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Synthesis of a new heterocyclic system - 3H-pyrrolo [3,2-c] - phenothiazine

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Abstract

Based on classic Fischer reaction a new heterocyclic system - 3H-pyrrolo [3,2-c] – phenothiazine is developed and spectral characteristics are studied.

Keywords: Pirrolofenotiazine, Indole

Introduction

It is hard to find the heterocyclic system other than phenothiazine derivatives of which, having simple structure, show such an amazing biological activity. Among phenothiazine derivatives prepara-tions stimulating and acting on cardiovascular systems and central nervous system, narcotic and spasmolytic, curare-like, sedative agents and a variety of compounds with other actions can be found (Mashkovskii, 2000; Arzamastsev, 2004). The goal of the given work was creation of new heterocyclic system combining fragments of phenothiazine and pyrrole in one molecule.

Methodology

Stages of synthesis have been implemented on the basis of classic Fischer reaction (Suvorov, Mamaev, Rodionov, 1959; Palavandishvili, 1984). **Hydrochloride 3-amino-phenothiazine (1)** (Figure 1) has been selected by us as initial compound (Antonov, 1950). Diazotization of compound (1) and further reduction of diazo-com-pound to hydrazine have been implemented according to routine method (Kanaoka, Ban, Miyashita, Irie, Vonemitsu, 1966; Sikha-rulidze, Khoshtaria, Kurkovskaya, Tretyakova, Efimova, Suvorov, 1979). Interaction of obtained hydrochloride 3-phenothiazine-hy-drazine with ethyl ether of pyruvic acid (2) (Figure 1) leads to formation of phenothiazine-3-il-hydrazone ethyl ether of pyruvic acid (2) in the form of mixture of geometric isomers. The latter was divided into syn- and anti- forms by means of column chromatog-raphy (2, a, b).).

Electronic absorption spectrum is taken in ethanol on spectrophotometer Varian Cary100Conc UV-Visible. IR spectra are re-corded on spectrometer Thermo Nicolet Avatar 370 in vaseline oil. Nuclear-magnetic resonance (NMR) spectra of 1H are recorded on spectrometer Bruker WM-250 (250 MHz) in acetone-d6, with inter-nal TMS standard. Elemental analysis is carried out on the analyzer HP-165B CHN. Melting temperatures are determined on the appa-ratus Mel-Temp 30. Control over the course of a reaction and purity of products has been carried out on Silufol UV-254 plates. Reaction products have been purified by means of crystallization and column chromatography with the use of silica gel of 100/250 mc grade. Mixture of ether-hexane (3:1) is used as eluent.

Due to instability of 3-amino-phenothiazine to oxygen and atmospheric moisture the mentioned amine was received ac-cording to the method modified by us (Kanaoka, Ban, Miyashi-ta, Irie, Vonemitsu, 1966), differing by the fact that reduction of 3-nitrophenothiazine is carried out in argon atmosphere, which afterwards is transformed to stable hydrochloride (1) and further is stored and used in this form. Calculated amount of Sn solution in 30 ml of HCl is added to the solution of 11 g (5,1 mmole) of 3-nitro-phenothiazine in absolute ethanol dropwise, by stirring. Reaction is conducted at 60°C temperature during 12 hours. The precip-itated crystals are filtered and thoroughly washed with absolute hexane up to neutral reaction and then they are dried in vacuum over concentrated H2SO4. Then 9 g of 3-amino-phenothiazine is obtained, which is dissolved in the absolute ether without addi-tional purification and gaseous HCl is blown through this solution. After crystallization the yield of pure hydrochloride is 1,75% and melting temperature is 174°C.

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Results

By comparing the NMR 1H spectra of the solutions of hydrazone stereoisomeric forms (2) in acetone-d6 is observed the sygnal bias of proton of exocyclic NH group of isomere 2a in the low field (11,5 ppm) in comparison with the appropriate sygnal of proton of isomere 2b (8,0 ppm) at the expense of intramolecular hydrogen bonding, formation of which is indicated by changes in IR and UV spectra.

In IR spectra of syn- and anti-forms of hydrazones (2 a,b) sub-stantial differences in characteristic absorption frequencies of CO and NH groups are observed. Absorption band of carbonyl group anti-isomere (2,b) is located at 1690 cm-1, while for syn-form (2,a) the bias of this absorption band to the area of low frequencies (1660 cm-1) is observed.

Differences are observed also for absorption bands of NH group. For instance, in the case of anti-form (2b) stretching vi-bra-tions of NH bond are manifested in the area of 3340 cm-1, but of syn-form (2a) - in the area of 3290 cm-1.

Presence of hydrogen bonding in stereoisomeric forms of hy-drazone (2, a,b) is also manifested in UV spectra. Bathochromic bias of long-wave absorption band, characteristic for syn-isomere, also takes place in the case of compound 2a (on the 45 nm), com-pared with its anti-form, reinforcing the conclusions made on the basis of IR and NMR 1H spectra.

