SYNTHESIS OF 7-SUBSTITUTED 3-AMINOTHIENO[2,3-d:4,5-d']-DIPYRIMIDIN-4(3H)-ONES

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The synthesis of 3-amino-7-(ethoxycarbonylmethylthio)thieno[2,3-d:4,5-d']-dipyrimidin-4(3H)-one was accomplished. 7-Substituted 3-aminothieno[2,3-d:4,5-d']-dipyrimidin-4(3H)-ones were synthesized by its reaction with nucleophilic reagents – dimethylamine, morpholine, piperidine, hydrazine hydrate, and sodium hydroxide.

Reactions involving the cyclization of esters or amides of 5-aminothieno[2,3-d]-pyrimidine-6-carboxylic acids with reagents such as formamide, urea, phenyl isocyanate, methyl isothiocyanate, and orthoformic ester are used for the synthesis of thieno[2,3-d:4,5-d']-dipyrimidin-4(3H)-ones [1-3]. 3-Alkylthieno[2,3-d:4,5-d']-dipyrimidin-4(3H)-ones, which have a marked effect on the central nervous system, were synthesized by the reaction of pyrimido[5',4':4,5]thieno[3,2-d][1,3]oxazin-4-ones with primary amines [1, 2]. We recently obtained the first representatives of 3-aminothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-ones [4]. However, the data in [3, 4] showed that the cyclization reactions are accompanied by side processes in some cases. For example, in the reaction of methyl 5-amino-4-dialkylamino-thieno[2,3-d]pyrimidine-6-carboxylates with formamide, replacement of the 4-dialkylamino group in the thienopyrimidine ring by an amino group occurs along with cyclization [3]. In addition, insufficient study has thus far been devoted to the chemical properties of thieno[2,3-d:4,5-d']dipyrimidine derivatives. The aim of the present research was to synthesize 3-amino-7-(ethoxycarbonylmethylthio)thieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one and and to study its reaction with nucleophiles.

2,4-Dichloropyrimidine-5-carbonitrile (I) served as the starting compound for the synthesis. The action on I of ethyl thioglycolate was used to synthesize II, which in the presence of a catalytic amount of sodium ethoxide undergoes cyclization to ethyl 5-amino-2-(ethoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (III) (method A). Compound III is also conveniently synthesized without isolation of intermediate II (method B). Singlets of a CH_2S group at 3.97 ppm and an NH_2 group at 7.29 ppm are characteristic signals in the PMR spectrum of III. Absorption bands of an $SCH_2CO_2C_2H_5$ group at 1720 cm^{-1} ($\nu_{C=O}$) and a $CO_2C_2H_5$ group in the 6 position of the thienopyrimidine ring at 1660 cm^{-1} ($\nu_{C=O}$) and ν_{NH_2} bands at 3480 and 3353 cm^{-1} are observed in the IR spectrum of a chloroform solution of this compound. The intensity ratio and the frequencies of these bands remain constant with a charge in the concentration of the solutions over the range 0.02-0.001 M; this constitutes evidence for the existence of an intramolecular hydrogen bond (IMHB) between the o-oriented amino and carbonyl groups in III. The absorption of a C=O group at low frequencies (~1660 cm^{-1}) was also previously noted [4, 5] for esters of other 5-aminothieno[2,3-d]pyrimidine-6-carboxylic acids.

Refluxing of III with orthoformic ester in the presence of acetic anhydride leads to the formation of 5-ethoxymethyleneamino derivative IV. 3-Amino-7-(ethoxycarbonylmethylthio)-thieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (V) was synthesized by reaction of the latter with hydrazine hydrate. In addition to signals of protons of pyrimidine rings and an ester group, the PMR spectrum of V contains a singlet of a 3-amino group at 5.88 ppm in the region characteristic for condensed N-aminopyrimidines [6, 7]. A molecular ion peak M^+ with m/z 337 and intense peaks of fragment ions with m/z 291 and 264, which are due to the detachment of C_2H_5OH and $COOC_2H_5$ fragments, respectively, from the M^+ ion, are observed in the mass spectrum of this compound.

