# SYNTHESIS OF 5-AMINO DERIVATIVES OF ETHYL 2-METHYLTHIOTHIENO-[2,3-d]PYRIMIDINE-6-CARBOXYLATE AND THEIR REACTION WITH HYDRAZINE

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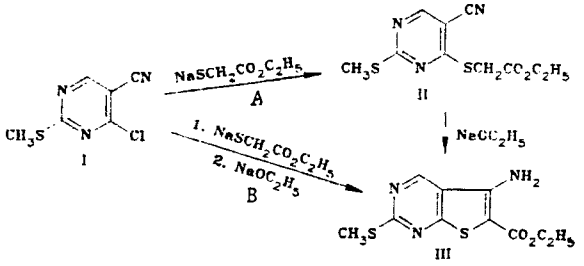
A study has been made of the reaction of the ethyl esters of 5-amino-, 5-ethoxymethyleneamino-, and 5-acetylamino-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylic acids with hydrazine. Certain derivatives of 3-aminothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-ones have been synthesized.

Various derivatives of thieno[2,3-d]pyrimidine possess antiviral [1], antiphlogistic [2, 3], and antiallergic [4, 5] activity, and have a depressive action on the central nervous system [2, 6]. Compounds containing amino and ester groups at the 5- and 6-positions of this heterocycle can serve as good starting materials for the synthesis of other heterocyclic systems and various derivatives of the thienopyrimidine series. In this connection we have studied the reaction of some 5-amino derivatives of ethyl 2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate with hydrazine.

Reaction of 2-methylthio-4-chloropyrimidine-5-carbonitrile (I) with the sodium salt of thioglycolic acid resulted in the synthesis of compound II, which, when treated with sodium ethoxide, was converted to the known ethyl ester III [7] (method A). Compound III was also obtained by a direct route (method B), which differed from that described in [7] in that sodium ethoxide was used as the cyclizing agent instead of sodium carbonate. This made it possible to shorten the time of reaction (from 4 to 1 h) and increase the yield of reaction product.




According to the information in [7], acetylation of compound III with acetic anhydride depending on the time of reaction leads to the formation of either the monoacetylamino derivative (IV) (boiling for 3 h) or diacetylamino derivative (V) (boiling for 4 h) of thieno[2,3-d]pyrimidine. We showed that even after 45 min there was no initial compound III in the reaction mixture according to the results of TLC and that a mixture of products IV and V was formed. On boiling compound III with ethyl orthoformate in the presence of a catalytic amount of acetic anhydride the 5-ethoxymethyleneamino derivative VI was obtained.

When compound III reacts with hydrazine only the methylthio group is replaced and the 2-hydrazino derivative (VII) of thieno[2,3-d]pyrimidine is formed. When the 5-acetylamino derivative IV is heated with hydrazine, along with replacement of the methylthio group cyclization occurs with the participation of hydrazine and 3-amino-7-hydrazino-2-methylthieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VIII) is formed. Compounds III and IV react with hydrazine only when there is a large excess of the latter and at high temperatures. By comparing the data obtained with similar findings for corresponding pyrimidine compounds [8], in which substitution of the methylthio group at the 2-position occurs at 0-5°C, it can be assumed that the lower reactivity of this group in the thienopyrimidine series is due to the electron donor effect of the thiophene ring.

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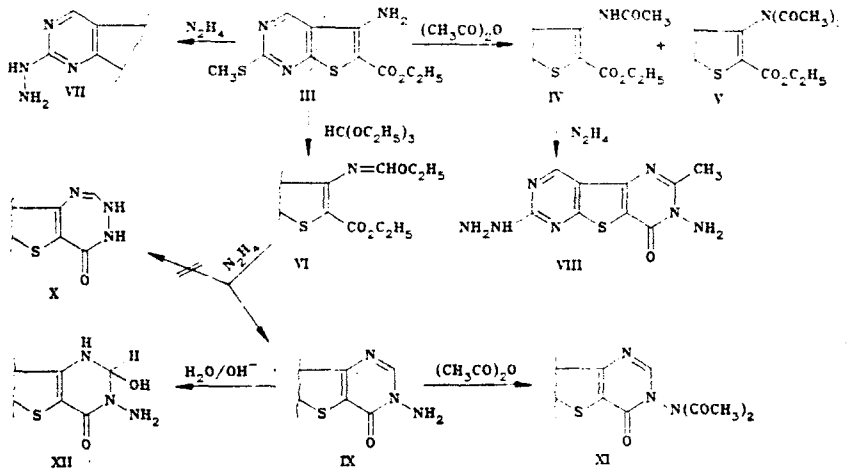

