}) : 1650; 1611; 1519; 1475; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.53 (s, 3H, MeCO); 4.23 (s, 2H, CH_2Ph); 6.95 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.23 (t, 2H, *J* = 8.7 Hz, H-3', H-5'); 7.42 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.67 (s, 1H, H-2); 7.86 (dd, 2H, *J* = 8.7, 5.4 Hz, H-2', H-6'); 8.20 (d, 2H, *J* = 8.8 Hz, H-3", H 5"); 8.57 (d d, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.85 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.4 (CH_2Ph); 114.6 (C-1); 115.5 (d, *J* = 21.9 Hz, C-3', C-5'); 117.4 (C-6); 119.8 (C-8); 122.1 (C-3); 124.0 (C-3", C-5"); 128.8 (C-2); 129.2 (C-5); 129.8 (C-2", C-6"); 131.2 (d, *J* = 9.0 Hz, C-2', C-6'); 135.9 (d, *J* = 3.0 Hz, C-1'); 139.6 (C-8a); 141.3, 146.4, 147.0 (C-7, C-1", C-4"); 164.9 (d, *J* = 253.5 Hz, C-4'); 183.9 (COAr); 193.1 (COMe).

1-Acetyl-3-(4-chlorobenzoyl)-7-(4-nitrobenzyl)-indolizine (**6c**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 211-3°C were obtained; Yield 43 %. Anal. Calcd. $C_{24}H_{17}ClN_2O_4$: C 66.59; H 3.96; Cl 8.19; N 6.47. Found C 66.87; H 4.22; Cl 8.43; N 6.61. IR (cm^{-1}) : 1650; 1610; 1515; 1474; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.52 (s, 3H, MeCO); 4.22 (s, 2H, CH_2Ph); 6.94 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.52 (d, 2H, *J* = 8.4 Hz, H-3', H-5'); 7.66 (s, 1H, H-2); 7.76 (d, 2H, *J* = 8.4 Hz, H-2', H-6'); 8.19 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.56 (d d, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.86 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.4 (CH_2Ph); 114.7 (C-1); 117.5 (C-6); 119.7 (C-8); 122.0 (C-3); 124.0 (C-3", C-5"); 128.8, 130.2 (C-2', C-3', C-5', C-6'); 128.9 (C-2); 129.2 (C-5); 129.8 (C-2", C-6"); 138.0, 138.1, 141.5, 146.3, 147.0 (C-7, C-1', C-4', C-1", C-4"); 139.6 (C-8a); 184.0 (COAr); 193.1 (COMe).

1-Acetyl-3-(4-bromobenzoyl)-7-(4-nitrobenzyl)-indolizine (**6d**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 207-9°C were obtained; Yield 41 %. Anal. Calcd. $C_{24}H_{17}BrN_2O_4$: C 60.39; H 3.59; Br 16.74; N 5.87. Found C 60.67; H 3.90; Br 17.11; N 6.14. IR (cm^{-1}) : 1651; 1607; 1516; 1474; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.53 (s, 3H, MeCO); 4.31 (s, 2H, CH_2Ph); 6.98 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.45 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.65, 7.75 (2d, 4H, *J* = 8.5 Hz, H-2', H 3', H-5', H-6'); 7.84 (s, 1H, H-2); 8.23 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.59 (dd, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.88 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

1-Acetyl-3-(3-nitrobenzoyl)-7-(4-nitrobenzyl)-indolizine (**6e**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 221-3°C were obtained; Yield 61 %. Anal. Calcd. $C_{24}H_{17}N_3O_6$: C 65.01; H 3.86; N 9.48. Found C 65.30; H 4.13; N 9.71. IR (cm^{-1}) : 1715; 1614; 1517; 1477; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.65 (s, 3H, MeCO); 4.33 (s, 2H, CH_2Ph); 7.20 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.46 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.82 (s, 1H, H-2); 7.83 (t, 1H, *J* = 7.8 Hz, H-5'); 8.23 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.11-8.14, 8.49-8.54 (2m, 2H, H-4', H-6'); 8.60-8.62 (m, 2H, H-8, H-2'); 9.98 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