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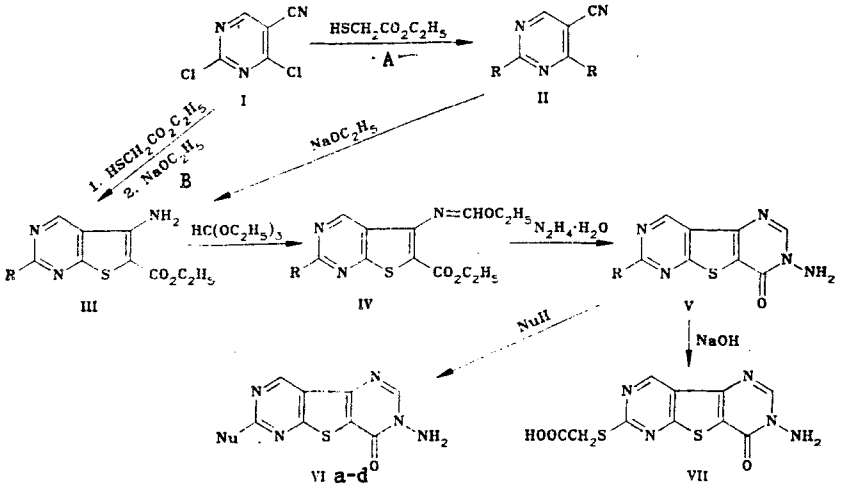

VI a Nu = $(CH_3)_2N$, b Nu = morpholino, cNu = piperidino, dNu = NH_2NH; II—V R = $=SCH_2CO_2C_2H_5$

Nucleophilic substitution of the ethoxycarbonylmethylthio groups occurs when V is heated with secondary amines or hydrazine hydrate, and derivatives VIa-d are formed. The reaction of ester V with sodium hydroxide at room temperature leads to a hydrolysis product — VII. The structures of VIa-d were confirmed by data from the mass spectra, in which peaks of molecular ions with m/z values corresponding to the molecular masses of these compounds are observed.

EXPERIMENTAL

The IR spectra of suspenions in mineral oil (in chloroform in the case of III) were recorded with a Specord 75 IR spectrometer. The PMR spectra were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with a Kratos MS-50 spectrometer (70 eV) with direct introduction of the samples into the ion source. Monitoring of the course of the reactions and the purity of the compounds was accomplished by TLC on DC-Alufolien Aluminiumoxid 150 F 254 neutral (Typ T) plates with development by means of UV light.

Compound I was obtained by the method in [8].

2,4-Bis(ethoxycarbonylmethylthio)pyrimidine-5-carbonitrile (II). An 8.16-g (68 mmoles) sample of ethyl thioglycolate was added dropwise to a solution of sodium ethoxide obtained from 1.56 g (68 mmoles) of sodium metal and 60 ml of absolute ethanol. After 15 min, the solution was added dropwise with stirring at 25-30°C to a solution of 6 g (34 mmoles) of I in 60 ml of absolute ethanol, and the mixture was stirred for 1 h at 20°C. The precipitate was removed by filtration, washed with water, and recrystallized to give 10.4 g (88%) of II with mp 57-58°C (from ethanol) and R_f 0.50 (benzene). IR spectrum: 1713 (C=O), 2213 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 1.16 (3H, t, CH_3), 1.18 (3H, t, CH_3), 3.85 (2H, s CH_2S), 3.92 (2H, s, CH_2S), 41.5 (4H, q, CH_2O), 8.32 ppm (1H, s, CH). Found, %: C 45.3; H 4.7; N 12.5. $C_{13}H_{15}N_3O_4S_2$. Calculated, %: C 45.7; H 4.4; N 12.3.

