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SYNTHESIS OF 3-N-SUBSTITUTED *exo*-3,4-DIAZATRICYCLO[5.2.1.$0^{2,6}$]DEC-4-ENES

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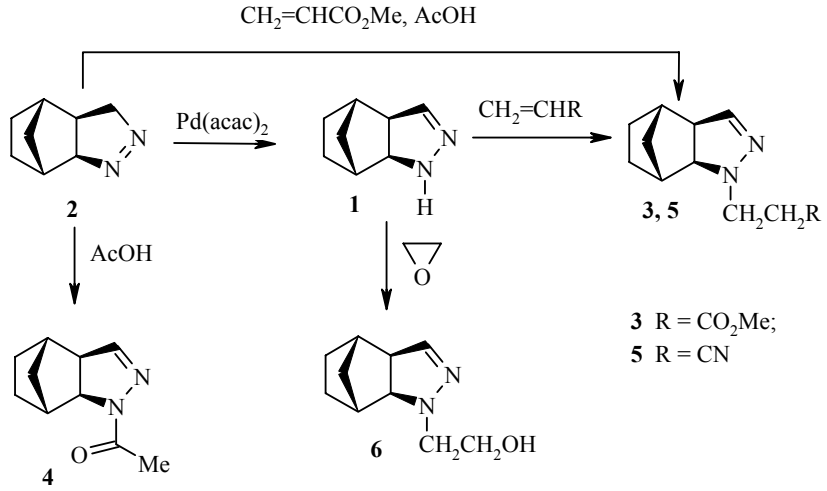
Treatment of exo-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene with methyl acrylate, acrylonitrile, ethylene oxide, acetic acid and nitrosonium cation gave a series of 3-N-substituted exo-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-enes.

Keywords: pyrazolines, *exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene, alkylation, acylation, nitrosation.

Pyrazolines are valuable compounds for the synthesis of differently structured organic compounds and are of interest as pharmacologically active compounds with a broad spectrum of activity (antiviral, analgesic, antitumor, psychotropic etc) [1-8]. There are quite detailed reports in the literature of the alkylation, acylation, and several other chemical reactions of monocyclic pyrazolines [9-13] but norbornane series pyrazolines have not been studied. The structural features of the polycyclic pyrazolines (in particular those containing a norbornane fragment) might be used to develop routes to the synthesis of various heterocyclic structures and of practically interesting compounds. Hence the pyrazoline – methyl *exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene-5-carboxylate gave the 5-amino-*exo*-3-azatricyclo[5.2.1.$0^{2,6}$]decan-4-one, which has anti-inflammatory, analgesic, nootropic, and marked antiarthritic activity [6, 7].

With the aim of synthesizing novel 3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-enes we have studied the reactions of *exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (**1**) with methyl acrylate, acrylonitrile, ethylene oxide, acetic acid, and the nitrosonium cation. Compound **1** was prepared by the catalytic isomerization of *exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene (**2**) in THF solution in the presence of $Pd(acac)_2$ with a yield of 70%.



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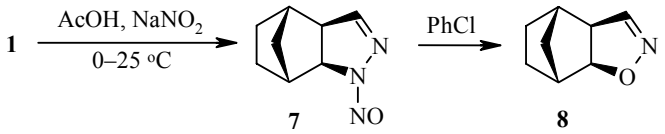
Treatment of pyrazoline **1** with an equimolar amount of methyl acrylate in methanol medium at room temperature gives 3-(2'-methoxycarbonylethyl)-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (**3**) in 23% yield, and a yield of 42% using pyridine medium at 60ºC. In this case, and in contrast to pyrazoline-3-carboxylates [1], a regioselective alkylation at the N-3 atom is observed. It is known that acids catalyze the isomerization of 1-pyrazolines to 2-pyrazolines [1] and the addition of amines to the activated C=C bond [1]. In connection with this we have carried out the reaction of pyrazoline **2** with methyl acrylate at room temperature in acetic acid solution. The yield of compound **3** is 13% under these conditions. An increase in the reaction temperature to 100ºC gives both the alkylation product **3** and the N-acylated pyrazoline **4** in yields of 17 and 24% respectively. The latter can be prepared in quantitative yield by refluxing pyrazoline **2** in excess AcOH.