1-Acetyl-3-(4-nitrobenzoyl)-7-(4-nitrobenzyl)-indolizine (**6f**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 241-2°C were obtained; Yield 75 %. Anal. Calcd. $C_{24}H_{17}N_3O_6$: C 65.01; H 3.86; N 9.48. Found C 65.28; H 4.09; N 9.65. IR (cm^{-1}) : 1669; 1616; 1512; 1478; 1343.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 2.66 (s, 3H, MeCO); 4.35 (s, 2H, CH_2Ph); 7.25 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.47 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.82 (s, 1H, H-2); 7.96 (d, 2H, *J* = 8.7 Hz, H-2', H-6'); 8.25 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.47 (d, 2H, *J* = 8.7 Hz, H-3', H-5'); 8.62 (d d, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.95 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 26.2 (MeCO); 41.5 (CH_2Ph); 115.3 (C-1); 120.0 (C-6); 120.5 (C-8); 122.8 (C-3); 124.3 (C-3", C-5"); 124.5 (C-3', C-5'); 129.9 (C-2", C-6"); 130.3 (C-2', C-6'); 130.8 (C-2); 133.8 (C-5); 141.9, 143.7, 145.2, 146.4, 147.1 (C-7, C-8a, C-1', C-1", C-4");); 150.0 (C-4'); 185.2 (COAr); 198.1 (COMe).

1-Acetyl-3-(4-methoxybenzoyl)-7-(4-nitrobenzyl)-indolizine (**6g**). The product was recrystallized from

methanol/chloroform and yellow crystals with mp 155-6°C were obtained; Yield 56 %. Anal. Calcd. $C_{25}H_{20}N_2O_5$: C 70.09; H 4.71; N 6.54. Found C 70.35; H 5.04; N 6.71. IR (cm^{-1}) : 1650; 1611; 1517; 1477; 1346.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.52 (s, 3H, MeCO); 3.92 (s, 3H, MeO); 4.21 (s, 2H, CH_2Ph); 6.89 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.04 (d, 2H, *J* = 8.6 Hz, H-3', H-5'); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.69 (s, 1H, H-2); 7.82 (d, 2H, *J* = 8.6 Hz, H-2', H-6'); 8.19 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.54 (d d, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.81 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.4 (CH_2Ph); 55.5 (MeO); 113.9 (C-3', C-5'); 114.3 (C-1); 117.1 (C-6); 119.7 (C-8); 122.4 (C-3); 124.1 (C-3", C-5"); 128.4 (C-2); 129.1 (C-5); 129.8 (C-2", C-6"); 131.1 (C-2', C-6'); 132.2 (C-1'); 139.3 (C-8a); 140.8, 146.5, 147.1 (C 7, C-1", C-4"); 162.7 (C-4'); 184.5 (COAr); 193.2 (COMe).

Methyl 3-(4-chlorobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7a**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 179-181°C were obtained; Yield 58 %. Anal. Calcd. $C_{24}H_{17}ClN_2O_5$: C 64.22; H 3.82; Cl 7.90; N 6.24. Found 64.57; H 4.13; Cl 8.27; N 6.49.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, MeO); 4.21 (s, 2H, CH_2Ph); 6.89 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.50 (d, 2H, *J* = 8.4 Hz, H-3', H-5'); 7.76 (s, 1H, H-2); 7.77 (d, 2H, *J* = 8.4 Hz, H-2', H-6'); 8.19 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.27 (d d, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.85 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

Methyl 3-(4-bromobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7b**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 204-6 °C were obtained; Yield 65 %. Anal. Calcd. $C_{24}H_{17}BrN_2O_5$: C 58.43; H 3.47; Br 16.20; N 5.68. Found C 58.77; H 3.70; Br 16.51; N 5.93.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, MeO); 4.21 (s, 2H, CH_2Ph); 6.88 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.67 (s, 4H, H-2', H-3', H-5', H-6'); 7.76 (s, 1H, H-2); 8.20 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.28 (dd, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.86 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