In contrast to ethyl esters III and IV, compound VI reacts with an equimolar quantity of hydrazine at 50°C, forming compound IX. In the PMR spectrum of compound IX together with the signals from the protons of the pyrimidine rings and the methylthio group, a singlet from an amino group occurs at 6.17 ppm while signals from ethoxy groups, characteristic of compound VI, are absent. In the IR spectrum of compound IX there is an absorption band (C=O) at 1673 $cm^{-1}$. Although the reaction may occur via two routes to form compounds IX and X, respectively, from the spectral data of the substance obtained we can assign the structure of 3-amino-7-methylthiothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (IX) to the reaction product. The structure of compound IX is also confirmed by its conversion to the diacetyl derivative XI. When thienodipyrimidinone IX is heated with a dilute solution of sodium hydroxide, its covalent hydrate XII is obtained. In the PMR spectrum of compound XII there is no signal at 8.77 ppm from an aromatic proton, but there is a singlet at 2.45 ppm, which we have attributed to the proton on the $C_{(2)}$ atom. In the mass spectrum of this compound the molecular ion peak is absent. The peak of the $[M - H_2O]^+$ fragment with m/z 265 has the highest intensity. However, in the IR spectrum an absorption band (OH) occurs at 3200 $cm^{-1}$. The data obtained confirm the structure of compound XII.

## EXPERIMENTAL

PMR spectra were recorded on a BAS 487C Tesla (80 MHz) spectrometer, with HMDS as internal standard. IR spectra were recorded as KBr pellets on a Specord 75-IR instrument. Mass spectra of compound XII were recorded on a Kratos MS-50 (70 eV) spectrometer with direct introduction of sample into the ion source. The course of the reactions and purity of the compounds were monitored by means of TLC on DS-Alufolien Aluminiumoxid 150 F 254 neutral (Typ T) plates, which were developed under UV light.

2-Methylthio-4-chloropyrimidine-5-carbonitrile (I) was synthesized according to [7] and ethyl thioglycolate was prepared according to [9].

Ethyl (2-Methylthio-5-cyanopyrimidinyl-4-thio)acetate (II). To a solution of sodium ethoxide obtained from 0.25 g (11 mmole) of metallic sodium and 10 ml of absolute ethanol was added dropwise 1.32 g (11 mmole) of ethyl thioglycolate. The solution obtained was added dropwise with agitation and at a temperature of 30°C to a solution of 2 g (11 mmole) of compound I in 15 ml of absolute ethanol. The mixture was agitated for 1 h at 20°C. The precipitate was filtered off and recrystallized. Yield 1.7 g (59%), mp 75.5-76.5°C (from isopropanol). $R_f$ 0.76 (benzene). PMR spectrum ($CCl_4$): 1.20 (3H, t, $CH_3$); 2.42 (3H, s, $SCH_3$); 3.85 (2H, s, $SCH_2$); 4.10 (2H, q, $CH_2$); 8.25 ppm (1H, s, CH). IR spectrum: 1739 (C=O), 2220 $cm^{-1}$ (C≡N). Found, %: C 44.8, H 3.9, N 15.9. $C_{10}H_{11}N_3O_2S_2$. Calculated, %: C 44.6, H 4.1, N 15.6.

Ethyl 5-Amino-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate (III). A. To a solution of 0.5 g (1.8 mmole) of compound II in 10 ml of absolute ethanol was added dropwise a solution of sodium ethoxide obtained from 0.04 g (1.8 mmole) of metallic sodium and 5 ml of absolute ethanol. The mixture was agitated at 40°C for 30 min, cooled to 5°C, and the precipitate was filtered off and recrystallized. Yield 0.4 g (80%), mp 190-193°C (from isopropanol).

B. The sodium salt of thioglycolic acid was prepared and added to a solution of compound I according to the method for synthesis of compound II. Then the reaction mixture was heated

for 30 min at 40°C, an equimolar quantity of sodium ethoxide in ethanol was added dropwise, the mixture was then agitated for a further 30 min at 40°C, and compound III was isolated according to method A. Yield 84%, mp 190-195°C (from isopropanol). According to the results of [7], yield 77%, mp 190-192°C.