Cyclization of hydrazone (2) under action of ethyl ether of polyphosphoric acid has lead to tetracyclic system – ethyl ether of 3H-pyrrolo[3,2-c]phenothiazine-2 of carbolic acid (3). Conse-quen-tial saponification of ether (3) to the corresponding 2-carbox-ylic acid (4) and thermal decarboxylation gave targeted 3H-pyrrolo [3,2-c] phenothiazine (5) (Figure 1).

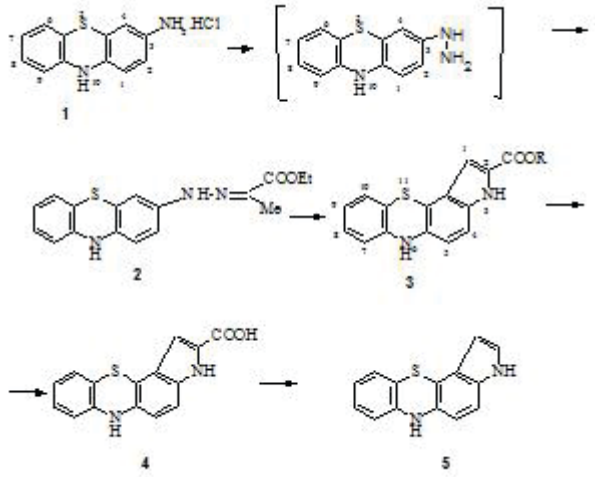

Figure 1. Scheme of the synthesis of 3H-pyrrolo [3,2-c] - phenothiazine

Conclusion

Phenothiazine-3-il-hydrazone of ethyl ether of pyruvic acid (2) (Figure 1). Hydrochloride (**1**) (3,7 g, 18,5 mmole) is dissolved when heating in 20 ml of absolute ethanol, then 10 ml of concentrated HCl is added when stirring and the solution is cooled down to –5÷ –10°C. During stirring a solution of 1,6 g (23,1 mmole) of NaNO2 is added dropwise into 7 ml of absolute ethanol. Stirring lasts during 1,5 hours at -5°C. 9.02 g (40 mmole) of SnCl2.2H2O in 30 ml of concentrated HCl is added dropwise to the obtained solution of diazonium salt and stirring lasts another 3 hours, after which pre-cipitated crystals of phenothizine-3-il-hydrazine undergo filtration, thorough washing by boiling hexane and fast filtration. Saturated solution of sodium acetate is added to the filtrate at room tempera-ture, with pH raising up to 3 and 2,5 ml (20 mmole) of ethyl ether of pyruvic acid in 4 ml of ethanol is added dropwise. Precipitated crys-tals undergo filtration, washing by water up to neutral reaction and drying in the air. As a result 3,8g of hydrazone (65%) is obtained. Received mixture of hydrazone stereoisomeres is divided on the column with silicagel (eluent is ether-hexane 3:1). Ratio of syn- and anti-forms is 1:4.

Syn-isomere (syn-2) is dark-yellow powder. Melting tem-perature is 236-238°C. UV spectrum, $\lambda_{max,}nm\ (lg\varepsilon)$: 219 (4.44), 239 (4.67), 251 (4.88), 312 (4.62), 320 (4.30). IR spectrum: 1660 (C=O), 3290 (NH). NMR 1H spectrum, δ, ppm (J, Hz): 1.36 (3H, t, J = 7.1, CH_2CH_3); 2.19 (3H, c, CH3); 4.31 (2H, k, J = 7.1, CH_2CH_3); 7.63 (1H, dd, $J_{1.2}$ = 9.0, $J_{2.4}$=0.4, H-2); 7.4–7.7 (3H, m, H 7,8,9); 7.72 (1H, d, $J_{2.4}$=0.4, H-4); 7.34 (1H, d, J1.2=9.0, H-1); 8.04 (1H, m, H-6); 8.0 (1H, brs, N(10)H); 11.5 (1H, brs.,C(3)NH). It is found, %: C 62.2; H 5.5; N 12.2; S 9.5. $C_{17}H_{17}N_3O_2S$. It is calculated, %: C 62.38; H 5.19; N 12.84; S 9.78.