Methyl 3-(4-nitrobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7c**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 181-2 °C were obtained; Yield 60 %. Anal. Calcd. $C_{24}H_{17}N_3O_7$: C 62.57; H 3.73; N 9.15. Found C 62.81; H 3.98; N 9.41.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, MeO); 4.21 (s, 2H, CH_2Ph); 6.92 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.42 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.82 (s, 1H, H-2); 7.94 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.21 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.28 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 8.38 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 9.90 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

Ethyl 3-(4-chlorobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7d**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 173-5 °C were obtained; Yield 57 %. Anal. Calcd. $C_{25}H_{19}ClN_2O_5$: C 64.87; H 4.14; Cl 7.66; N 6.05. Found C 65.11; H 4.29; Cl 7.98; N 6.41.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, 3H, *J* = 7.1 Hz, Me); 4.21 (s, 2H, CH_2Ph); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 6.89 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.42 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.50 (d, 2H, *J* = 8.4 Hz, H-3', H-5'); 7.71 (s, 1H, H-2); 7.77 (d, 2H, *J* = 8.4 Hz, H-2', H-6'); 8.19 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.25 (d d, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.85 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

Ethyl 3-(4-bromobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7e**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 179-181°C were obtained; Yield 58 %. Anal. Calcd. $C_{25}H_{19}BrN_2O_5$: C 59.19; H 3.47; Br 15.75; N 5.52. Found C 59.47; H 3.69; Br 16.11; N 5.70.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, 3H, *J* = 7.1 Hz, Me); 4.21 (s, 2H, CH_2Ph); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 6.88 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.41 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.67, 7.68 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 7.75 (s, 1H, H-2); 8.20 (d, 2H, *J* = 8.8 Hz, H-3", H-5"); 8.27 (dd, 1H, *J* = 2.0, 0.8 Hz, H-8); 9.85 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

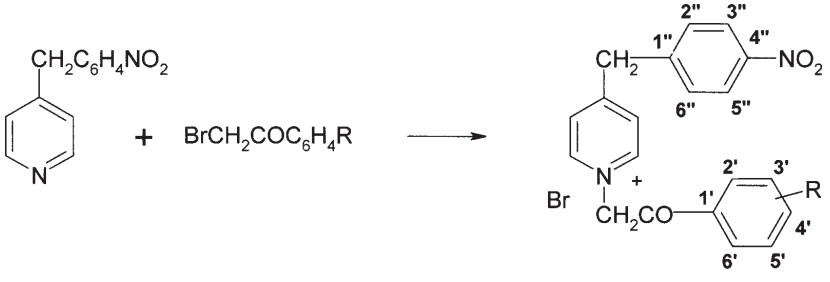
Ethyl 3-(4-nitrobenzoyl)-7-(4-nitrobenzyl)-indolizine-1-carboxylate (**7f**). The product was recrystallized from methanol/chloroform and yellow crystals with mp 238-240°C were obtained; Yield 60 %. Anal. Calcd. $C_{25}H_{19}N_3O_7$: C 63.42; H 4.05; N 8.88. Found C 63.70; H 4.27; N 9.13.

^{1}H-NMR (300 MHz, $CDCl_3$+TFA)δ: 1.36 (t, 3H, *J* = 7.1 Hz, Me); 4.23 (s, 2H, CH_2Ph); 4.35 (q, 2H, *J* = 7.1 Hz, CH_2); 6.95 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.42 (d, 2H, *J* = 8.8 Hz, H-2", H-6"); 7.71 (s, 1H, H-2); 7.94 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.21 (d, 2H, *J* = 8.8 Hz, H-3", H 5"); 8.27 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 8.38 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 9.90 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

Results and discussion

The indolizines **6** and **7** were obtained by 1,3-dipolar cycloaddition reactions between pyridinium *N*-ylides (generated *in situ* from the corresponding pyridinium salts) and electron deficient alkynes. The pyridinium bromides **3** were prepared by *N*-alkylation of 4 nitrobenzylpyridine **1** with the corresponding 2-bromoacetophenones **2** in methanol at reflux (scheme1).

