The Synthesis of N-nitroso bis (1aβ,2α,7α,7aβ-tetrahydro-1β-methylene-2,7-methano-1H-cyclopropa[b]naphthalene) amine

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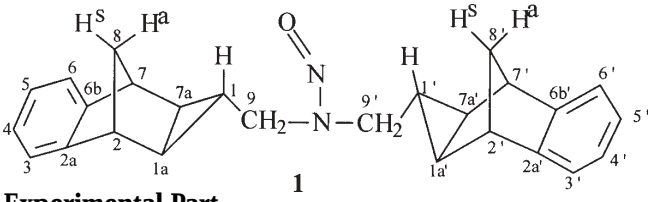
*The synthesis and the spectral characterisation of N-nitroso bis(1aβ, 2α,7α,7aβ-tetrahydro- 1β-methylene-2,7-methano-1H-cyclopropa[b]naphtalene)amine(**1**) is reported. Also, the syntheses and the spectral characterisations of the following intermediates: N-(1aβ, 2α,7α,7aβ-tetrahydro-2,7-methano-1H cyclopropa[b]naphthalene-1β-methylene-1aβ, 2β, 7β, 7aβ-tetrahydro-2,7-methano-1H-cyclopropa[b] naphtalene-1β-carbinylamine (**4**) and N-Bis(1aβ, 2α,7α,7aβ-Tetrahydro-1β-methylene- 2,7-methano-1H-cyclopropa[b]naphtalene)amine(**5**) are reported.*

Keywords: N-nitrosoamine; nitrosation reaction; benzonorbornadiene

N-nitrosoamines were employd for the induction of tumors in the urinary bladder of the male rats for the research of the drugs with action in the cancer treatment [1].

Also, N-nitrosamines may serve as useful models for the NMR study of carbonium ions because in both species the electron deficient atoms are trigonal [2].

In this paper we describe the synthesis of N-nitroso bis(1aβ, 2α,7α,7aβ-tetrahydro-1β-methylene-2,7-methano-1H-cyclopropa[b]naphtalene)amine **1**.



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Experimental Part

Melting points are uncorrected. The NMR spectra were registered on a Varian Gemini 300 apparatus at 300 MHz for ^{1}H and 75 MHz for ^{13}C, using TMS as internal standard. The IR spectra were registered on a Bruker Vertex 70 spectrophotometer.

Benzonorbornadiene **6** was obtained by the cycloaddition of benzyne (generated from diazoanthranilic acid) to cyclopentadiene[3]. The *anti* methyl ester **9** was prepared according to the method developed by M. Avram and her coworkers [4].

(1aβ, 2β,7β,7aβ-tetrahydro-1β-(hydroxymethyl)-2,7-methano-1H-cyclopropa[b]naphtalene (**10**) was synthesized according to [5] as a colourless oil by $LiAlH_4$-reduction (90 % yield) of the methyl ester **9**. The spectral data of **10** confirm the proposed structure.

IR spectrum (CS_2; CCl_4; cm^{-1}): 733 s; 1016 s; 1100 s; 1392 m; 1443 m; 2851 m; 2907 m; 2953 s; 3000 m; 3324 m; 3602 w.

^{1}H-NMR spectrum ($CDCl_3$, δ ppm, J Hz): 0.96 (d; 2H; H^{1a} H^{7a}; 2.5); 1.26 (d; H^{8a}; 10.1); 1.51 (d; H^{8s}; 10.1); 2.12 (tt; H^{1}; 2.5; 7.1) 3.29 (s; 2H; H^{2} H^{7}); 3.35 (d; 2H; H^{9}; 7.1); 7.03 (dd; H^{4} H^{5}; 3.1; 5.2); 7.19 (dd; H^{3} H^{6}; 3.1; 5.2).

^{13}C- NMR spectrum ($CDCl_3$, δ, ppm): 26.19 (C^{1a}; C^{7a}); 30.50 (C^{1}); 38.91 (C^{8}); 42.93 (C^{2}; C^{7}); 64.62 (C^{9}); 120.75 (C^{3}; C^{6}); 124.95 (C^{4}; C^{5}); 151.04 (C^{2a}; C^{6a}).

(1aβ,2β,7β,7aβ-tetrahydro-1β-formyl-2,7-methano-1H-cyclopropa[b]naphtalene (**2**) was synthesized according to [5] as a colourless solid mp 59-60°C by the CrO_3 Py_2-oxidation (90 % yield) of the alcohol **10**. The spectral data of **2** confirm the proposed structure.