Use of acrylonitrile in the reaction with pyrazoline **1** (MeOH, 20ºC) gives a 68% yield of the 3-(2-cyanoethyl)-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (**5**) which was separated in the pure state using column chromatography.

Passage of a twofold molar excess of gaseous ethylene oxide through an aqueous methanol solution of compound **1** (water–methanol, 3 : 10) at 60ºC over 2 h gave 3-(2'-hydroxyethyl)-*exo*-3,4-diazatricyclo-[5.2.1.$0^{2,6}$]dec-4-ene (**6**) in 78% yield.

The reaction of the pyrazoline **1** with nitrosonium cation (prepared from $NaNO_2$ and AcOH) takes place over 15 min at 0ºC to form 3-nitroso-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (**7**) in 46% yield. Compound **7** is thermally unstable above 130ºC and it is isomerized by refluxing over 2 h in chlorobenzene medium with evolution of nitrogen to form the difficult to obtain dihydroisoxazole **8** in 49% yield.



The structure and composition of the compounds **2-8** obtained were confirmed by elemental analytical data and by ^1H and ^{13}C NMR spectroscopy using the ^1H–^1H COSY and CHCORR methods. The spin-spin splitting of the C-2 and C-6 protons ($^3J_{1,2}$ = $^3J_{6,7}$ = 0 Hz) and chemical shifts of the C-10 atoms (δ_c, 32.30-33.81 ppm) [14] pointed to an *exo*-position for the pyrazoline fragment in the synthesized pyrazolines **2-7**. In the ^1H NMR spectrum of the pyrazoline **4** the signal for the C-2 proton appears as a doublet at 4.04 ppm, the low field shift of which when compared with starting pyrazoline **1** ($\Delta\delta_H$ = 0.46 ppm) is due to the presence of the acetyl substituent at atom N-3. The ^{13}C NMR spectrum of compound **5** shows carbon atom signals for the groups $\underline{C}H_2N$, $\underline{C}H_2CN$, and CN at 50.40, 17.26, and 118.13 ppm respectively. In the ^1H NMR spectrum of the nitrosopyrazole **7** the signal for the proton at C-2 is seen to low field when compared with the proton signal of the pyrazoline **1** ($\Delta\delta_H$ = 0.65 ppm). Elemental analytical data and IR spectroscopy (in particular the absence of the N–H group absorption band at 3280 cm^{-1} and the presence of the characteristic N–N=O group absorption band at 1420 cm^{-1}) also confirm the structure of the nitroso compound **7**.

It should be noted that we did not observe the formation of the products of isomerization of the norbornane ring in the reaction mixture in any of the experiments we carried out.

Hence we propose a convenient route for the synthesis of a series of 3-N-substituted 3,4-diazatricyclo-[5.2.1.$0^{2,6}$]dec-4-enes which are synthons for fine organic synthesis and in the preparation of novel biologically active substances.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz respectively) using $CDCl_3$ or C_6D_6 with TMS as internal standard. IR spectra were recorded on UR-20 and Specord M-80 instruments as thin layers or in vaseline oil. GLC was performed on a Chrom-5 chromatograph with flame ionization detection (1200×5 mm column with 5% SE-30 on Inerton N-AW DMCS (0.125-0.160 mm)) using helium gas carrier. Melting points were recorded on a Boetius microblock. Elemental analysis of the compounds was carried out on an HEKAtech GmbH Analysen–technik's Euro-EA CHN-analyzer. TLC was performed on Silufol and Alufol chromatography plates from the Kavalier company. Preparative separation was brought about using column chromatography on silica (Lancaster, 70-230 mesh).