The structure of the bromides **3** was confirmed by ^{1}H-NMR spectra, which present all the predictable signals. The methylene protons appear as a singlet, each of them being influenced by the neighboring groups as follows: the methylene linked to the benzyl moiety is more shielded (δ = 4.45-4.50 ppm) than the methylene linked to the quaternary nitrogen atom and the carbonyl group (δ = 6.35-6.53 ppm). The nitro group grafted on the benzyl moiety has no significant influence on the ^{1}H-NMR signals of the pyridinic protons as compared with previously presented 4-benzyl substituted pyridinium bromides (table 1). Some differences can be noted in comparison with 4-benzoyl and 4-cyano substituted pyridinium bromides described in



1 2 3

Scheme 1

Table 1

REPRESENTATIVE ^{13}H-NMR DATA FOR BROMIDES OF TYPE **3**

Compound	H-2	H-3	CH2N
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
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

previous literature data, where both benzoyl and cyano group, respectively, have a divergent influence on the ^{1}H-NMR signals. In these compounds the methylene group linked to the quaternary nitrogen atom is more deshielded (δ = 6.60-6.88 ppm), and also the protons from the pyridinium ring are deshielded by about 0.5 ppm (table 1).

The protons from the nitrobenzyl moiety appear as two doublets with the coupling constant J = 8.8 Hz. The *ortho* protons with respect to the nitro group are deshielded (δ = 8.23 ppm) with approximately 0.7-0.8 ppm due to influence of the nitro group as compared with the *meta* protons (δ= 7.45 ppm).

The ^{13}C-NMR spectrum was recorded for the bromide **3a**, the representative compound in the series, and compared with similar compounds. The spectrum presents all the expected signals. Due to the influence of the quaternary nitrogen atom, the α and γ carbons from the pyridinic ring are more deshielded (δ = 145.7 ppm) than the beta carbons (δ = 128.0 ppm). The effect of the 4-nitrobenzyl group is similar to that of the 4-benzyl and the 4-*tert*-butyl group [6c], with the only significant difference at C-4, which appears with around 10 ppm more deshilded in the case of the *tert*-butyl substitution. (table 2).

The geminal (δ = 147.4 ppm for C-4") and the *para* (δ = 142.8 for C-1") aromatic carbon atoms from the 4-nitrobenzyl radical are strongly deshielded by the nitro group, while the carbon atoms from the benzoyl moieties present normal limits for the chemical shifts of such type of compounds.

