Synthesis of bicyclo[3.3.1]nonane derivatives containing fused heterocyclic rings

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Abstract

The condensation reactions of 3,7-dihalobicyclo[3.3.1]nonan-2,6-dione or 3-bromobicyclo[3.3.1]nonan-2-one (racemates) with 4-amino-2,4-dihydro-*3H*-triazolothione, 2-thiobenzimidazole and thiocarbamide were performed. New compounds containing bicyclo[3.3.1]nonane framework with fused thiazole, imidazothiazole and 1,8a-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine rings were synthesized.

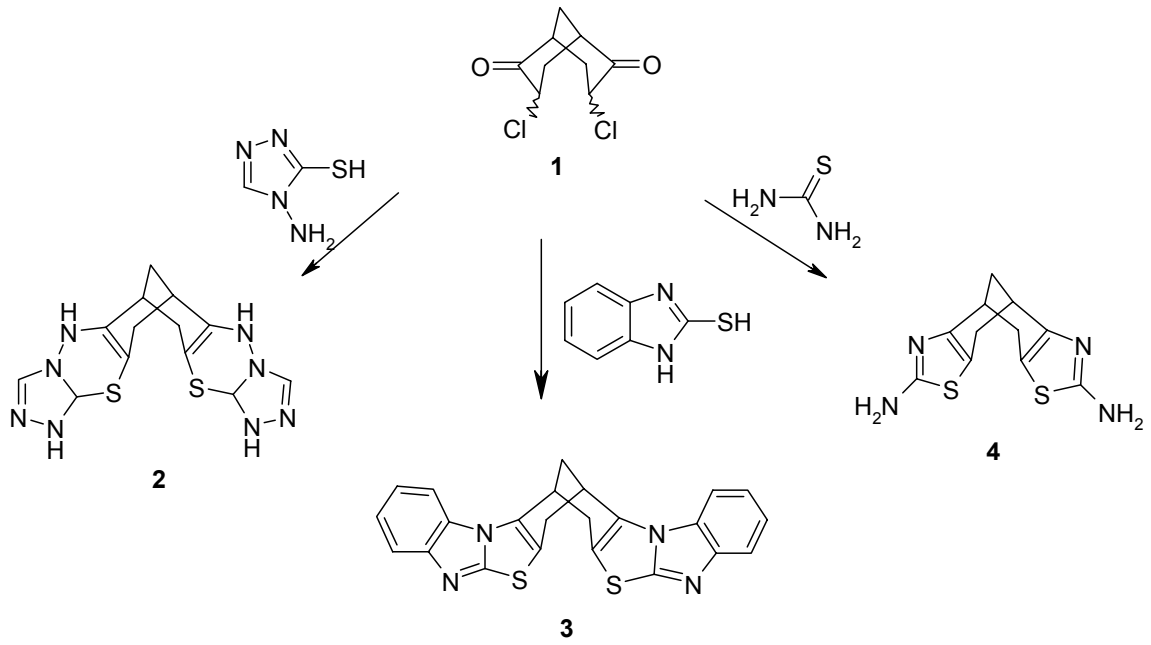
Keywords: 3,7-Dihalobicyclo[3.3.1]nonan-2,6-diones, 3-bromobicyclo[3.3.1]nonan-2-one, thiazole, imidazothiazole, 1,8a-dihydro-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine

Introduction

Previously it was reported that compounds containing two properly allocated pyrimidine, indole and other rings in its structure possess self-assembling properties and can form supramolecular structures[1,2] as well as the natural compounds[3]. The presence of bicyclo[3.3.1]nonane core in synthetic compounds is necessary to keep two heterocyclic parts of molecule at such positions that they could form intermolecular hydrogen or electrostatic bonds which would support regular intermolecular structures. On the other hand, bicyclo[3.3.1]nonane derivatives with heterocyclic moieties are target compounds in re-synthesis of natural compounds[4-6] and synthesis of their analogues (taxoids) used in drug research[7,8]. A series of new compounds containing two polar heterocyclic moyeties, fixed in a proper conformation by the framework of bicyclo[3.3.1]nonane and their analogues with one heterocyclic moiety were synthesized.