***exo*-3,4-Diazatricyclo[5.2.1.0^{2,6}]dec-3-ene (2)** was obtained by a known method [5].

***exo*-3,4-Diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (1)**. $Pd(acac)_2$ (0.012 g, 0.04 mmol) was added with stirring to a solution of *exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-3-ene (**2**) (2.64 g, 20 mmol) in THF (30 ml), the reaction mixture was refluxed for 5 h, passed through a thin layer of silica, and solvent was removed at reduced pressure. Yield 1.84 g (70%); mp 63ºC. IR spectrum, ν, cm^{-1}: 848, 928, 1040, 1592 (C=N), 2872-2960, 3280 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08-1.51 (6H, m, H_2-8, H_2-9, H_2-10); 2.24 (1H, br. s, H-7); 2.29 (1H, br. s, H-1); 3.00 (1H, d, $^3J_{2,6}$ = 9.2, H-6); 3.58 (1H, d, $^3J_{2,6}$ = 9.2, H-2); 4.29 (1H, br. s, NH); 6.57 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.90 (C-9); 28.04 (C-8); 32.58 (C-10); 39.54 (C-7); 43.78 (C-1); 57.13 (C-6); 63.43 (C-2); 146.26 (C-5). Found, %: C 71.05; H 8.31; N 20.60. $C_8H_{16}N_2$. Calculated, %: C 70.55; H 8.88; N 20.57.

3-(2'-Methoxycarbonylethyl)-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (3). A. A mixture of pyrazoline **1** (1 g, 7 mmol) and methyl acrylate (0.7 g, 8 mmol) in MeOH (50 ml) was stirred at 20ºC for 144 h. The solvent was removed at reduced pressure and the residue was purified by column chromatography on silica (R_f 0.59, AcOEt-petroleum ether, 1: 1). Yield 0.37 g (23%).

B. A mixture of compound **1** (0.5 g, 4 mmol), methyl acrylate (0.35 g, 4 mmol), and pyridine (0.3 g, 4 mmol) was heated for 12 h at 60ºC. Yield 0.34 g (42%).

C. A mixture of pyrazoline **2** (1 g, 7 mmol) and methyl acrylate (0.7 g, 8 mmol) in AcOH solvent (6.2 g) was stirred at 20ºC for 48 h. The reaction product was poured into cold water (100 ml). The oil separated was extracted with ether (3×50 ml), the ether extract washed with water to pH ~ 7, and dried over Na_2SO_4. Yield 0.21 g (13%). IR spectrum, ν, cm^{-1}: 1440, 1584 (C=N), 1740 (C=O), 2872-2960. ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.95-1.04 (3H, m, H_{anti}-10, H_{endo}-8, H_{endo}-9); 1.25-1.33 (3H, m, H_{exo}-8, H_{exo}-9, H_{syn}-10); 2.07 (1H, br. s, H-7); 2.13 (1H, br. s, H-1); 2.45 (2H, t, ^3J = 7.0, $\underline{C}H_2CO_2$); 2.70 (1H, d, $^3J_{2,6}$ = 9.5, H-6); 2.91 (1H, d, $^3J_{2.6}$ = 9.5, H-2); 3.05-3.14 (2H, m, NCH_2); 3.47 (3H, s, CH_3); 6.11 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.28 (C-9); 28.28 (C-8); 33.06 (C-10); 33.14 ($\underline{C}H_2CO_2$); 39.83 (C-7); 42.10 (C-1); 50.12 (NCH_2); 51.20 (CH_3); 57.50 (C-6); 69.76 (C-2); 143.02 (C-5); 172.40 (C=O). Found, %: C 65.03; H 8.45; N 12.48. $C_{12}H_{18}N_2O_2$. Calculated, %: C 64.84; H 8.16; N 12.60.