IR spectrum (CS_2; CCl_4; cm^{-1}): 750m; 1708 s; 2820m; 2903 w; 2922 w; 2980 s; 3018w; 3050w.

^{1}H-NMR spectrum ($CDCl_3$, δ ppm, J Hz): 1.23 (2H, m); 1.69(d, 2.5, 2H); 2.6(dt; 2.5, 4.5, 1H); 3.35(br s, 2H); 7.03(m, 4H);9.1(d, 4.5, 1H).

^{13}C- NMR spectrum ($CDCl_3$, δ, ppm): 30.03 (C); 38.60 (C); 39.58 (C); 42.94 (C); 121.30 (C); 125.40 (C); 149.74(C); 198.25(C).

(1aβ, 2β, 7β,7aβ-tetrahydro-2,7-methano-1H-cyclopropa[b]naphtalene-1β-acid chloride (**12**).

The synthesis of compound **12** was performed according to [6] and the product analyzed by the spectral methods:

IR spectrum (CS_2; CCl_4; cm^{-1}): 994 s; 1071 s; 1370 s; 1772 vs; 2912 w; 2987 s; 3020 w; 3055 w; 3072 w.

^{1}H-NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.41 (bd; 10.5; 1H; H^{8sin}); 1.46 (dt; 10.5; 1.6; 1H; H^{8anti}); 2.00 (bd; 2.4; 2H; H^{1a}; H^{7a}); 2.98 (t; 2.4 1H; H^{1}); 3.48 (bs; 2H; H^{2}; H^{7}); 7.00-7.22 (m; 4H; H^{arom})

^{13}C-NMR spectrum ($CDCl_3$, δ, ppm): 34.38 ($C^{1a;7a}$); 38.98 (C^{1}); 39.76 (C^{8}); 43.28 ($C^{2;7}$); 121.54 ($C^{3;6}$); 125.62 ($C^{4;5}$); 149.04 ($C^{2a;6a}$); 171.73 (C^{9}).

(1aβ,2β,7β,7aβ-tetrahydro-2,7-methano-1H-cyclopropa[b]naphtalene-1β-carboxamide(**13**)

The synthesis of compound **13** was performed according to [6] and the product analyzed by spectral methods:

IR spectrum (KBr; cm^{-1}): 738 m; 754 m; 772 m; 1428 s; 1615 m; 1645 s; 2810 w; 2970 w; 2855 w; 3055 w; 3195 m; 3392 m.

^{1}H-NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.31 (d; 9.9; 1H; $H^{8\ sin}$); 1.43 (d; 9.9; 1H; $H^{8\ anti}$); 1.62 (bs; 2H; H^{1a}; H^{7a}); 2.31 (bs; 1H; H^{1}); 3.34 (bs; 2H; H^{2}; H^{7}); 5.78 (2H; NH_2); 6.95-7.20 (m; 4H; H^{arom}).

^{13}C-NMR spectrum ($CDCl_3$, δ, ppm): 29.97 ($C^{1a;7a}$); 30.36 (C^{1}); 39.46 (C^{8}); 43.04 ($C^{2;7}$); 121.20 ($C^{3;6}$); 125.30 ($C^{4;5}$); 149.89 ($C^{2a;6a}$); 173.43 (C^{9}).

(1β-cyano-1aβ,2β, 7β,7aβ-tetrahydro-2,7-methano-1H-cyclopropa[b]naphtalene (**14**)

The synthesis of compound **14** was performed according to [6] and the product analyzed by spectral methods:

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IR spectrum (CCl_4; cm^{-1}): 1094 s; 1380 w; 1453 m; 1481 w; 2248 s; 2910 w; 2986 m; 3053 w; 3072 w.

^{1}H-NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.37 (s; 2H; $H^{8\,sin}$; $H^{8\,anti}$); 1.77(d; 2.6; 2H; H^{1a}; H^{7a}); 2.23 (t; 2.6; 1H; H^1); 3.42 (s; 2H; H^2; H^7); 7.05-7.30 (m; 4H; H^{arom}).

^{13}C-NMR spectrum ($CDCl_3$,δ,ppm): 11.50 (C^1); 28.70 ($C^{1a;7a}$); 37.90 (C^8); 42.30 ($C^{2;7}$); 119.50 (C^9); 121.7 ($C^{3;6}$); 126.0 ($C^{4;5}$); 148.20 ($C^{2a;6a}$).