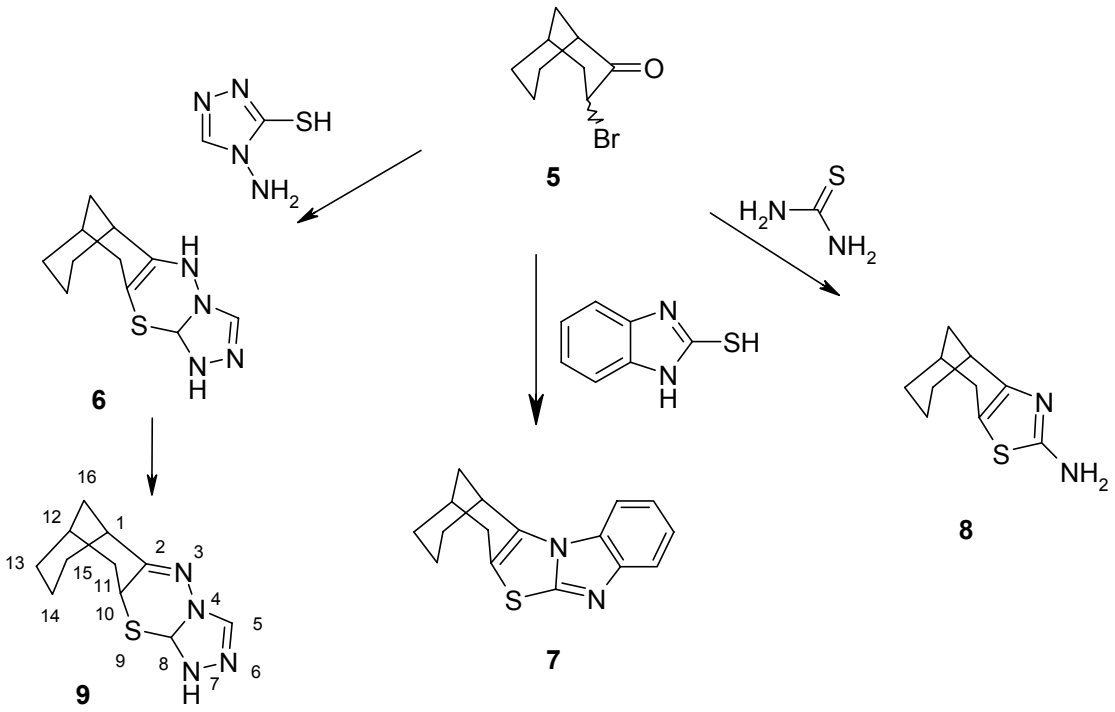
Results and Discussion

Compounds **2-4** bearing two heterocyclic rings were synthesized by the condensation of 3,7-dichlorbicyclo[3.3.1]nonan-2,6-dione (**1**) (racemate)[9-11] with 4-amino-2,4-dihydro-*3H*-triazolothione[12], 2-thiobenzimidazole and thiocarbamide (Scheme 1).



Scheme 1

The yields of products **2-4** has decreased by 10-20% in the cases if the dibromo analogue[9-11] of compound **1** was used. The formation of bigger amounts of by-products in these cases was observed. Compounds **6-8** bearing one heterocyclic ring were synthesized analogously by the condensation of 3-bromobicyclo[3.3.1]nonan-2-one[13] (**5**) (racemate) with 4-amino-2,4-dihydro-*3H*-triazolothione, 2-thiobenzimidazole and thiocarbamide (Scheme 2).