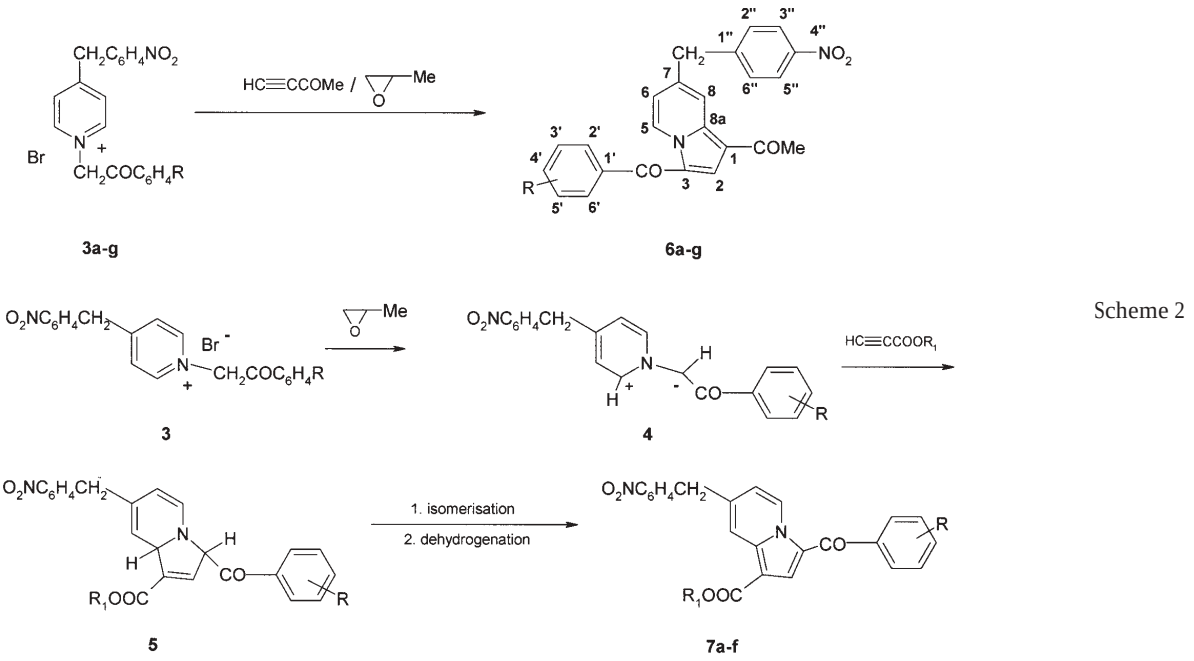
The carbon atoms of the two methylene groups are assigned in respect of the influence of the neighbouring groups at δ = 41.0 ppm for the methylene group linked to the 4 nitrobenzyl moiety and the more deshielded methylene group appears at 66.1 ppm due to the influence of the quaternary nitrogen atom and the ketone group.

Carbanion monosubstituted pyridinium *N*-ylides are typically unstable compounds, and are usually 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. Another method for the *in situ* generation of *N*-ylides consists in the use of epoxides as the 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 consisting in the first step in the

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-(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



Scheme 2

6a: R = H; **6b**: R = 4-F; **6c**: R = 4-Cl; **6d**: R= 4-Br; **6e**: R= 3-NO_2; **6f**: R= 4-NO_2; **6g**: R= 4-OMe; **7**: R_1= Me; **7a**: R =4-Cl; **7b**: R = 4-Br; **7c**: R = 4-NO_2; R_1= Et; **7d**: R = 4-Cl; **7e**: R = 4-Br; **7f**: R = 4-NO_2

formation of the alkoxide due to the attack of the bromide ion onto the oxirane ring, subsequently followed by the ring opening. The alkoxide, consecutively, performs the actual deprotonation of the pyridinium salts generating the *N*-ylides. The indirect epoxide method is very practical due to the advantage of using it as an one-pot, multi-step sequences of reactions, with the salt formation taking place in the same pot as the *N*-ylide generation and the consecutive 1,3 dipolar cycloaddition.

By treating the pyridinium bromides **3** with 3-butyn-2-one, methyl and ethyl propiolate as acetylenic dipolarophiles in an epoxide medium, the compounds **6** and **7** were obtained in moderate yields (scheme 2).

The structure of cycloadducts **6** and **7** was assigned by elemental analysis, FT-IR and NMR spectroscopy.

The IR spectra were recorded only for the 1-acetyl substituted indolizines, considered representative for the series, in order to highlight the presence of the main functional groups. The carbonyl groups in the compounds **6** are affected by conjugation within the system and present signals at a smaller wavelengths than the usually values for carbonyl containing compounds.

The carbonyl group in the acetyl moiety is found to be at 1629-1631 cm^{-1}. The carbonyl group in the benzoyl moiety is found at 1649-1669 cm^{-1} as an effect of the *para* electron withdrawing substituents. The IR spectra of the unsubstituted **6a** and 3-nitro-substituted **6e** present the similar bands at about 1710 and 1715 cm^{-1}, fact which may bring on the conclusion that the carbonyl group in the benzoyl moiety is affected by various substitutions of the aromatic ring while the carbonyl group in the acetyl moiety remains unaffected down the series.