Ethyl 5-Acetylamino- and 5-Diacetylamino-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylates (IV, V). A mixture of 1 g (3.7 mmole) of compound III and 9 ml of acetic anhydride was boiled for 45 min, cooled to 20°C, and the precipitate was filtered off and washed with 10 ml of cold ethanol. 0.7 g (60%) of compound IV was obtained, mp 179-182°C (from methanol). The filtrate was kept at a temperature of −10 to −15°C for 2 days, the precipitate was filtered off, and 0.3 g (23%) of compound V was obtained, mp 134-136°C (from methanol). According to the results of [7], yield of compound IV was 45%, mp 173-176°C, yield of compound V was 31%, mp 134-136°C.

Ethyl 2-Methylthio-5-ethoxymethyleneaminothieno[2,3-d]pyrimidine-6-carboxylate (VI). A mixture of 4 g (15 mmole) of compound III, 48 ml of ethyl orthoformate, and 5-6 drops of acetic anhydride was boiled for 4 h with agitation, cooled to 5°C, and the precipitate was filtered off, washed with ethanol, and recrystallized. Yield 4.5 g (93%), mp 149.5-151°C (from methanol). $R_f$ 0.73 (benzene). PMR spectrum ($CF_3COOH$): 0.8-1.2 (6H, m, 2 $CH_3$); 2.37 (3H, s, $SCH_3$); 3.72-4.22 (4H, m, 2−$CH_2$); 7.72 (1H, s, CH); 8.85 ppm (1H, s, CH). IR spectrum: 1700 $cm^{-1}$ (C=O). Found, %: C 48.3, H 5.0, N 13.3. $C_{13}H_{15}N_3O_3S_2$. Calculated, %: C 48.0, H 4.7, N 12.9.

Ethyl 5-Amino-2-hydrazinothieno[2,3-d]pyrimidine-6-carboxylate (VII). A mixture of 0.5 g (1.8 mmole) of compound III, 0.9 ml (18 mmole) of 99% hydrazine hydrate, and 2 ml of DMF was boiled for 5 h, cooled to 20°C, 5 ml of ethanol was added, and the precipitate was filtered off and recrystallized. Yield 0.27 g (57%), mp 238-239.5°C (from a DMF–water mixture). $R_f$ 0.42 (ethanol). PMR spectrum (DMSO-$D_6$): 1.45 (3H, t, $CH_3$); 3.97-4.40 (4H, m, $CH_2$, $NH_2$); 7.07 (2H, s, $NH_2$); 8.52 (1H, s, NH); 8.90 ppm (1H, s, CH). IR spectrum 1638 (C=O), 3266, 3273 ($NH_2$), 3400 $cm^{-1}$ (NH). Found, %: C 42.7, H 4.5, N 27.9. $C_9H_{11}N_5O_2S$. Calculated, %: C 42.7, H 4.4, N 27.7.

3-Amino-7-hydrazino-2-methylthieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (VIII). A mixture of 0.4 g (1.3 mmole) of compound IV and 0.6 ml (12 mmole) of 99% hydrazine hydrate was boiled for 45 min, cooled to 20°C, and the precipitate was filtered off, washed with ethanol, and recrystallized. Yield 0.2 g (57%), mp 320-325°C (from DMF). $R_f$ 0.47 (ethanol). PMR spectrum (DMSO-$D_6$): 2.58 (3H, s, $CH_3$); 5.77 (2H, s, $NH_2$); 8.9 ppm (1H, s, CH). IR spectrum: 1672 (C=O), 3145, 3253, 3319 $cm^{-1}$ ($NH_2$, NH). Found, %: C 41.3, H 3.6, N 36.9. $C_9H_9N_7OS$. Calculated, %: C 41.1, H 3.4, N 37.2.

3-Amino-7-methylthiothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (IX). To a solution of 4 g (12 mmole) of compound VI in 75 ml of ethanol was added 0.65 ml (12 mmole) of 99% hydrazine hydrate. The mixture was agitated for 45 min at 50°C, cooled to 20°C, and the precipitate was filtered off and recrystallized. Yield 3.2 g (98%), mp 282-283°C (from DMF). $R_f$ 0.74 (ethyl acetate). PMR spectrum (DMSO-$D_6$): 2.85 (3H, s, $SCH_3$); 6.17 (2H, s, $NH_2$); 8.77 (1H, s, CH); 9.47 ppm (1H, s, CH). IR spectrum: 1673 (C=O), 3158, 3266 $cm^{-1}$ ($NH_2$). Found, %: C 41.1, H 2.9, N 26.8. $C_9H_7N_5OS_2$. Calculated, %: C 40.7, H 2.7, N 26.4.

