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LETTERS TO THE EDITOR

Synthesis of 2-(Aminoalkyl)-3-(aminophenyl)bicyclo[2.2.1]heptanes

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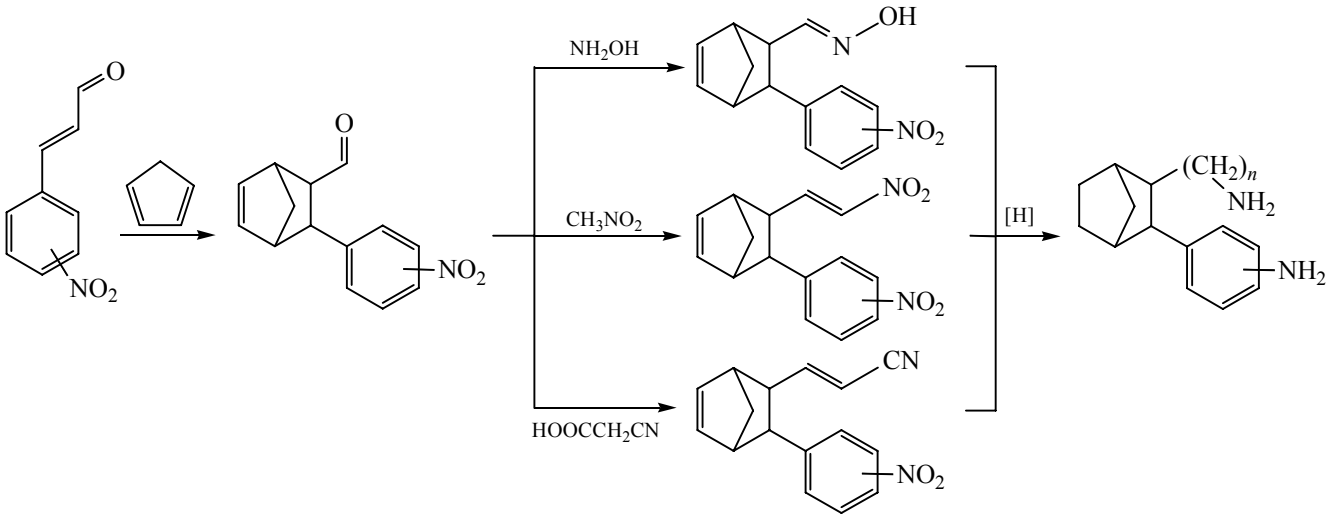
Mono- and diamines containing bicyclic scaffold are used in medicine as an active component of pharmaceuticals with thymoanaleptic and tonic effect [1], in the treatment of drug dependence [2], and may also be of interest as promising monomers for polycondensation polymers [3, 4].

A disadvantage of the known methods for synthesizing bicyclic mono- and diamines is the requirement to use different dienophiles for obtaining each member of the homologous series of bicyclic compounds. At the same time, the synthesis of functionalized unsaturated compounds is laborious and multistage. In addition, increasing the distance between the electron-withdrawing functionality and the double bond reduced the reactivity of these compounds in the Diels–Alder reaction. As a result, the process of obtaining bicyclic derivatives contains ever growing number of stages and becomes technologically poor.

In this regard, we have developeed an approach to the synthesis of homologous series of new bicyclic diamines based on the Diels–Alder reaction involving dienophiles containing highly reactive groups capable of further chemical transformations. The developed approach towards synthesis of 2-(aminoalkyl)-3-(aminophenyl)bicyclo[2.2.1]heptanes allows preparing homologous series of bicyclic diamines under mild conditions with good yields (Scheme 1).

Scheme 1.



n = 1, 2, 3.

The proposed scheme includes preliminary preparation of 3-(nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehydes by reacting *p*- or *m*-nitrocinnamic aldehydes with cyclopentadiene in CH_2Cl_2. Further the prepared bicyclic aldehydes reacted with H-labile compounds like hydroxylamine, nitromethane, or cyanoacetic acid. Substituted *N*-hydroxy-1-[3-(nitrophenylbicyclo)[2.2.1]hept-5-en-2-yl]methane imines, 5-[2-nitroethenyl]-6-(nitrophenyl)bicyclo[2.2.1]hept-2-enes, and 3-[3-(nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl]propene-2-nitriles were reduced to the corresponding amines under the Schwenk–Papa reaction conditions [5]. 2-(Aminoalkyl)-3-(aminophenyl)bicyclo[2.2.1]heptanes were isolated as the mixtures of stereoisomers with a yield of about 40% with respect to the starting nitrocinnamic aldehyde.