(1aβ, 2β, 7β,7aβ-tetrahydro-2,7-methano-1H-cyclopropa[b]naphtalene-1β-carbynylamine (**3**)

The synthesis of compound **3** was performed according to [6] and the product analyzed by spectral methods:

IR spectrum (CCl_4; cm^{-1}): 1063 m; 1082 m; 1369 m; 1451 m; 1620 w; 2240 s; 2870 w; 2972 s; 3020 s; 3078 m; 3348 m; 3420 m.

^{1}H-NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 0.86 (d; 2.6; 2H; H^{1a}; H^{7a}); 1.22 (d; 9.9; 1H; $H^{8\,sin}$); 1.51 (dt;9.9;1.4;1H; $H^{8\,anti}$); 1.95 (tt; 6.9; 2.6; 1H; H^1); 2.47 (d; 6.9; 1H; H^9); 3.25 (s; 2H; H^2; H^7); 6.95-7.15 (m; 4H; H^{arom}).

^{13}C-NMR spectrum ($CDCl_3$,δ, ppm): 26.65 ($C^{1a;7a}$); 31.63 (C^1); 38.67 (C^8); 42.87 ($C^{2;7}$); 44.31(C^9); 120.48 ($C^{3;6}$); 124.72 ($C^{4;5}$); 150.83 ($C^{2a;6a}$).

N-Bis(1aβ,2α,7α,7aβ-Tetrahydro-1β-methylene- 2,7-methano-1H-cyclopropa[b]naphtalene)amine(**5**)

a) N-(1aβ,2α,7α,7aβ-Tetrahydro-2,7-methano-1H-cyclopropa[b]naphthalene-1β-methylene)- 1aβ,2β,7β,7aβ-Tetrahydro-2,7-methano-1H-cyclopropa[b]naphtalene-1β-carbinylamine (**4**)

The aldehide **2** (0.7g; 3.8mmoles) was dissolved in 30 mL of commercial absolute ethanol. To this alcoholic solution, the amine **3** (0.7g; 3.8mmoles) was added. The mixture was refluxed for 2 h. Then, the reaction was cooled and the solvent was removed at reduced pressure. It obtained the Schiff base **4** as a colourless oil (1.1g, yield 80%).

b) N-Bis(1aβ,2α,7α,7aβ-Tetrahydro- 1β-methylene- 2,7-methano-1H-cyclopropa[b]naphtalene)amine (**5**)

A solution of Schiff base **4 (**1.3g; 3.7 mmol) in 25 mL diethylether was added dropwise to a magnetically stirred suspension of 26.5 mmol of lithium aluminum hydride in 100 mL of diethyl ether. The reaction mixture was stirred at room temperature for 3 h and for an additional hour at solvent reflux. It was then cooled and quenched with chilled water added dropwise, followed by addition of a 10% solution of sulfuric acid until the precipitate was completely dissolved. The aqueous phase was separeted and was extracted with ether(3 X 50mL). The combined organic phases were washed with a saturated aqueous sodium chloride solution and dried. Removal of the solvent gave the secondary amine **5** as a colourless oil (0.9g, yield 69%).

IR(CCl_4; cm^{-1}): 1090s; 1120m; 1140m; 1260m; 1280m; 1400m; 1450m; 2880m; 2920s; 2980vs; 3020m; 3070 m; 3348 m; 3420 m.

^{1}H-NMR spectrum($CDCl_3$, δ ppm, J Hz): 0.98(d, 2.4, 4H, H-1a; H-7a; H-1'a;H-7'a); 1.22(dl; 9.1; 2H; H-8^a; H-8'^{a}); 1.52(dt; 9.1; 1.4; H-8^s; H-8'^{s}); 2.14(tt; 6.9; 2.4; 2H; H-1; H-1'); 2.41(d;6.9; 4H; H-9; H-9'); 3.29(m; 4H; H-2; H-7; H-2'; H-7'); 7.00-7.25(m; 8H; H-3-6; H-3'-6').

^{13}C-NMR spectrum ($CDCl_3$, δ, ppm): 26.97(C-1a; C-7a; C-1'a; C-7'a); 28.71(C-1; C-1'); 38.86(C-8; C-8'); 43.06(C-2; C-7; C-2'; C-7'); 52.08(C-9; C-9'); 120.70(C-3; C-6; C-3'; C-6'); 124,88(C-4; C-5); 151.21(C-2a; C-6a; C-2'a; C-6'a).