At about 1514-1521 cm^{-1} the asymmetric N-O stretch in NO_2 can be observed as a very strong band. In the compounds **6a** and **6e** this band appears slightly weakened. The symmetric N-O stretch is observed as a very strong band at about 1343-1346 cm^{-1}.

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 observations.

The NMR spectra of the cycloadducts present all the anticipated signals. The ^{1}H-NMR spectra of the compounds **6** and **7** are in agreement with previously described indolizines. 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 $^5J_{5,8}$ = 0.8 Hz, in the case of the indolizines **6**. The *para* coupling constant between H-5 and H-8 is found to be increased at 1.0 Hz in the case of cycloadducts **7**, fact which might be explained by the influence of the substituent attached at C-1 in the pyridine ring. Due to conjugation the carbomethoxy or carboethoxy groups attached at C-1 in indolizines **6** might influence the increasing of the coupling constant in contrast with the acetyl groups, which present a weaker influence. The H-5 proton appears to be the most deshielded (δ = 9.80-9.95 ppm) in all the cycloadducts, due to its proximity to the nitrogen atom and to the spatial interaction with the carbonyl group from the phenacyl moiety. No dissimilarities in the chemical shifts of the H-5 can be noted between the compounds **6** and **7**. The H-8 proton appears also deshielded due to the proximity of the acetyl (δ = 8.54-8.62 ppm), carbomethoxy or carboethoxy groups (δ= 8.20-8.27 ppm). An important difference in the chemical shifts of H-8 may be noted, due to different substitutions in the case of compounds **6** and **7**. The chemical shifts of proton H-6 (δ= 6.88-6.95 ppm) appear at expected values. Based on this assessment for the chemical shifts of the pyridine ring protons in the new synthesized indolizines, one can conclude that attaching a nitro group to the benzyl moiety results in no significant difference for ^{1}H-NMR chemical shifts compared to previously described 7-benzyl substituted indolizines [6c]. The proton H-2 appears as a sharp singlet, slightly deshielded due to the contribution of both phenacyl and various substituents at C-1.

The ^{13}C-NMR spectra were recorded only for randomly selected compounds, because of their similarity, the main goal being to underline the influence of various substituents at C 7 in the pyridine ring. In a previous paper it was shown that, by attaching a benzyl group to C-7, a remarkable deshielding effect can be noticed (δ_{C-7} = 142.2 -144.7 ppm). A similar effect is achieved by attaching a *p*-nitrobenzyl group, the presence of the nitro group increasing the chemical shift for C-7 with about 3-4 ppm ($\delta_{C-7} \approx$147.0 ppm). The C-1 chemical shifts present the expected values for such compounds (about 114.6-115.2 ppm). Also the atoms C-5, C-6 and C-8 from the indolizines **6** and **7** are deshielded in respect with the other atoms of the pyridine system, since they are in α and γ positions in respect to the nitrogen atom of the pyridine ring. Moreover the carbon C-8a is highly deshielded (about 140 ppm) in comparison with the C-5 carbon atom, due to its α position with respect to the nitrogen atom on one side, and to the influence of the phenacyl moiety. The chemical shift for C-1 is of about 114.1-115.1 ppm, slightly deshielded due to the contribution of the acetyl group in compound **6**. For comparison, previous literature data record for the carboethoxy substitution at C-1 chemical shifts of about 105.7-106.7 ppm. The C-2 catom in the pyrrole ring appears at δ = 128.4-130.1 ppm, normal values for such type of compounds. The chemical shifts of the carbon atoms in aroyl and 4-nitrobenzyl moieties appear in the expected ranges, in accordance with the various substitutions.

Conclusions

Thirteen new 7-substituted indolizines were obtained by 1,3-dipolar cycloadditions of pyridinium *N*-ylides to non-symmetrical acetylenic dipolarophiles (3-butyn-2-one, metyl propiolate and ethyl propiolate). The title compounds were obtained in epoxypropane, which acted as both reaction media and deprotonation agent. 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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