The NMR spectra of the final compounds obtained are insufficiently informative due to the overlapping signals. Therefore, the purity and structures of the target bicyclic diamines was confirmed by gas chromatography-mass spectrometry. The mass spectra of all the bicyclic diamines obtained contained the signals of the molecular ion and characteristic fragment ions.

3-(3-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde. A mixture of 4.425 g (0.025 mol) of 3-(3-nitrophenyl)propen-2-al, 90 mL of methylene chloride and 41 mL (0.5 mol) of cyclopentadiene was refluxed for 20 h. The solvent and excess cyclopentadiene were removed to give 3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde as yellow-orange oil, R_f 0.28 ($CHCl_3$). ^{1}H NMR spectral data corresponded to the reported in [6].

3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde was obtained analogously from 3-(4-nitrophenyl)propen-2-al. R_f 0.28 ($CHCl_3$). ^{1}H NMR spectral data corresponded to the reported in [6].

2-(Aminomethyl)-3-(3-aminophenyl)bicyclo[2.2.1]heptane. A solution of 2.09 g (0.03 mol) of hydroxylamine hydrochloride in 2.5 mL of warm water was added with stirring to a solution of 6.08 g (0.025 mol) of 3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde in 10 mL of ethanol. After 10 min a solution of 1.50 g (0.0375 mol) of NaOH in 2.0 mL of water was added, and the mixture was stirred for another 4 h at room temperature. Then 40 g of crushed ice was added, and the reaction mixture was saturated with CO_2. At the bottom of the flask was formed yellow-brown oily oxime. The obtained *N*-hydroxy-1-{3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl}-methane imine was kept in cold for 1 day, then filtered off and dried to obtain 5.99 g of crude product which was used without further purification.

A solution of 14.23 g (0.21 mol) of KOH in 210 mL of water was added to a solution of *N*-hydroxy-1-{3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-yl}methane imine in 210 mL of THF (THF–H_2O = 1 : 1, c_{KOH} = 0.5 mol/L). To this mixture was added in portions 50 g (0.93 g-atom Al) of Ni/Al-alloy (Ni–Al, 50:50) within 3 h maintaining moderate gas evolution. The reaction mixture was refluxed for 3 h and filtered while hot. The precipitate was washed with warm THF. The organic layer was evaporated. The aqueous layer was extracted with toluene (3 × 50 mL), washed with water, and extracted with an HCl solution (1 : 3, 150 mL). The aqueous layer was alkalinized with 40% aqueous solution of NaOH, then extracted with toluene (3 × 50 mL), dried with KOH, and concentrated. The residue was sublimated at 160°C (2 mmHg). Yield 2.16 g [40% based on the starting 3-(3-nitrophenyl)-propen-2-al]. Mass spectrum, *m*/*z* (I_{rel}, %): 217 (44) $[M + 1]^+$, 216 (13) $[M]^+$, 199 (100) $[M - 17]^+$, 158 (68), 106 (21).

2-(Aminomethyl)-3-(4-aminophenyl)bicyclo[2.2.1]-heptane was obtained similarly. Yield 2.27 g (42%), bp 178–179°C (2 mmHg). Mass spectrum, *m*/*z* (I_{rel}, %): 217 (80) $[M + 1]^+$, 216 (14) $[M]^+$, 199 (100) $[M - 17]^+$, 158 (78), 106 (96).

2-(2-Aminoethyl)-3-(3-aminophenyl)bicyclo[2.2.1]-heptane. A solution of 1.25 g (0.0312 mol) of sodium hydroxide in 4 mL of ice-water mixture was added with cooling and stirring to a mixture of 6.08 g (0.025 mol) of 3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde, 1.525 g of nitromethane (1.1 mL, 0.025 mol) and 10 mL of methanol, maintaining the temperature below 10–15°C. After stirring for 15–20 min, 16–20 mL of water with crushed ice was added. The resulting solution was added dropwise to an excess of 20% solution of HCl, then extracted with diethyl ether (3 × 50 mL), washed with water, dried over Na_2SO_4, and evaporated to give 4.70 g (0.016 mol) of 5-[2-nitroethenyl]-6-(3-nitrophenyl)bicyclo[2.2.1]hept-2-ene, which was used without further purification.

