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CONVERSION OF 2-ETHYL-3,3,5,5-TETRAMETHYL- AND 2-ETHYL-1,3,3,5,5-PENTAMETHYL-1,2,4,5-TETRAHYDRO-3H-BENZ-2-AZEPINES BY THE ACTION OF ETHYL PROPIOLATE

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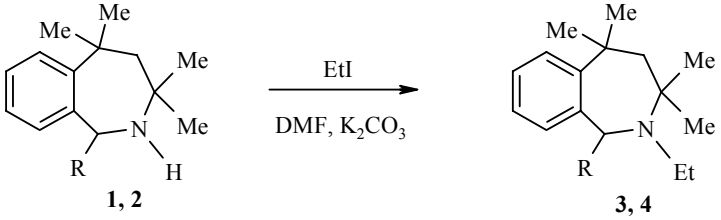
It has been shown that, on interacting 2-ethyl-3,3,5,5-tetramethyl- and 2-ethyl-1,3,3,5,5-pentamethyl-1,2,4,5-tetrahydro-3H-benz-2-azepines with ethyl propiolate in methanol, fission of the azepine ring occurs at the C(1)–N(2) bond involving a molecule of solvent. The indicated azepines do not react with acetylenedicarboxylic acid ester under these conditions.

Keywords: activated alkynes, tetrahydrobenz-2-azepines, fission.

Tandem expansion reactions of the tetrahydropyridine ring condensed with heterocyclic fragments under the action of activated alkynes, described by us for the firtst time, have been used to develop a new preparative method for the synthesis of tetrahydroazocines condensed with pyrrole, indole, thiophene, and pyrimidine rings [1-4]. It was shown recently that the hydrogenated azepine ring in hexahydro-azepino[4,3-*b*]indoles and -[3,4-*b*]indoles is also subject to tandem fission under these conditions, as a result of which hexahydroazonino[5,6-*b*]indoles are formed [5]. The reaction proceeds easily in both acetonitrile and methanol.



1, 2 **3, 4**

1, 3 R = H; **2, 4** R = Me

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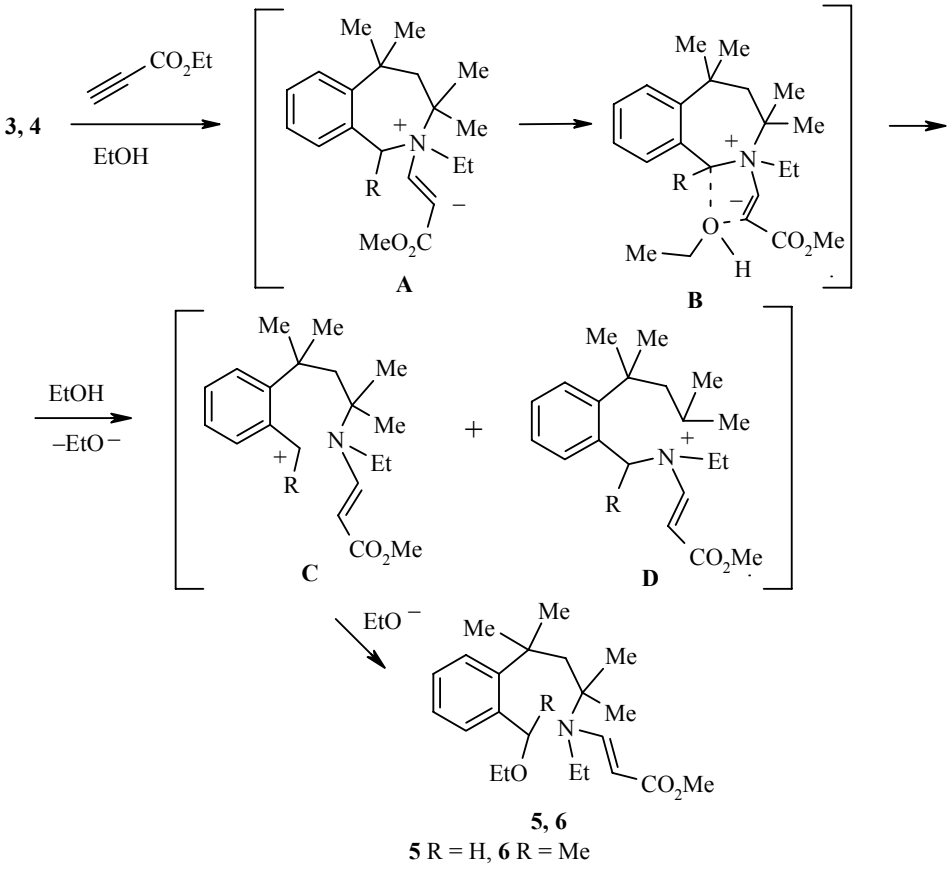
In order to establish the effect of the aromatic fragment and the substituents in the azepine ring we have studied the interaction of 2-ethyl-3,3,5,5-tetramethyl- and 2-ethyl-1,3,3,5,5-pentamethyl-1,2,4,4-tetrahydro-3H-benz-2-azepines **3** and **4** with acetylenedicarboxylic acid ester (ADCE) in methanol and with ethyl propiolate in ethanol.

