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

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The synthesis and the spectral characterisation of N-nitroso bis(1αβ, 2α, 7α, 7αβ-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-(1αβ, 2α, 7α, 7αβ-tetrahydro-2, 7-methano-1H-cyclopropa[b]naphtalene-1β-methylene-1αβ, 2β, 7β-tetrahydro-2, 7-methano-1H-cyclopropa[b]naphtalene-1β-carbinylation (4) and N-Bis(1αβ, 2α, 7α, 7αβ-Tetrahydro-1β-methylene-2, 7-methano-1H-cyclopropa[b]naphtalene) amine (5) are reported.

Keywords: N-nitrosoamine; nitrosation reaction; benzonorbornadiene

N-nitrosoamines were employed 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-nitrosoamines 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[1αβ, 2α, 7α, 7αβ-tetrahydro-1β-methylene-2, 7-methano-1H-cyclopropa[b]naphtalene]amine (1).

Experimental Part

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

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

(1αβ, 2β, 7β, 7αβ-tetrahydro-1β-(hydroxymethyl)-2, 7-methano-1H-cyclopropa[b]naphtalene amine (10) was synthesized according to [5] as a colourless oil by Cr2O72- oxidation (90 % yield) of the alcohol 10. The spectral data of 2 confirm the proposed structure.

IR spectrum (CS2; cm-1): 750 m; 1708 s; 2820 m; 2903 w; 2922 w; 2980 s; 3018w; 3050w.

1H-NMR spectrum (CDCl3, δ ppm, J Hz): 1.23 (2H, m); 1.69 (d, 2.5, 2H); 2.6 (dt, 2.5, 4.5, 1H); 3.35 (brs, 2H); 7.03 (m, 4H) 9.1 (d, 4.5, 1H).

13C-NMR spectrum (CDCl3, 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).

(1αβ, 2β, 7β, 7αβ-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 (CS2; cm-1): 994 s; 1071 s; 1772 vs; 2912 w; 2987 s; 3020 w; 3055 w; 3072 w.

1H-NMR spectrum (CDCl3, δ ppm, J Hz): 1.41 (bd; 10.5; 1H; H5); 1.46 (dt; 10.5; 1.6; 1H; H6); 2.00 (bd; 2.4; 2H; H7); 2.98 (t; 2.4 H7); 3.48 (bs; 2H; H7; H8); 7.00-7.22 (m; 4H; Harom).

13C-NMR spectrum (CDCl3, δ ppm): 34.38 (C(1αβ); 38.98 (C(5)); 39.76 (C(4)); 43.28 (C(2)); 121.54 (C(3)); 125.62 (C(4)); 149.04 (C(5)); 171.73 (C(6)).

(1αβ, 2β, 7β, 7αβ-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; 1655 s, 2810 w; 2970 w; 2855 w; 3055 w; 3195 m;

1H-NMR spectrum (CDCl3, δ ppm, J Hz): 1.31 (d; 9.9; 1H; H7); 1.43 (d; 9.9; 1H; H8); 1.62 (bs; 2H; H5; H6); 2.31 (bs; 1H; H8); 3.34 (bs; 2H; H7; H8); 5.78 (2H; H2); 6.95-7.20 (m; 4H; HHarom).

13C-NMR spectrum (CDCl3, δ ppm): 29.97 (C(1αβ); 30.36 (C(5)); 39.46 (C(4)); 43.04 (C(2)); 121.20 (C(3)); 125.30 (C(4)); 149.89 (C(5)); 173.43 (C(6)).

(1β-cyano-1αβ, 2β, 7β, 7αβ-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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obtained the Schiff base and the solvent was removed at reduced pressure. It mixture was refluxed for 2 h. Then, the reaction was cooled.

\[
\begin{align*}
1.22 (d; 9.9; 1H; H_8 sin); 1.51 (dt; 9.9; 1.4; 1H; H_8 a); 2.47 (d; 6.9; 1H; H_9); 3.28 (sl, 2H, H_2'H_7'); 3.41 (d, 7.0, 2H, H_9'); 6.98-7.15 (m, 4H, Harom).
\end{align*}
\]

IR spectrum (CCl₃; cm⁻¹): 1094 s; 1380 w; 1453 m; 1456 m; 1481 w; 2248 s; 2910 w; 2966 m; 3053 w; 3072 w.

\[
\begin{align*}
&1H-NMR spectrum (CDCl₃, δ, ppm, J, Hz): 0.86 (d; 2.6; 2H; H_5; H_6); 1.22 (d; 9.9; 1H; H_8 sin); 1.51 (dt; 9.9; 1H; H_8 a); 2.47 (d; 6.9; 1H; H_9); 3.28 (sl, 2H, H_2'H_7'); 3.41 (d, 7.0, 2H, H_9'); 6.98-7.15 (m, 4H, Harom).
\end{align*}
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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 aldehyde 2 with the amine 3 and was not characterized. The reduction of Schiff base 4 with LiAlH₄ 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, ¹H- and ¹³C-NMR).

The chemical shifts both in ¹H-RMN and ¹³C-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 connectivities of the aromatic protons and by the chemical shifts of signals that have the same multiplicity. The chemical shifts of aromatic protons in each neighbour (part experimental).

The system AA 'BB' of the eight aromatic protons in each neighbour (part experimental).

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\begin{align*}
&N-Nitroso bis[1aβ,2α,7α,7aβ-Tetrahydro-1β-methylene-2,7-methano-1H-cyclopropa[b]naphthalene]amine (1)
\end{align*}
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To a mixture of 37% aqueous sodium nitrite (10mL), amine 5 (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%).

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\begin{align*}
&b) \text{N-Bis[1aβ,2α,7α,7aβ-Tetrahydro-1β-methylene-2,7-methano-1H-cyclopropa[b]naphthalene]amine (5)}
\end{align*}
\]

A solution of Schiff base 4 (1.3g; 3.7 mmol) in 25 mL diethyl ether was added dropwise to a magnetically stirred suspension of 26.5 mmol of lithium aluminium 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 separated 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%).
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 aldehyde 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 cyclopropicarboxylic 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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