Scheme 2

Compounds **4** and **8** were synthesized in two steps by Hantzsh[14]. The first step of condensation was performed in ethanol by reflux for 3 hours. The second step required melting of reaction mixture without solvent. 2-Thiobenzimidazole reacted with alpha-haloketones **1**, **5** and gave final condensation products under milder conditions. Thus, compounds **3** and **7** have been synthesized in ethanol solution by reflux within 3 hours. The reaction of 4-amino-2,4-dihydro-*3H*-triazolothione with **1**, **5** in boiling ethanol was completed within 10 hours. Surprisingly, compound **6** has showed significant unstability. It has partially rearranged to **9** in several hours by standing.

The structures of compounds **2-4** and **6-9** were confirmed by comparison of experimental and calculated chemical shifts in ^{1}H and ^{13}C spectra. The means of chemical shifts were calculated using VAMP[15] program using geometries of **3-9** optimized with the semi-empirical PM3 method[16].

Experimental Section

General Procedures. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrophotometer model FT-IR Spectrum BX II. ^{1}H-NMR spectra were recorded on Varian Unity Inova (300 MHz). The purity of compounds was checked on silica gel coated plates (Merck).

9,20-Dithio-3,4,6,7,14,15,17,18-octaazahexacyclo[10.10.10^{2,10}.0^{4,8}.0^{13,21}.0^{15,19}]tricosa-2(10),5,13(21),16-tetraene (2). The solutions of 0.23 g (0.2 mmol) 4-amino-2,4-dihydro-*3H*-1,2,4-triazol-3-thione in 10 mL ethanol and 0.221 g (0.1 mmol) 3,7-dichloromobicyclo[3.3.1]nonan-2,6-dione in 15 mL ethanol were joined, refluxed with stirring for 2 h and cooled to room temperature. Obtained crystalline product was filtered off to give 0.282 g (67%) **2** (dihydrobromide), m. p. > 300 °C. IR (cm $^{-1}$): 3429 (N-H), 1615 and 1632 (C=C), 1480 and 1443 (C=N). ^{1}H NMR (CD_3COOD) δ: 2.21 - 2.43 (4H, m, CH_2), 2.57 – 2.65 (2H, m, CH), 3.40 (4H, br. s, CH_2), 3.49 (4H, br. s, CH_2), 8.82 (N=C-H, 2H, s), 10.12 (s, N-H, HBr). Anal. Calcd. for $C_{13}H_{18}Cl_2N_8S_2$ (421.37): C, 37.05%; H, 4.31%; Cl, 16.83%; N, 26.59%; S, 15.22%; Found: C, 36.87%; H, 4.47%; N, 26.85%

12,26-Dithio-3,10,17,24-tetraazacyclo[13.13.1.0^{2,13}.0^{3,11}.0$^{4,\ 9}$.0$^{16,\ 27}$.0$^{17,\ 25}$.0$^{18,\ 23}$] nonacosa-2(13),4,6,8,10,16(27),18,20,22,24-decaene (3). The solutions of 0.22 mg (0.1mol) 3-bromobicyclo[3.3.1]nonan-2-one in 10 mL ethanol and 0.33 g (0.22 mmol) 2-thiobenzimidazole in 10 mL ethanol were joined and refluxed with stirring for 3 h. Solvent was evaporated, oily product was triturated with 10% NaOH and washed with H_2O, dissolved in $CHCl_3$, dried with Na_2SO_4 and fractionated on silica gel column using EtOAc to give 0.198 g (48%) **7**. IR (cm $^{-1}$): 1632 (C=C). ^{1}H NMR (CD_3COOD) δ: 1.92 - 1.95 (2H, m, CH_2), 2.02 - 2.06 (2H, m, CH_2), 3.14 - 3.19 (2H, m, CH_2), 3.61 - 3.66 (2H, m, CH), 7.43- 7.46 (4H, m, ArH), 7.73 - 7.76 (4H, m, ArH). Anal. Calcd. for $C_{23}H_{16}N_4S_2$ (412.54): C, 66.96%; H, 3.91%; N, 13.58%; S, 15.54%; Found: C, 67.14%; H, 4.08%; N, 13.66%