Azepines **3** and **4** were obtained by the ethylation with ethyl iodide of benzazepines **1** and **2**, synthesized by the procedure described in [6].

Unlike azepinoindoles [5], benzazepines **3** and **4** do not react with ADCE, and for the reaction with ethyl propiolate in ethanol it was necessary to boil for 48 h.



This is seemingly caused by steric obstacles to the approach of the alkyne to the nitrogen atom of the azepine ring. On reaction with ethyl propiolate multicomponent mixtures were formed from which products were isolated, by chromatography in 19-22% yield, from the decomposition of the azepine ring involving a molecule of ethanol, *viz.* the aminoacrylates **5**, **6**.

The reaction begins with the formation of the ammonium zwitter-ion **A**, which is converted through the transition state **B** into aminoacrylates **5** and **6**. The presence of secondary and tertiary carbon atoms in the α-position to the ammonium nitrogen atom seemingly causes fission of the C(1)–N^+ and C(3)–N^+ bonds with the formation of stable cations of type **C** and **D**. These cations, apart from reacting with ethanol, undergo processes of isomerization and rearrangement characteristic of carbocations, which also explains the formation of multicomponent mixtures.

In the mass spectra compounds **5** and **6** have peaks for molecular ions corresponding to their empirical formulas. In the ^{1}H NMR spectra the presence of two doublets at 5.62-5.65 and 7.55-7.60 ppm for the protons of the acryloyl group with J = 13.1 Hz are characteristic. This shows the *trans* configuration of this fragment.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker WP 400 (400 MHz) instrument in $CDCl_3$, internal standard TMS. The IR spectra were recorded on a INFRALYUM FT 801 Fourier spectrometer in KBr pellets. The ESI mass spectra were recorded on a Agilent 1100 Series LC/MSD Trap System VL mass spectrometer. Silufol UV 254 plates were used for TLC (visualization with iodine vapor), neutral Al_2O_3 Fluka 507c (size 0.05-0.15 mm) was used for column chromatography.

2-Ethyl-3,3,5,5-tetramethyl-1,2,4,5-tetrahydro-3H-benz-2-azepine (3) and 2-Ethyl-1,3,3,5,5-pentamethyl-1,2,4,5-tetrahydro-3H-benz-2-azepine (4) (General Method). Anhydrous potassium carbonate (10 g, 72 mmol) was added to a solution of azepines **1** or **2** (48 mmol) in DMF (25 ml). After 15 min ethyl iodide (10.92 g, 5.6 ml, 70 mmol) was added dropwise. The mixture was heated at 60°C until disappearance of the starting material (check by TLC). The mixture was poured into water (100 ml), extracted with ether, and the extract dried over magnesium sulfate. After distilling off the solvent (DMF in vacuum) the residue was chromatographed, eluent ethyl acetate–hexane, 1:20. Azepines **3** (6.8 g: 68%) and **4** (4.5 g: 38.3%) were isolated.

Compound 3. Yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.2, C$\underline{H}_3$CH$_2$); 1.15 (3H, s, CH$_3$); 1.17 (3H, s, CH$_3$); 1.31 (1H, d, *J* = 13.8, H-1); 1.35 (3H, s, CH$_3$); 1.3 (3H, s, CH$_3$); 1.42 (3H, s, CH$_3$); 1.61 (1H, d, *J* = 13.8, H-4); 2.67 (2H, q, *J* = 7.2, CH$_3$C$\underline{H}_2$); 3.67 (1H, d, *J* = 15.1, H-1); 4.18 (1H, d, *J* = 15.1, H-1); 7.13-7.32 (4H, m, H Ar). Found, %: C 83.29; H 11.00; N 6.26. M$^+$ 231. $C_{16}H_{25}N$. Calculated, %: C 82.91; H 10.82; N 6.01. M 231.