N-Nitroso bis(1aβ,2α,7α,7aβ-Tetrahydro- 1β-methylene-2,7-methano-1H-cyclopropa[b]naphtalene)amine (**1**)

To a mixture of 37% aqueous sodium nitrite (10mL), amine **5** (5 g, 14.16 mmoles) and 40 mL of diethylether maintained at 20°C, the azotic acid 35% (50 mL) was added by dropwise such as the aqueous layer to impart a permanent green colour. The reaction mixture was allowed to stand an additional 30 min and the layers were separated. The ether layer was washed with potassium carbonate 10% and then dried over anhydrous potassium carbonate. Evaporation of the ether *in vacuo* gave the N-nitrosoamine **1** (4 g; 74%) as a uncolorless solid which was recrystallised from methanol (m.p. 181-182°C).

IR(CS_2; CCl_4; cm^{-1}): 759vs; 790s; 1091m; 1110m; 1128m; 1350m; 1456m; 2860w; 2930s; 2974s; 2974s; 2974s; 3018m.

^{1}H-NMR spectrum($CDCl_3$, δ ppm, J Hz):

substituent sin:1.03(d,3.0, 2H, $H^{1a}H^{7a}$); 1.13(dl, 9.8, 1H, H^{8a}); 1.35(dt, 9.8, 1.6, 1H, H^{8s}); 1.92(tt, 7.0, 2.6, 1H, H^1); 3.28(sl, 2H, H^2H^7); 3.41(d, 7.0, 2H, H^9); 6.98-7.15(m, 4H, $H^3H^4H^5H^6$)

substituent anti: 0.92(d, 2.6, 2H, $H^{1'a}H^{7'a}$); 1.21(dl, 9.8, 1H, $H^{8'a}$); 1.42(dt, 9.8, 1.6, 1H, $H^{8's}$); 2.08(tt, 7.0, 3.0, 1H, $H^{1'}$); 3.32(sl, 2H, $H^{2'}H^{7'}$); 3.96(d, 7.0, 2H, $H^{9'}$); 6.98-7.15(m, 4H, $H^{3'}H^{4'}H^{5'}H^{6'}$)

^{13}C-NMR spectrum ($CDCl_3$, δ, ppm):

substituent sin: 26.47($C^{1a}C^{7a}$); 38.46(C^8); 42.76(C^2C^7); 47.79(C^9); 120.83(C^3C^6); 125.11(C^4C^5); 150.18($C^{2a}C^{6b}$)

substituent anti: 27.02($C^{1'a}C^{7'a}$); 38.65($C^{8'}$); 42.76($C^{2'}C^{7'}$); 54.17($C^{9'}$); 120.93($C^{3'}C^{6'}$); 125.18($C^{4'}C^{5'}$); 150.62($C^{2'a}C^{6'b}$)

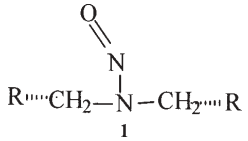
Anal. Calcd. for $C_{26}H_{26}N_2O$: C, 81.65; H, 5.53; N, 7.32; Found: C, 81.95; H, 5.23; N, 7.12.

Results and Discussions

The N-nitrosamine **1** was synthesized starting from the aldehyde **2**[5] (scheme 1).

The Schiff base **4** was obtained by the condensation of the aldehide **2** with the amine **3** and was not characterized. The reduction of Schiff base **4** with $LiAlH_4$ gave the secondary amine **5** (90% yield). The N-nitrosamine **1** was prepared by the nitrosation of the secondary amine **5** with dinitrogen tetroxide. The structure of the N-nitrosamine **1** was assigned by the elemental analysis and of the spectral data (IR, ^{1}H- and ^{13}C-NMR.

In the ^{1}H-RMN and ^{13}C-RMN spectra, close chemical shifts of signals that have the same multiplicity can be observed. The proofs for a nitrosamine structure are given by the sin anti isomerism of this group in respect with its vicinities.