3-Diacetylamino-7-methylthiothieno[2,3-d:4,5-d']dipyrimidin-4(3H)-one (XI). A mixture of 1 g (3.7 mmole) of compound IX and 10 ml of acetic anhydride was boiled for 3 h, cooled to 5°C, and the precipitate was filtered off and recrystallized. Yield 0.4 g (31%), mp 205-207°C (from DMF). $R_f$ 0.53 (ethyl acetate). PMR spectrum ($CF_3COOH$): 2.15 (6H, s, 2−($CH_3$); 2.52 (3H, s, $SCH_3$); 8.27 (1H, s, CH); 9.25 ppm (1H, s, CH). IR spectrum: 1659, 1666 $cm^{-1}$ (2 C=O). Found, %: C 44.4, H 3.0, N 19.7. $C_{13}H_{11}N_5O_3S_2$. Calculated, %: C 44.7, H 3.2, N 20.0.

3-Amino-1,2,3,4-tetrahydro-7-methylthio-2-hydroxythieno[2,3-d:4,5-d']dipyrimidin-4-one (XII). A mixture of 0.5 g (1.8 mmole) of compound IX and 10 ml of 1% NaOH was boiled for 3 h, cooled to 20°C, and the precipitate was filtered off and recrystallized. Yield 0.29 g (57%), mp 294-296°C (decomp., from DMF). $R_f$ 0.70 (methanol). PMR spectrum ($CF_3COOH$): 2.40 (3H, s, $SCH_3$); 2.45 (1H, s, CH); 8.95 ppm (1H, s, CH). IR spectrum: 1673 (C=O), 3200 (OH), 3292, 3413 $cm^{-1}$ ($NH_2$). Mass spectrum: 265 $[M - H_2O]^+$. Found, %: C 38.0, H 3.3, N 24.9. $C_9H_9N_5O_2S_2$. Calculated, %: C 38.2, H 3.2, N 24.7.

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# 2-ALLYLAMINOTHIAZOLIN-4-ONE IN ACYLATION REACTIONS

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2-Acetylallylamino-4-acetoxythiazole is obtained via treatment of 2-allylaminothiazolin-4-one with acetic anhydride for a short period of time. After extended reaction times with a mixture of acetic anhydride and acetic acid a noncondensed bicyclic derivative of thiazolidin-4-one is obtained.

2-Aminothiazolines are polyfunctional compounds which are capable of forming substitution products in acylation reactions at any of four nucleophilic sites in the molecules: at the endo- and exocyclic nitrogen atoms, at the $C_{(4)} = O$ carbonyl group, and at the carbon atom in the 5-position of the ring [1, 2]. Since the literature does not contain any reports concerning the acylation of 2-alkylaminothiazolin-4-ones [3, 4], which are potentially tautomeric compounds, we decided to investigate the acylation reaction of 2-allylaminothiazolin-4-one and the structures of the products formed in this reaction.

Acylation of 2-phenylaminothiazolin-4-one has been shown [1] to give three isomers: 2-acetylphenylaminothiazolin-4-one (acidic catalysis), 2-phenylimino-3-acetylthiazolidin-4-one (basic catalysis), and 2-phenylimino-3-acetyl-4-acetoxythiazoline (both cases).

Using the previously described method [1, 2], we were unable to isolate a single monoacyl derivative (IIa, b) after acylation of 2-allylaminothiazolin-4-one (I), under either basic or general acid-catalyzed reaction conditions. Acylation of thiazolinone I with acetic anhydride for a short reflux period resulted in the isolation of a diacetyl derivative from the reaction mixture, based on its elemental analysis and mass spectrum. In analogy with [1], we had assumed that this compound has the structure 2-allylamino-3-acetyl-4-acetoxythiazoline (IIIb). However, results of physicochemical characterization revealed that the compound was actually 2-acetylallylamino-4-acetoxythiazole (IIIa) (see top of following).

IR and UV spectral data, as well as mass spectroscopy and PMR and $^{13}C$-NMR spectroscopy, were used to decide the question of the site of addition of the acetyl groups.

The IR spectrum of compound IIIa contains CH stretching vibrational bands in the 3100 $cm^{-1}$ region, as well as intense carbonyl group stretches at 1780 and 1664 $cm^{-1}$ [5]. Although the assignment of the first of these carbonyl bands to the vibrations of an O-acetyl group does not raise any doubts, it is impossible to assign unequivocally the second band

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