Compound 4. Yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (3H, t, *J* = 7.2, C$\underline{H}_3$CH$_2$); 1.05 (3H, s, CH$_3$); 1.26 (3H, s, CH$_3$); 1.42 (3H, s, CH$_3$); 1,51 (3H, s, CH$_3$); 1.53 (3H, d, *J* = 6.9, 1-CH$_3$); 1.61 (1H, d, *J* = 15.0, H-4); 2.14 (1H, d, *J* = 15.0, H-4); 2.70 (2H, q, *J* = 7.2, CH$_3$C$\underline{H}_2$); 4.48 (1H, q, *J* = 6.9, H-1); 7.12-7.38 (4H, m, H Ar). Found, %: C 83.00; H 10.83; N 5.87. M$^+$ 245. $C_{17}H_{27}N$. Calculated, %: C 83.37; H 11.02; N 5.71. M 245.

Methyl (*E*)-3-{1,1,3-Trimethyl-3-[2-(ethoxymethyl)phenyl]butyl}(ethyl)aminoacrylate (5). A mixture of benzazepine **3** (1 g, 4.3 mmol) and ethyl propiolate (0.52 g, 5.3 mmol) was boiled for 48 h (check by TLC). The solvent was distilled in vacuum. The residue was chromatographed (eluent ethyl acetate–hexane, 1:40 to 1:10). Compound **5** (0.32 g: 20%) was isolated as a yellow oil. IR spectrum, ν, cm^{-1}: 1730 (CO), 1645 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, s, CH$_3$); 1.17 (3H, t, *J* = 6.8, NCH$_2$C$\underline{H}_3$); 1.25 (3H, t, *J* = 7.1, C$\underline{H}_3$CH$_2$O); 1.28 (3H, t, *J* = 7.1, C$\underline{H}_3$CH$_2$O); 1.42 (3H, s, CH$_3$); 1.44 (3H, s, CH$_3$); 1.51 (3H, s, CH$_3$); 1.69 (2H, s, CH$_2$); 3.20 (2H, m, NC$\underline{H}_2$CH$_3$); 4.12 (2H, q, *J* = 7.1, CH$_3$C$\underline{H}_2$O); 4.40 (2H, s, CH$_2$O); 4.42 (2H, m, CH$_3$C$\underline{H}_2$CO$_2$); 5.62 (1H, d, *J* = 13.1, CH=); 7.55 (1H, d, *J* = 13.1, CH=). Found, %: C 73.21; H 10.01; N 3.91. M$^+$ 375. $C_{23}H_{37}NO_3$. Calculated, %: C 73.60; H 9.87; N 3.73. M 375.

Methyl (*E*)-3-{1,1,3-Trimethyl-3-[2-(1-ethoxyethyl)phenyl]butyl}(ethyl)aminoacrylate (6) was obtained by the procedure described above from benzazepine **4** (1 g, 4 mmol) in a yield of 0.35 g (22%) as a light-yellow oil. IR spectrum, ν, cm^{-1}: 1740 (CO), 1638 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, s, CH$_3$); 1.19 (3H, t, *J* = 6.9, NCH$_2$C$\underline{H}_3$); 1.26 (3H, t, *J* = 7.1, C$\underline{H}_3$CH$_2$CO$_2$); 1.29 (3H, t, *J* = 7.1, C$\underline{H}_3$CH$_2$CO$_2$); 1.43 (3H, s, CH$_3$); 1.45 (3H, s, CH$_3$); 1.53 (3H, s, CH$_3$); 1.62 (3H, d, *J* = 6.9, C$\underline{H}_3$CH); 1.70 (2H, s, CH$_2$); 3.32 (2H, m, N-C$\underline{H}_2$CH$_3$); 4.12 (2H, q, *J* = 6.9, CH$_3$C$\underline{H}_2$O); 4.32 (1H, q, *J* = 6.9, CH$_3$C$\underline{H}$); 4.43 (2H, q, *J* = 7.1, CH$_3$C$\underline{H}_2$CO$_2$); 5.70 (1H, d, *J* = 13.5, CH=); 7.60 (1H, d, *J* = 13.5, CH=). Found, %: C 74.25; H 10.41; N 3.91. M$^+$ 375. $C_{24}H_{39}NO_3$. Calculated, %: C 73.60; H 10.02; N 3.60. M 375.

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