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INTERACTION OF 7-CHLORO-9-METHYLTHIO-3-PHENYLPYRIMIDO-[5,4-*f*][1,2,4]TRIAZOLO[3,4-*b*][1,3,4]-THIADIAZEPINE WITH SOME NUCLEOPHILES

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*The reactions of 7-chloro-9-methylthio-3-phenylpyrimido[5,4-f][1,2,4]triazolo[3,4-b][1,3,4]-thiadiazepine (**1**) with some nucleophiles have been studied. Substitution of the chlorine atom with hydrogen occurs with ammonia in DMSO to give 9-methylthio-3-phenylpyrimido[5,4-f][1,2,4]-triazolo[3,4-b][1,3,4]thiadiazepin-7(8H)-one. With a methanolic solution of ammonia the 7-methoxy derivative is formed. Reaction of compound **1** with an excess of sodium methoxide in methanol gave 6,7-dimethoxy-9-methylthio-3-phenyl-5,6-dihydropyrimido[5,4-f][1,2,4]triazolo[3,4-b][1,3,4]thia-diazepine. The corresponding 7-substituted derivatives were obtained when compound **1** was heated with morpholine or 2-(dimethylamino)ethylamine. The azomethine bond of the thiadiazepine ring is reduced by sodium borohydride to give the corresponding 5,6-dihydro derivatives.*

Keywords: amines, pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine, reduction, nucleophilic substitution.

Pyrrolo[2,1-*c*]benzodiazepine antibiotics and some of their heterocyclic analogs show anticancer activity [1]. It has been proposed that the cytotoxicity and antitumour activity of these compounds results from the formation of a covalent bond between the azomethine unit of the diazepine ring and the C(2)- amino group guanine nucleus in the minor groove of the DNA double spiral [2-5]. We have synthesized for the first time the first example of new heterocyclic systems – pyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]triazepine [6] – which can be described as structural analogs of the antibiotics mentioned above. It seemed expedient to us to investigate the interactions of one derivative of this heterocycle with some nucleophiles with the objective of synthesizing new examples of these little studied heterosystems for biological testing.

7-Chloro-9-methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (**1**) studied here was synthesized by cyclocondensation [6] between 4-amino-3-phenyl-1,2,4-triazol-5-thione and 4,6-dichloropyrimidin-5-carbaldehyde. A ^{1}H NMR study of compound **1** in DMSO-d_6 showed that at increased temperatures the signal of C(6)-H shifted irreversibly by 0.2 ppm to strong field which indicated that a reaction occurred between compound **1** and water present in the solvent.

In fact the reaction of compound **1** with water in DMSO at 80°C gave 9-methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]triazepin-7(8H)-one (**2**) in 74% yield (scheme). The easy reaction of water with compound **1** stimulated further investigation of reactions with sodium methoxide and