Ethyl 5-Amino-2-(ethoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (III). A) Four to six drops of a 1 M solution of sodium ethoxide in ethanol were added with stirring at 20-25°C to a solution of 4.5 g (13 mmoles) of II in 40 ml of absolute ethanol, and the mixture was stirred at the same temperature for another 10 min. It was then cooled to 0-5°C, and the precipitate was removed by filtration and recrystallized to give 4.3 g (95%) of III with mp 140.5-141.5°C (from ethanol) and R_f 0.23 (benzene). PMR spectrum (d_6-DMSO): 1.14 (3H, t, CH_3), 1.24 (3H, t, CH_3), 3.87-4.42 (4H, m, CH_2O), 3.97 (2H, s, CH_2S), 7.29 (2H, s, NH_2), 9.19 ppm (1H, s, CH). Found, %: C 45.3; H 4.6; N 12.1. $C_{13}H_{15}N_3O_4S_2$. Calculated, %: C 45.7; H 4.4; N 12.3.

B) A solution of the sodium salt of ethyl thioglycolate, prepared from 1.98 g (86 mmoles) of sodium metal, 60 ml of ethanol, and 10.3 g (86 mmoles) of ethyl thioglycolate as described in the synthesis of II, was added dropwise with stirring at 25-30°C to a solution of 7.5 g (43 mmoles) of I in 60 ml of ethanol, after which the mixture was stirred for 1 h. Four to six drops of a 1 M solution of sodium ethoxide in ethanol were then added, and the

mixture was stirred for another 10 min. It was then cooled to 0-5°C, and the precipitate was removed by filtration, washed with water, and recrystallized to give 10.8 g (79%) of III with mp 140.5-141.5°C (from ethanol).

Ethyl 5-Ethoxymethyleneamino-2-(ethoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (IV). A mixture of 0.7 g (2.1 mmoles) of III, 7 ml of ethyl orthoformate, and one to two drops of acetic anhydride was refluxed for 4 h, after which it was cooled to 0-5°C, and the precipitate was removed by filtration and recrystallized to give 0.71 g (88%) of IV with mp 98.5-99.5°C (from ethanol) and R_f 0.51 (benzene). IR spectrum: 1693 (C=O), 1720 cm^{-1} (C=O). PMR spectrum (d_6-DMSO): 1.02-1.5 (9H, m, CH_3), 3.90-4.52 (8H, m, CH_2O + CH_2S), 7.97 (1H, s, CH=N), 8.82 ppm (1H, s, CH). Found, %: C 48.0; H 4.9; N 10.2. $C_{16}H_{19}N_3O_5S_2$. Calculated, %: C 48.4; H 4.8; N 10.6.

3-Amino-7-(ethoxycarbonylmethylthio)thieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (V). A 0.23-ml (4.8 mmoles) sample of 99% hydrazine hydrate was added to a solution of 1.5 g (3.7 mmoles) of IV in 50 ml of ethanol, and the mixture was stirred for 40 min at 40-50°C. It was then cooled to 20°C, and the precipitate was removed by filtration and recrystallized to give 1.18 g (93%) of V with mp 169-170°C (from ethanol) and R_f 0.53 (chloroform). IR spectrum: 1653 (C=O); 1707 (C=O); 3173, 3307 cm^{-1} (NH_2). PMR spectrum (d_6-DMSO): 1.15 (3H, t, CH_3), 4.0 (2H, s, CH_2S), 4.06 (2H, q, CH_2O), 5.88 (2H, s, NH_2, vanished when D_2O was added), 8.45 (1H, s, CH), 9.12 ppm (1H, s, CH). Mass spectrum, m/z (%): 337 M^+ (23), 291 $[M - C_2H_5OH]^+$ (23), 264 $[M - COOC_2H_5]^+$ (100), 219 $[264 - CHS]^+$ (9). Found, %: C 43.1; H 3.7; N 20.5. $C_{12}H_{11}N_5O_3S_2$. Calculated, %: C 42.7; H 3.3; N 20.8.