3-Acetyl-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (4). A solution of pyrazoline **2** (2.0 g, 15 mmol) in AcOH (2.67 g, 45 mmol) was refluxed for 3 h. AcOH was evaporated *in vacuo*. Yield 2.59 g (99%), colorless liquid, bp 138ºC (5 mm Hg). IR spectrum, ν, cm^{-1}: 1408, 1594 (C=N), 1654 (C=O), 2878-2956. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15-1.17 (2H, m, H_2-10); 1.23-1.28 (2H, m, H_2-8); 1.50-1.55 (2H, m, H_{exo}-8, H_{exo}-9); 2.24 (3H, s, CH_3); 2.31 (1H, br. s, H-7); 2.76 (1H, br. s, H-1); 3.01 (1H, d, $^3J_{2,6}$ = 8.7, H-6); 4.04 (1H, d, $^3J_{2,6}$ = 8.7, H-2); 6.67 (1H, d, $^3J_{5,6}$ = 1.2, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.65 (CH_3); 24.74 (C-9); 27.42 (C-8); 32.30 (C-10); 39.55 (C-7); 40.51 (C-1); 55.97 (C-6); 62.20 (C-2); 148.80 (C-5); 169.01 (C=O). Found, %: C 67.72; H 7.87; N 15.52. $C_{10}H_{14}N_2O$. Calculated, %: C 67.39; H 7.92; N 15.72.

3-(2'-Cyanoethyl)-*exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (5). A solution of pyrazoline **1** (0.53 g, 4 mmol) and acrylonitrile (0.23 g, 4 mmol) in methanol (50 ml) was stirred for 5 days at 20ºC. Solvent was removed at reduced pressure and the residue was chromatographed on silica (R_f 0.60, AcOEt–petroleum ether,

1 : 1). Yield 0.5 g (68%). IR spectrum, ν, cm^{-1}: 1420, 1456, 1584 (N–N), 1672 (C=N), 2248 (CN), 2872-2968. ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.94-1.03 (3H, m, H_{endo}-8, H_{endo}-9, H_{anti}-10); 1.27 (1H, d, $^2J_{10syn,10anti}$ = 9.8, H_{syn}-10); 1.31-1.36 (2H, m, H_{exo}-8, H_{exo}-9); 2.08 (1H, br. s, H-7); 2.11 (1H, br. s, H-1); 2.33 (2H, t, ^3J = 6.9, $\underline{C}H_2CN$); 2.72 (1H, $^3J_{2,6}$ = 9.9, H-6); 2.89-3.05 (2H, m, H-2, $\underline{C}H_2CH_2CN$); 6.16 (1H, s, H-5). ^{13}C NMR spectrum (C_6D_6), δ, ppm: 17.26 ($\underline{C}H_2CN$); 24.86 (C-9); 28.98 (C-8); 33.81 (C-10); 40.77 (C-7); 42.69 (C-1); 50.40 ($\underline{C}H_2CH_2CN$); 58.18 (C-6); 70.21 (C-2); 118.13 (CN); 143.19 (C-5). Found, %: C 69.83; H 8.05; N 21.78. $C_{11}H_{15}N_3$. Calculated, %: C 69.81; H 7.99; N 22.20.