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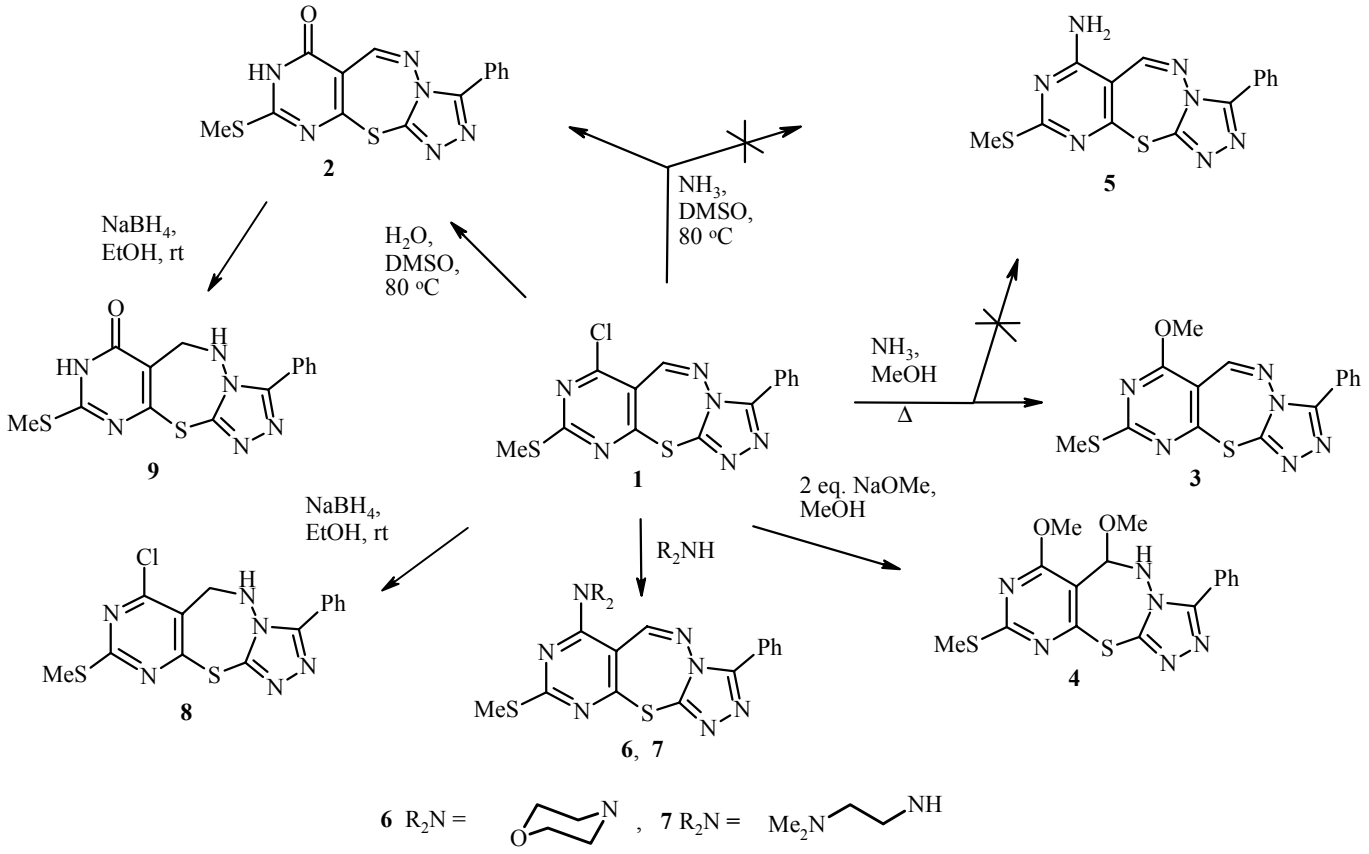
2
5
NaBH4, EtOH, rt
H2O, DMSO, 80 °C
NH3, DMSO, 80 °C
9
1
NH3, MeOH Δ
3
NaBH4, EtOH, rt
2 eq. NaOMe, MeOH
R2NH
8
6, 7
4
6 R2N =
7 R2N =

various amines. We note that introduction of amino groups into the molecule is of particular interest because aromatic or heteraromatic condensed systems with mobile basic chains are potential intercalators [7-9].