The reduction of 5-[2-nitroethenyl]-6-(3-nitrophenyl)bicyclo[2.2.1]hept-2-ene was carried out similarly to the reduction of N-hydroxy-1-[3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-yl]methanimine using 190 mL of THF, 190 mL of water, 12.69 g (0.19 mol) of KOH and 47.48 g (0.88 g-atom Al) Ni/Al-alloy (Ni–

Al, 50 : 50). 2-(2-Aminoethyl)-3-(3-aminophenyl)bicyclo[2.2.1]heptane was purified by sublimation in a vacuum (2 mm Hg) at 180°C. Yield 1.84 g (32%). Mass spectrum, *m*/*z* (I_{rel}, %): 232 (16) $[M + 2]^+$, 231 (100) $[M + 1]^+$, 230 (67) $[M]^+$, 199 (50) $[M - 31]^+$, 186 (22), 158 (25), 106 (13), 44 (87).

2-(2-Aminoethyl)-3-(4-aminophenyl)bicyclo[2.2.1]-heptane was obtained similarly. Yield 2.01 g (35%). Mass spectrum, *m*/*z* (I_{rel}, %): 232 (15) $[M + 2]^+$, 231 (100) $[M + 1]^+$, 230 (24) $[M]^+$, 199 (40) $[M - 31]^+$, 158 (26), 106 (9), 44 (33).

2-(3-Aminopropyl)-3-(3-aminophenyl)bicyclo[2.2.1]-heptane. A mixture of 6.08 g (0.025 mol) of 3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and 5 mL of piperidine was added to a solution of 4.92 g (0.058 mol) of cyanoacetic acid in 10 mL of anhydrous pyridine. The reaction mass was heated on a water bath until carbon dioxide evolution ceased, then cooled and poured into a mixture of ice and conc. hydrochloric acid. The reaction product was extracted with diethyl ether (3 × 80 mL), washed with a 10% solution of Na_2CO_3 (3 × 100 mL) and with water to neutral pH, and dried over $MgSO_4$. Then the solvent was removed to obtain 3.72 g of 3-[3-(3-nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-yl]propen-2-nitrile, which was used in the next step without further purification.

The reduction of 3-[3-(3-nitrophenyl)bicyclo[2.2.1]-hept-5-ene-2-yl]propen-2-nitrile was carried out similarly to the reduction of *N*-hydroxy-1-[3-(3-nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl]methanimine using 130 mL of THF, 130 mL of water, 8.76 g (0.130 mol) of KOH and 35.18 g (0.65 g-atom Al) of Ni/Al-alloy (Ni–Al, 50 : 50). The reaction product was purified by vacuum sublimation (2 mmHg) at 200°C. Yield 1.89 g (31%). Mass spectrum, *m*/*z* (I_{rel}, %): 245 (100) $[M + 1]^+$, 244 (59) $[M]^+$, 243 (30) $[M - 1]^+$, 227 (32) $[M - 17]^+$, 199 (10), 198 (17), 184 (13), 158 (10), 106 (26), 70 (31).

2-(3-Aminopropyl)-3-(4-aminophenyl)bicyclo-[2.2.1]heptane was obtained similarly. Yield 1.95 g (32%). Mass spectrum, *m*/*z* (I_{rel}, %): 245 (100) $[M + 1]^+$, 244 (65) $[M]^+$, 243 (67) $[M - 1]^+$, 227 (33) $[M - 17]^+$, 213 (25) $[M - 31]^+$, 199 (15), 198 (25), 184 (27), 170 (15), 158 (12), 106 (32), 70 (34).

The NMR spectra of the $CDCl_3$ solutions were recorded on a Varian Mercury-300 BB (300.73 MHz) spectrometer, internal reference HMDS. Mass spectra were recorded on a Varian Saturn 2100 spectrometer with ionizing electrons energy of 70 eV and a cathode emission current of 240 mA. Thin-layer chromatography was performed on ALUGRAM/UV plates, detecting with UV light.

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