3-Amino-7-dimethylaminothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VIa). A mixture of 1.0 g (2.9 mmoles) of V, 70 ml of ethanol, and 15 ml of a 33% aqueous solution of dimethylamine was refluxed for 1.5 h, after which it was cooled to 20°C, and the precipitate was removed by filtration and recrystallized to give 0.52 g (67%) of VIa with mp 309-310.5°C (from DMF) and R_f 0.81 (ethanol). IR spectrum: 1660 (C=O); 3160, 3280 cm^{-1} (NH_2). PMR spectrum (CF_3COOD): 3.01 (6H, s, CH_3N), 8.58 (1H, s, CH), 9.03 ppm (1H, s, CH). Mass spectrum, m/z %): 262 M^+ (100), 247 $[M - CH_3]^+$ (49), 233 $[M - CH_3N]^+$ (79), 218 $[M - (CH_3)_2N]^+$ (18). Found, %: C 46.1; H 3.9; N 32.1. $C_{10}H_{10}N_6OS$. Calculated, %: C 45.8; H 3.8; N 32.0.

3-Amino-7-morpholinothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VIb). A mixture of 0.7 g (2.1 mmoles) of V and 5 ml (57 mmoles) of morpholine was refluxed for 3 h, after which it was cooled to 20°C, and the precipitate was removed by filtration, washed with ethanol, and recrystallized to give 0.6 g (94%) of VIb with mp 300-302°C (from DMF) and R_f 0.74 (ethanol). IR spectrum: 1666 (C=O); 3186, 3300 cm^{-1} (NH_2). PMR spectrum (CF_3COOD): 3.73 (8H, m $(CH_2)_2N$ + $(CH_2)_2O$), 8.58 (1H, s, CH), 9.08 ppm (1H, s, CH). Found, %: C 47.5; H 4.0; N 27.3; M^+ 304. $C_{12}H_{12}N_6O_2S$. Calculated, %: C 47.4; H 4.0; N 27.6; M 304.

3-Amino-7-piperidinothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VIc). Compound VIc was synthesized in the same way as VIb using a tenfold molar amount of piperidine with respect to V; the reaction time was 30 min. The product was obtained in 81% yield and had mp 275.5-276.5°C (from DMF) and R_f 0.85 (ethanol). IR spectrum: 1653 (C=O); 3227, 3307 cm^{-1} (NH_2). PMR spectrum (CF_3COOD): 1.31 (6H, m, CH_2), 3.58 (4H, m, $(CH_2)_2N$), 8.65 (1H, s, CH), 9.04 ppm (1H, s, CH). Found, %: C 51.5; H 4.6; N 27.9; M^+ 302. $C_{13}H_{14}N_6OS$. Calculated, %: C 51.6; H 4.7; N 27.8; M 302.

3-Amino-7-hydrazinothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VId). A mixture of 0.87 g (2.6 mmoles) of V, 50 ml of ethanol, and 0.2 ml (4 mmoles) of 99% hydrazine hydrate was refluxed with stirring for 4 h, after which it was cooled to 20°C, and the precipitate was removed by filtration and recrystallized to give 0.59 g (92%) of VId with mp > 300°C (dec.) (from DMF) and R_f 0.39 (ethanol). IR spectrum: 1680 (C=O); 3220 broad, 3293, 3426 cm^{-1} (NH_2, NH). PMR spectrum (CF_3COOD): 8.78 (1H, s, CH), 9.23 ppm (1H, s, CH). Found, %: C 38.3; H 2.8; N 39.3; M^+ 249. $C_8H_7N_7OS$. Calculated, %: C 38.6; H 2.8; N 39.3; M 249.