Reaction of compound **1** with an equivalent amount of sodium methoxide at room temperature gave the 7-methoxy derivative **3**. With two equivalents of sodium methoxide in boiling methanol nucleophilic substitution at the chlorine atom is accompanied by addition of methanol to the azomethine fragment of the thiadiazepin ring to give the 6,7-dimethoxy derivative **4**. When compound **1** was heated with ammonia in DMSO or methanol the 7-oxo- and 7-methoxy derivatives **2** and **3** were obtained instead of the expected product **5**. This is explained by ammonia playing the role of base only, while water, present in DMSO, and methanol react as nucleophiles. Reaction of compound **1** with morpholine or 2-(dimethylamino)ethylamine in DMSO at 60°C led to formation of the corresponding 7-substituted amino derivatives **6** or **7**. Reduction of compounds **1** and **2** with sodium borohydride occurred at room temperature only at the azomethine unit of the thiadiazepin ring to give the 5,6-dihydro derivatives **8** and **9**. In the ^{1}H NMR spectra of compounds **8** and **9** a doublet for the methylene group at position 6 of the heterosystem was observed at 4.37 and 4.13 ppm respectively in place of the characteristic singlet of the azomethine group. In the IR spectrum of compound **8** and NH absorption was observed at 3204 cm^{-1}, while in the IR spectrum of compound **9** absorption bands for to NH groups and a CO were observed at 3311, 3289, and 1638 cm^{-1} respectively.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a Perkin-Elmer FT-IR Spectrum BX II spectrophotometer. ^{1}H NMR spectra were obtained with a Tesla BS-587A spectrometer (80 MHz) with TMS as internal standard. The course of reactions and the purity of products were monitored by TLC on Silica gel 60 F_{254} strips (Merck).

7-Chloro-9-methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (1) was synthesized by a known method [6].

9-Methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-7(8H)-one (2). A. Water (0.01 ml, 0.56 mmol) was added to a solution of compound **1** (0.202 g, 0.56 mmol) in DMSO (3 ml) and the mixture was heated for 3 h at 80°C. After cooling the white precipitate was filtered off and recrystallized to give compound **2** (0.14 g, 74%).

B. Compound **1** (0.1 g, 0.28 mmol) was added to a saturated solution of ammonia in DMSO (3 ml) and the mixture was heated for 5 h at 80°C. After cooling the white precipitate was filtered off and recrystallized to give compound **2** (0.05 g, 52%); mp 284-285°C (2-propanol–DMSO, 5:1). IR spectrum, ν, cm^{-1}: 3170 (NH), 1684 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.62 (3H, s, SCH_3); 4.14 (1H, br. s, NH); 7.57-7.90 (5H, m, Ph); 8.45 (1H, s, CH=N). Found,%: C 49.45; H 2.86; N 24.76. $C_{14}H_{10}N_6OS_2$. Calculated, %: C 49.11; H 2.94; N 24.55.

7-Methoxy-9-methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiazepine (3). A. A solution of sodium methoxide in methanol, prepared from sodium (0.013 g, 0.56 mmol) and absolute methanol (5 ml), was added to a suspension of compound **1** (0.202 g, 0.56 mmol) in methanol (10 ml). The mixture was stirred for 2h at room temperature. The white residue was filtered off and recrystallized to give compound **3** (0.13 g, 65%).

B. Compound **1** (0.1 g, 0.28 mmol) was added to a saturated solution of ammonia in absolute methanol (5 ml). The reaction mixture was refluxed for 5 h. After cooling, the solvent was evaporated at low pressure, the residue was washed with water, filtered off, and recrystallized to give compound **3** (0.06 g, 60%); mp 227-228°C (2-propanol–DMSO, 5:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 (3H, s, SCH_3); 4.08 (3H, s, OCH_3); 7.49-7.97 (5H, m, Ph); 8.30 (1H, s, CH=N). Found, %: C 50.86; H 3.30; N 23.75. $C_{15}H_{12}N_6OS_2$. Calculated, %: C 50.55; H 3.39; N 23.58.

6,7-Dimethoxy-9-methylthio-3-phenyl-5,6-dihydrophenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]-triazepine (4). A solution of sodium methoxide in methanol, prepared from sodium (0.026 g, 1.12 mmol) and absolute methanol (5 ml), was added to a suspension of compound **1** (0.202 g, 0.56 mmol) in methanol (10 ml). The mixture was refluxed for 2 h. After cooling the precipitate was filtered off and recrystallized to give compound **4** (0.05 g, 24%); mp 207-209°C (methanol). IR spectrum, ν, $cm^{-1:}$ 3273 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.61 (3H, s, SCH_3); 4.04 (6H, s, $2OCH_3$); 7.55-8.05 (5H, m, Ph); 7.79 (1H, s, CH=N); 10.01 (1H, s, NH). Found, %: C 49.95; H 4.05; N 21.85. $C_{16}H_{16}N_6O_2S_2$. Calculated, %: C 49.47; H 4.15; N 21.63.