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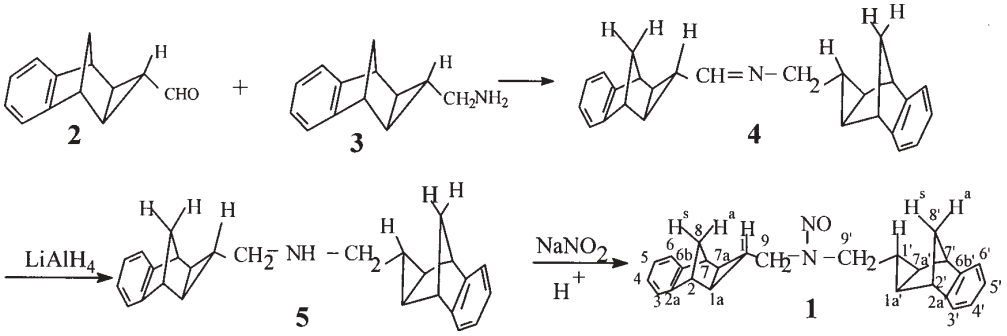
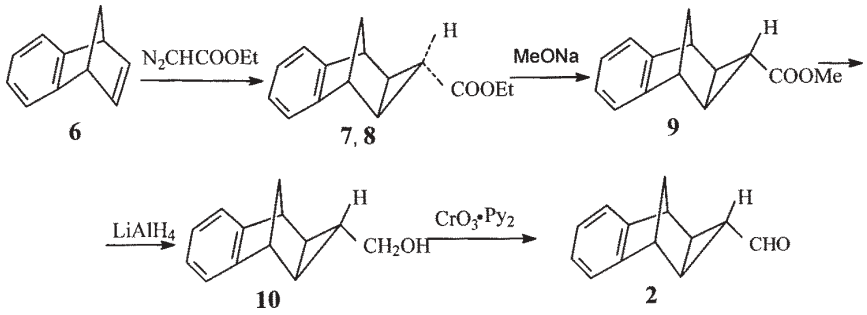
The chemical shifts both in ^{1}H-RMN and ^{13}C-RMN depend on the charge of the oxygen atom, that shields the neighbourhoods; as a consequence, the chemical shifts will be smaller for the sin substituents compared to those of the anti substituents. The difference in chemical shift between the sin and anti groups decrease with the distance from the nitroso group, being larger in the immediate proximity (part experimental).

The system AA'BB' of the eight aromatic protons in each aromatic ring, characteristic for an orto substitution, show peaks in within 7.00- 7.25ppm. The additional arguments are given by the conectivity experiments 2D [7].

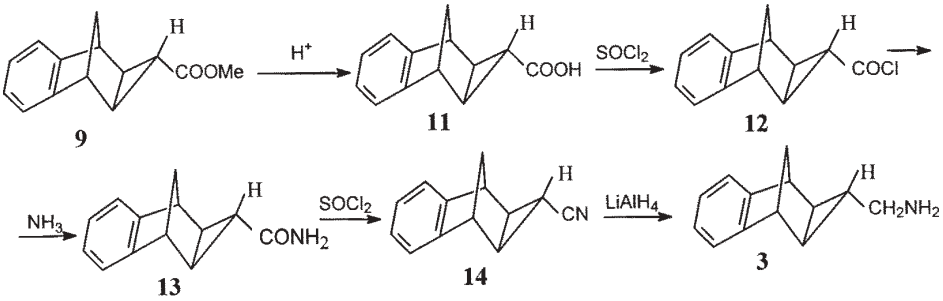
The aldehide **2** was obtained by the procedure described in the lit.[5] starting from benzonorbornadiene



Scheme 1



Scheme 2



Scheme 3

6 via the ethyl esters **7**, **8**, the methyl ester **9**, the alcohol **10**. The compound **2** was obtained by oxidation of the alcohol **10** with CrO_3 Py_2(Scheme 2). The aldehide **2** and the intermediates were characterized by the spectral data (IR, ^{1}H- and ^{13}C-NMR) (see experimental part).

The amine **3** was synthesized by the procedure described in the lit.[6] starting from the cyclopropancarboxylic acid **11** *via* the acid chloride **12**, the amide **13**, the nitrile **14** (scheme 3).

The amine **3** and the intermediates **9, 11**-**14** were characterized by the spectral data (IR, ^{1}H- and ^{13}C-NMR) (See Experimental). The acid **11** was obtained according to the method developed by M. Avram[4].

Conclusions

The synthesis and the spectral characterization of *N*-nitrosoamine **1** are described.

The structure of the new compounds was fully confirmed by their spectral data.

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