5,12-Dithio-3,10-diazatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),3,9(13),10-tetraen-4,11-diamine (4). The solutions of 0.22g (0.1 mmol) 3,7-dichlorbicyclo[3.3.1]nonan-2,6-dione in 20 mL ethanol and 0.18g (0.24 mmol) thiocarbamide in 20 mL ethanol were joined and refluxed with stirring for 3 h. The solvent was evaporated and the residue was kept at 180-200 °C for 1 h. Obtained product was recrystallized from ethanol to give 0.25 g (75%) **4** (dihydrochloride); m. p. 300-303 °C. IR (cm $^{-1}$): 3180, 3120, 3090, 3030 (NH_2), 1632 (C=C), 1583 (C=N). ^{1}H NMR (CD_3OD) δ: 1.96 (CH_2, 2H, s), 2.51 - 2.56 (CH_2, 2H, m), 2.62 (4H, d, J = 16 Hz, CH_2), 2.84 (4H, dd, J = 16 and 4 Hz, CH_2,), 3.26- 3.36 (CH, 2H, m). ^{13}C NMR ($CDCl_3$) δ: 19.2 (1-C), 19.5 (8-C), 20.5 (7-C), 20.7 (14-C), 28.6 (16-C), 136.9 (6- and 13-C), 170.8 (2- and 9-C), 177.9 (4- and 11-C). Anal. Calcd. for $C_{11}H_{14}Cl_2N_4S_2$ (337.29): C, 39.17%; H, 4.18%; Cl, 21.02%; N, 16.61%; S, 19.01%; Found: C, 39.06%; H, 4.34%; N, 16.37%.

9-Thio-3,4,6,7-tetraazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),5-diene (6). The solutions of 0.22 mg (0.1mol) 3-bromobicyclo[3.3.1]nonan-2-one in 10 mL ethanol and 0.127 g (0.11 mmol) 4-amino-2,4-dihydro-*3H*-1,2,4-triazol-3-thion in 10 mL ethanol were joined and refluxed with stirring for 10 h, cooled, neutralized with 10% Na_2CO_3, evaporated, dissolved in $CHCl_3$, dried with Na_2SO_4 and fractionated in silica gel column using the mixture of $CHCl_3$ and diethyl ether in ratio 5:1 to give 0.114 g (48%) **6**. IR (cm $^{-1}$): 3449 (N-H), 1638 (C=C), 1483 and 1445 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.87 - 2.07 (6H, m CH_2), 2.36 (2H, d, J = 5 Hz, CH_2), 2.67- 2.79 (2H, m, CH_2), 2.98 - 3.12 (1H, m, CH), 4.05- 4.08 (1H, m, CH), 7.30 (N-CH, 2H, s), 8.48 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ: 18.7 (14-C), 21.8 (12-C), 26.0 (1-C), 31.2 (15-C), 31.4 (11-C), 33.3 (13-C),

36.3 (16-C), 76.7 (8-C), 142.1 (5-C), 142.4 (10-C), 166.3 (2-C). Anal. Calcd. for $C_{11}H_{16}N_4S$ (236.34): C, 55.90%; H, 6.82%; N, 23.71%; S, 13.57%; Found: C, 56.02%; H, 7.01%; N, 23.69%