Anti-isomere (anti-2) is durty-yellow powder. Melting tempera-ture is 248–250 °C. IR spectrum ν, cm^{-1}: 1690 (C=O), 3340 (NH). UV spectrum, $\lambda_{max,}nm\ (lg\varepsilon)$: 220 (4.48), 240 (4.70), 248 (4.76), 308 (4.52), 315 (4.25). NMR 1H spectrum, δ, ppm. (J, Hz): 1.38 (3H, t, J = 7.1, CH_2CH_3); 2.23 (3H, c, CH3); 4.30 (2H, k, J = 7.1, CH_2CH_3); 7.60 (1H, dd, $J_{1.2}$ = 9.0, $J_{2.4}$=2.4, H-2); 7.4–7.7 (3H, m, H-7,8,9); 7.70 (1H, d, $J_{2.4}$ = 2.4, H-4); 7.34 (1H, d, $J_{1.2}$ = 9.0, H-1); 8.04 (1H, m, H-6); 8.0 (2H, brs, N(10)H and C(3)NH). It is found, %: C 62.4; H 5.6; N 12.0; S 9.6. $C_{17}H_{17}N_3O_2S$. It is calculated, %: C 62.38; H 5.19; N 12.84; S 9.78.

Ethyl ether of 3H-pyrrolo[3,2-c] phenothiazine-2-carboxyl-ic acid (3). 3 g (9,1 mmole) of well-dried phenothiazine-3-il-hy-dra-zone of ethyl ether of pyruvic acid (2) is added by small portions into ethyl ether of polyphosphoric acid (50 g) heated up to 50°C so that the mixture temperature does not rise above 90°C. The mixture is maintained at at 90°C for 4 hours and then it is cooled down to room temperature, decomposed on processed ice and left overnight. Precipitated crystals undergo filtration thorough washing by water up to neutral reaction and are dried over concentrated H2SO4 under vacuum at 30°C temperature. As a result, compound (3), dirty-yellow powder is obtained, with 60% yield and 312-314°C melting temperature.

NMR ^{1}H spectrum, δ, ppm. (J, Hz): 1.38 (3H, t, J = 7.2, CH_2CH_3); 4.41 (2H, k, J = 7.2, CH_2CH_3); 7.64 (1H, d, J1,3=2.2, H-1); 7.5–7.8 (3H, m, H-7,8,9); 7.95 (1H, d, $J_{4,5}$ = 9.1, H-4): 7.43 (1H, d, $J_{4,5}$ = 9.1, H-5); 8.11 (1H, m, H-10); 9.1 (1H, brs, N(6)H); 11.7 (1H, brs, N(3)H). It is found, %: C 65.6; H 4.5; N 9.2; S 10.5; $C_{17}H_{17}N_3O_2S$. It is calculated, %: C 65.80; H 4.51; N 9.03; S 10.32.

3H-pyrrolo[3,2-c]phenothiazine-2-carboxylic acid (4). Ethyl ether (3) (14 g, 45.1 mmole) is boiled during 5 hours in the mixture of 50 ml of ethanol and 50 ml of 10% water solution of NaOH, after which the solution is cooled down to room tem-perature, at that time solution turbidity is observed and precip-itation of crystals of acid (4) takes place. Precipitated crystals undergo filtration, thorough wash-ing by water up to neutral reaction and are dried over H2SO4 under vacuum; 12,6 g of the compound (4), grayish-yellow powder is ob-tained with quanti-tative yield and 340-343°C melting temperature. NMR 1H spec-trum, δ, ppm. (J, Hz): 7.67 (1H, d, J1.3= 2,2, H-1); 7.6-7.8 (3H, m, H-7,8,9); 7.95 (1H, d, J4,5 = 9.1, H-4): 7.44 (1H, d, J4,5 = 9.1, H-5); 8.11 (1H, m, H-10); 8.2 (1H, brs, N(6)H); 11.6 (1H, brs, N(3) H); OH sygnal is not recorded due to exchange with solvent. It is found, %: C 63.6; H 3.5; N 9.7; S 11.5. C15H10N2O2S; It is calculated, %: C 63.82; H 3.54; N 9.92; S 11.34.

3H-pyrrolo[3,2-c]phenothiazine (5). Acid (**5**) (10 g, 35.4 mmole) is decarboxylated and maintained for 1 minute at melting temperature in the inert gas environment. After cooling to the room

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temperature the product is cromatographed on the column with the use of Chemapol 100/50 silicagel; 3.37 g of dirty-yellow powder of compound (5) is obtained with 40% yield and 305-307°C melting temperature.

NMR ^{1}H spectrum, δ, ppm. (J, Hz): 7.05 (1H, dd, $J_{1,2}$ = 3.3 $J_{1,3}$ = 2.1 H-1); 7.84 (1H, d, $J_{4,5}$ = 8.8, H-4): 7.5–7.8 (3H, m, H-7,8,9); 7.65 (1H, dd, $J_{1,2}$ = 3.3 $J_{2,3}$ = 2.6, H-2); 7.23 (1H, d, J4,5 = 8.8, H-5); 8.10 (1H, m., H-10); 8.2 (1H, brs, N(6)H); 11.0(1H, brs, N(3)H). It is found, %: C 70.6; H 4.4; N 11.7; S 13.5. $C_{14}H_{10}N_2S$. It is calculated, %: C 70.58; H 4.20; N 11.76; S 13.44.

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