3-Amino-7-(carboxymethylthio)thieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VII). A 2-ml sample of a 10% aqueous solution of sodium hydroxide was poured into a suspension of 1 g (2.9 mmoles) of V in 20 ml of ethanol, and the mixture was stirred for 2.5 h at 20-25°C. It was then filtered, and the red precipitate was washed with ethanol and dissolved in 6 ml of cold water. The aqueous solution was acidified to pH 2-3 with 10% hydrochloric acid, and the precipitate was removed by filtration and recrystallized to give 0.69 g (75%) of VII with mp 223°C (dec.) (from DMF–water). IR spectrum: 1653 (C=O), 1700 (C=O), 3300 cm^{-1} broad (NH_2, OH). PMR spectrum (d_6-DMSO): 4.25 (2H, s, CH_2S), 6.30 (2H, s, NH_2), 8.83

(1H, s, CH), 9.38 ppm (1H, s, CH). Found, %: C 38.5; H 2.4; N 22.4. $C_{10}H_7N_5O_3S_2$. Calculated, %: C 38.8; H 2.3; N 22.6.

LITERATURE CITED

1. A. A. Santilli, D. H. Kim, and S. V. Wanser, J. Heterocycl. Chem., 8, 445 (1971).
2. A. A. Santilli and D. H. Kim, U. S. Patent No. 3635965; Chem. Abstr., 76, 99697 (1972).
3. J. Clark and G. Hitiris, J. Chem. Soc., Perkin 1, 2005 (1984).
4. S. P. Tumyavichyus and R. I. Matulyauskene, Khim. Geterotsikl. Soedin., No. 8, 1131 (1987).
5. F. J. Cuadrado, M. A. Perez, and J. L. Soto, J. Chem. Soc., Perkin 1, 2447 (1984).
6. J. Y. Merour, J. Heterocycl. Chem., 19, 1425 (1982).
7. P. K. Bridson, K. A. Davis, and L. S. Renner, J. Heterocycl. Chem., 22, 753 (1985).
8. E. F. Godefroi, J. Org. Chem., 27, 2264 (1962).

POLYFUNCTIONAL MACROHETEROCYCLES.

2.* SYNTHESIS OF CROWN COMPOUNDS THAT INCLUDE DIMETHYL ASPARTATE FRAGMENTS

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The reaction of 1-[1,2-bis(carbomethoxy)ethyl]aziridine with ethane-1,2-dithiol leads to 1,8-bis[1,2-bis(carbomethoxy)ethylamino]-3,6-dithiaoctane. Condensation with phthalic and terephthalic acid dichloride gives 9,10-benzo-8,11-dioxo-7,12-bis[1,2-bis(carbomethoxy)ethyl]-1,4-dithia-7,12-diazacyclotetradec-9-ene and 9,12-benzo-8,13-dioxo-7,14-bis[1,2-bis(carbomethoxy)ethyl]-1,4-dithia-7,14-diazacyclohexadeca-9,12-diene, respectively, while condensation with formaldehyde gives 7,9,18,20-tetrakis[1,2-bis(carbomethoxy)ethyl]-1,4,12,15-tetrathia-7,9,18.29-tetraazacyclodocosane. The corresponding disulfone is formed in the oxidation of 9,10-benzo-8,11-dioxo-7,12-bis[1,2-bis(carbomethoxy)ethyl]-1,4-dithia-7,12-diazacyclotetradec-9-ene with 30% hydrogen peroxide.

Crown compounds that contain exocyclic functional groups are widely used in the synthesis of polymers and their "immobilization" on solid supports, as well as in obtaining new types of macroheterocycles [2]. The effect of functional groups of crown compounds on complexing with metal ions and the stabilities of the resulting complexes has also been investigated [2].

We have previously synthesized sulfur-containing macrocyclic diamides and obtained their complexes with the copper(II) ion [3-7], which can be used as models for the investigation of copper-containing proteins ("blue proteins") [8, 9].

Continuing our study of the properties of model compounds of metalloproteins we have synthesized sulfur-containing macroheterocycles III-VI, which include dimethyl aspartate fragments.

*See [1] for Communication 1.

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