12-Thio-3,10-diazapentacyclo[13.3.1.0^{2,13}.0^{3,11}.0^{4,9}] nonadeca-2(13),4,6,8,10-pentaene (7). The solutions of 0.22 mg (0.1mol) 3-bromobicyclo[3.3.1]nonan-2-one in 10 mL ethanol and 0.165 g (0.11 mmol) 2-thiobenzimidazole in 10 mL ethanol were joined and refluxed with stirring for 4 h. Solvent was evaporated, solid product was triturated with 10% NaOH and washed with H_2O. Obtained oil was dissolved in $CHCl_3$, dried with Na_2SO_4 and fractionated in silica gel column using the mixture of $CHCl_3$ and MeOH in ratio 10:1 to give 0.175 g (65%) **7**. IR (cm $^{-1}$): 3138, 3054 (NH_2), 1630 (C=C), 1468 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.44 - 1.49 (CH_2, 2H, m), 1.74 - 1.78 (2H, m, CH_2), 1.79 - 1.83 (2H, m, CH_2), 1.97 - 2.04 (2H, m, CH_2), 2.40 - 2.49 (1H, m, CH_2), 2.58 (1H, d, J = 16 Hz, CH_2), 3.08 (1H, dd, J = 16 and 5 Hz, CH), 3.62 - 3.66 (1H, m, CH), 7.08-7.18 (2H, m, ArH), 7.64 (1H, d, J = 9Hz, ArH), 7.82 (1H, d, J = 9Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 27.1 (17-C), 27.7 (18-C), 27.8 (14-C), 29.5 (1-C), 30.9 (15-C), 32.1 (19-C), 33.1 (16-C), 110.6 (5-C), 120.5 (13-C), 121.05 (8-C), 122,1 (6-C), 123.1 (7-C), 129.8 (4-C), 130.2 (2-C), 147.8 (9-C), 156.5 (11-C). Anal. Calcd. for $C_{16}H_{16}N_2S$ (268.38): C, 71.61%; H, 6.01%; N, 10.44%; S, 11.95%; Found: C, 50.16%; H, 4.34%; N, 20.97%

5-Thio-3-azatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-4-amine (8). The solutions of 0.1 g (0.46 mmol) 3-bromo-bicyclo[3.3.1]-nonan-2-one in 10 mL ethanol and 0.038 g (0.51 mmol) thiocarbamide in 10 mL ethanol were joined and refluxed with stirring for 4 h. The solvent was evaporated and the residue was kept at 180-200 °C for 1 h. Obtained product was triturated with 10% NaOH, washed with H_2O, dried and fractionated in silica gel column using ethyl acetate to give 0.05 g (56%) **8**. IR (cm $^{-1}$): IR (cm $^{-1}$): 3135, 3140(NH_2), 1642 (C=C), 1578 (C=N). ^{1}H NMR ($CDCl_3$) δ: 0.98 - 1.01 (4H, m, CH_2), 1.18 - 1.40 (1H, m, CH), 1.69 - 1.82 (2H, m, CH_2), 2.25 – 2.38 (CH_2, 2H, m), 2.41 - 2.52 (1H, m, CH), 2.97 – 3.05 (CH_2, 2H, m), 3.60 (1H, br. s, NH_2), 5.21 (1H, br. s, NH_2). Anal. Calcd. for $C_{10}H_{14}N_2S$ (194.30): C, 61.82%; H, 7.26%; N, 14.42%; S, 16.50%; Found: C, 62.03%; H, 7.31%; N, 14.28%

9-Thio-3,4,6,7-tetraazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2,5-diene (9) was formed from **6** and isolated by chromatography on silica gel column using $CHCl_3$. IR (cm $^{-1}$): 3449 (N-H), 1638 (C=C), 1445 (C=N), 1483 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.31 - 1.68 (m, CH_2, 2H), 1.70 – 1.84 (8H, m, CH_2), 2.19 – 2.23 (1H, m, CH), 2.45 – 2.49 (1H, m, CH), 3.49 – 3.52 (1H, m, CH), 7.3 (N-CH, 2H, s), 8.48 (NH, 1H, s). ^{13}C NMR ($CDCl_3$) δ: 28.3 (14-C), 29.9 (15-C), 37.2 (1-C), 33.1 (11-C), 33.7 (13-C), 34.1 (16-C), 36.1 (12-C), 38.4 (10-C), 77.5 (8-C), 142.5 (5-C), 164.6 (2-C). Anal. Calcd. for $C_{11}H_{16}N_4S$ (236.34): C, 55.90%; H, 6.82%; N, 23.71%; S, 13.57%; Found: C, 55.74%; H, 6.63%; N, 23.55%

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