Substituted 7-Amino-9-methylthio-3-phenylpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thia-diazepines (6,7). A mixture of compound **1** (0.25 g, 0.7 mmol), morpholine or 2-(dimethylamino)ethylamine (0.7 mmol), triethylamine (0.073 g, 0.1 ml, 0.7 mmol), and DMSO (3 ml) was heated at 60°C for 4 h (if ethanol was used as solvent, the mixture was refluxed for 5 h). The mixture was then cooled to room temperature, the solid was filtered off, and recrystallized.

Compound 6. Yield 0.21 g (75%); mp 246-248°C (DMSO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 (3H, s, SCH_3); 3.68-3.77 (8H, m, $N(CH_2)_4O$); 7.59-7.83 (5H, m, Ph); 8.37 (1H, s, CH=N). Found, %: C 52.70; H 4.11; N 23.74. $C_{18}H_{17}N_7OS_2$. Calculated, %: C 52.54; H 4.16; N 23.83.

Compound 7. Yield 0.25 g (90%); mp 245-246°C (toluene–DMSO, 4:1). IR spectrum, ν, cm^{-1}: 3325 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.34 (6H, s, $2NCH_3$); 2.59 (3H, s, SCH_3); 2.91-2.98 (4H, m, NCH_2CH_2N); 4.26 (1H, s, NH); 7.44-7.97 (5H, m. Ph); 8.11 (1H, s, CH=N). Found, %: C 52.69; H 5.01; N 26.99. $C_{18}H_{20}N_8S_2$. Calculated, %: C 52.41; H 4.89; N 27.16.

7-Chloro-9-methylthio-3-phenyl-5,6-dihydropyimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (8). Sodium borohydride (0.021 g, 0.55 mmol) was added by portions with stirring to a suspension of compound **1** (0.2 g, 0.55 mmol) in absolute ethanol (5ml). The solution which formed was kept at room temperature for 2 h. The solvent was removed under reduced pressure, the residue was washed with water, filtered off, and recrystallized to give compound **8** (0.17 g, 85%); mp 143-145°C (octane–ethyl acetate, 2:1). IR spectrum, ν, cm^{-1}: 3204 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J* , Hz): 2.54 (3H, s, SCH_3); 3.19 (1H, br. s, NH); 4.37 (2H, d, J = 5.3, CH_2); 7.56-8.07 (5H, m, Ph). Found, %: C 46.45; H 3.02; N 23.23. $C_{14}H_{11}ClN_6S_2$. Calculated, %: C 46.34; H 3.06; N 23.16.

9-Methylthio-3-phenyl-5,6-dihydropyimido[5,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-7(8H)-one (9). Sodium borohydride (0.013 g, 0.35 mmol) was added in portions to a suspension of compound **2** (0.12 g, 0.35 mmol) in absolute ethanol (5 ml). The suspension was stirred for 6 h more at room temperature. The residue was filtered off and recrystallized to give compound **9** (0.08 g, 67%); mp 280-282°C (ethanol). IR spectrum, ν, cm^{-1}: 3311, 3289 (NH), 1638 (CO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.46 (3H, s, SCH_3); 3.40 (1H, s, NH); 4.13 (2H, d, J = 5.6, CH_2); 7.08 (1H, s, NH); 7.49-8.10 (5H, m, Ph). Found, %: C 48.95; H 3.62; N 24.42. $C_{14}H_{12}N_6OS_2$. Calculated, %: C 48.82; N 3.51; N 24.40.

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