3-(2'-Hydroxyethyl)-*exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (6). Ethylene oxide (0.64 g, 14 mmol) was passed through a solution of pyrazoline **1** (1 g, 7 mmol) in a mixture of MeOH (50 ml) and H_2O (15 ml) at 60ºC for 2 h. Solvent was removed under reduced pressure and the residue was chromatographed on silica (R_f 0.58, $CHCl_3$–MeOH, 10 : 1). Yield 1.03 g (78%), oily liquid. IR spectrum, ν, cm^{-1}: 1120-1256 (C–O), 1428-1528 (C=N), 2872-2952, 3064-3416 (OH). ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 0.95-1.16 (3H, m, H_{anti}-10, H_{endo}-8, H_{endo}-9); 1.33-1.45 (3H, m, H_{syn}-10, H_{exo}-8, H_{exo}-9); 2.17 (2H, br. s, H-7,H-1); 2.77 (1H, d, $^3J_{2,6}$ = 10, H-6); 2.79-2.86 (1H, m, NC$\underline{H}$); 2.97 (1H, d, $^3J_{2,6}$ = 10, H-2); 3.00-3.08 (1H, m, NC$\underline{H}$); 3.61-3.83 (2H, m, $\underline{C}H_2OH$); 6.25 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.68 (C-9); 28.66 (C-8) 33.64 (C-10); 40.19 (C-7); 42.44 (C-1); 57.12 ($\underline{C}H_2CH_2OH$); 57.44 (C-6); 61.45 ($\underline{C}H_2OH$); 71.09 (C-2); 144.31 (C-5). Found, % C 66.03; H 9.05; N 14.94. $C_{10}H_{16}N_2O$. Calculated, %: C 66.63; H 8.95; N 15.54.

3-Nitroso-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (7). $NaNO_2$ (3.55 g, 50 mmol) was added portionwise with stirring at 0-10ºC to a solution of pyrazoline **1** (1.0 g, 7 mmol) in AcOH (20 ml) and stirred for 15 min at room temperature. The reaction product was poured into water (25 ml) at 0ºC, extracted with chloroform (3×50 ml), and dried over sodium sulphate. Solvent was removed *in vacuo* and the residue was chromatographed on silica (R_f 0.65, AcOEt-petroleum ether, 1 : 1); Yield 0.55 g (46%), red-brown oil. IR spectrum, ν, cm^{-1}: 1258 (N–N), 1420 (N=O); 1594 (C=N), 2878-2956. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.14 (1H, d, $^2J_{10anti,10syn}$ = 11.3, H_{anti}-10); 1.22-1.34 (3H, m, H_{syn}-10, H_{endo}-8, H_{endo}-9); 1.61-1.64 (2H, m, H_{exo}-8, H_{exo}-9); 2.48 (1H, br. s, H-7); 2.82 (1H, br. s, H-1); 3.10 (1H, d, $^3J_{2,6}$ = 7.6, H-6); 4.23 (1H, d, $^3J_{2,6}$ = 7.6, H-2); 7.33 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.73 (C-9); 27.17 (C-8); 32.31 (C-10); 38.86 (C-7); 39.05 (C-1); 55.42 (C-6); 63.03 (C-2); 156.06 (C-5). Found, %: C 57.27; H 5.96; N 24.64. $C_8H_{11}N_3O$. Calculated, %: C 58.17; H 6.71; N 25.44.

3-Oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene (8). A solution of the nitroso compound **7** (0.47 g, 3 mmol) in chlorobenzene (20 ml) was refluxed under an argon atmosphere for 2 h. Solvent was removed *in vacuo* and the residue was chromatographed on silica (R_f 0.68, $CHCl_3$–MeOH, 5 : 1). Yield 0.16 g (49%), oily liquid. IR spectrum, ν, cm^{-1}: 1048 (NO), 1372 (CO), 1654-1686 (C=N), 2848-2920. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20-1.45 (4H, m, H_2-10, H_{endo}-8, H_{endo}-9); 1.52-1.70 (2H, m, H_{exo}-8, H_{exo}-9); 2.58 (1H, d, $^3J_{1,9}$ = 5.7, H-1); 2.70 (1H, br. s, H-7); 2.92 (1H, d, $^3J_{2,6}$ = 5.4, H-6); 4.66 (1H, d, $^3J_{2,6}$ = 5.4, H-2); 7.32 (1H, s, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.70 (C-9); 27.11 (C-8), 32.26 (C-10); 37.02 (C-7); 55.38 (C-1); 62.99 (C-6); 93.28 (C-2); 177.81 (C-5). Found, %: C 70.27; H 8.26; N 10.04. $C_8H_{11}NO$. Calculated, %: C 70.04; H 8.08; N 10.21.

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