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SYNTHESIS OF 3,4-DIAMINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES

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The reaction of 4-(amino-substituted)-2-methylthio-6-chloropyrimidine-5-carbonitriles with hydrazine and methylhydrazine was used to synthesize 3,4-diamino-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines. It was shown that the formation of pyrazolopyrimidines proceeds through intermediate 6-hydrazinopyrimidine-5-carbonitriles.

Pyrazolo[3,4-d]pyrimidines, as isoanalogs of biogenic purines, are of considerable interest from the standpoint of searching for biologically active substances. In this respect, derivatives of 3- and 4-aminopyrazolo[3,4-d]pyrimidines are especially interesting; substances possessing valuable pharmacological properties have been found among them [1-7]. 3-Aminopyrazolo[3,4-d]pyrimidines can also serve as useful intermediates for the production of more complex heterocycles [8, 9]. However, 3,4-diaminopyrazolo[3,4-d]pyrimidines have been insufficiently studied. In the literature there are only a few examples of the synthesis of compounds of this type [10]. Recently we reported on the synthesis of 4,5-diaminothieno[2,3-d]pyrimidines and their use for the production of 1-thia-3,4,6,8-tetraaza- and 1-thia-3,4,5,6,8-pentaazaacenaphthylenes [11-13]. Continuing investigations along this line, this work presents the results obtained in the development of the synthesis of 3,4-diamino-1H-pyrazolo[3,4-d]pyrimidines.

An analysis of the literature data showed that one of the methods of producing 3-aminopyrazolo[3,4-d]pyrimidines is the reaction of pyrimidine-5-carbonitriles possessing groups sensitive to nucleophiles in the 4- or 6-position of the pyrimidine ring with hydrazine [7, 10, 14]. Therefore, N-substituted 4-amino-2-methylthio-6-chloropyrimidine-5-carbonitriles (IIa-f), which are readily synthesized by the reaction of 2-methylthio-4,6-dichloropyrimidine-5-carbonitrile (I) with an excess of the corresponding amine, were selected as starting materials for the synthesis of the target compounds.

A study of the interaction of the carbonitriles IIa-e with hydrazine hydrate showed that when 4-alkylamino-2-methylthio-6-chloropyrimidine-5-carbonitriles (IIa,b) are heated in methanol solution with hydrazine hydrate, the corresponding 3-aminopyrazolo[3,4-d]pyrimidines (IIIa,b) are formed in yields of 69 and 64%, respectively. However, the reaction of compounds IId,e with hydrazine hydrate proceeds with the formation of 4-arylamino-6-hydrazino-2-methylthiopyrimidine-5-carbonitriles (IVd,e). The reaction was observed to stop at the step of hydrazinopyrimidine formation in the series of 4-aryl-6-chloropyrimidine-5-carbonitriles as well [15-17]. After brief heating of the hydrazinopyrimidine IVd in dioxane solution in the presence of a catalytic amount of hydrochloric acid, this compound was converted to the corresponding 3-aminopyrazolopyrimidine IIId. To bring about cyclization between the hydrazino and cyano groups in compound IVe, sodium ethylate was used as a reagent activating the cyano group [18].

The interaction of compounds IIa,c-f with methylhydrazine leads to the formation of 3,4-diaminopyrazolo[3,4-d]pyrimidines (Va,c-f), regardless of the nature of the substituent in the 4-position of the pyrimidine ring. The reaction of 6-chloropyrimidine-5-carbonitriles with methylhydrazine, depending on the intermediate formed (hydrazinopyrimidine or amidrazone), may lead to isomeric 1-methyl-1H- (V) or 2-methyl-2H-pyrazolo[3,4-d]pyrimidines (VI). The possibility that the reaction may proceed through the corresponding amidrazones is indicated by the data of [19, 20], according to which certain pyrimidine-5-carbonitriles are capable of adding amines or hydrazine at the cyano group. Therefore, an attempt was made to isolate the intermediate product of the reaction between the carbonitrile IIa and methylhydrazine. However, despite variation

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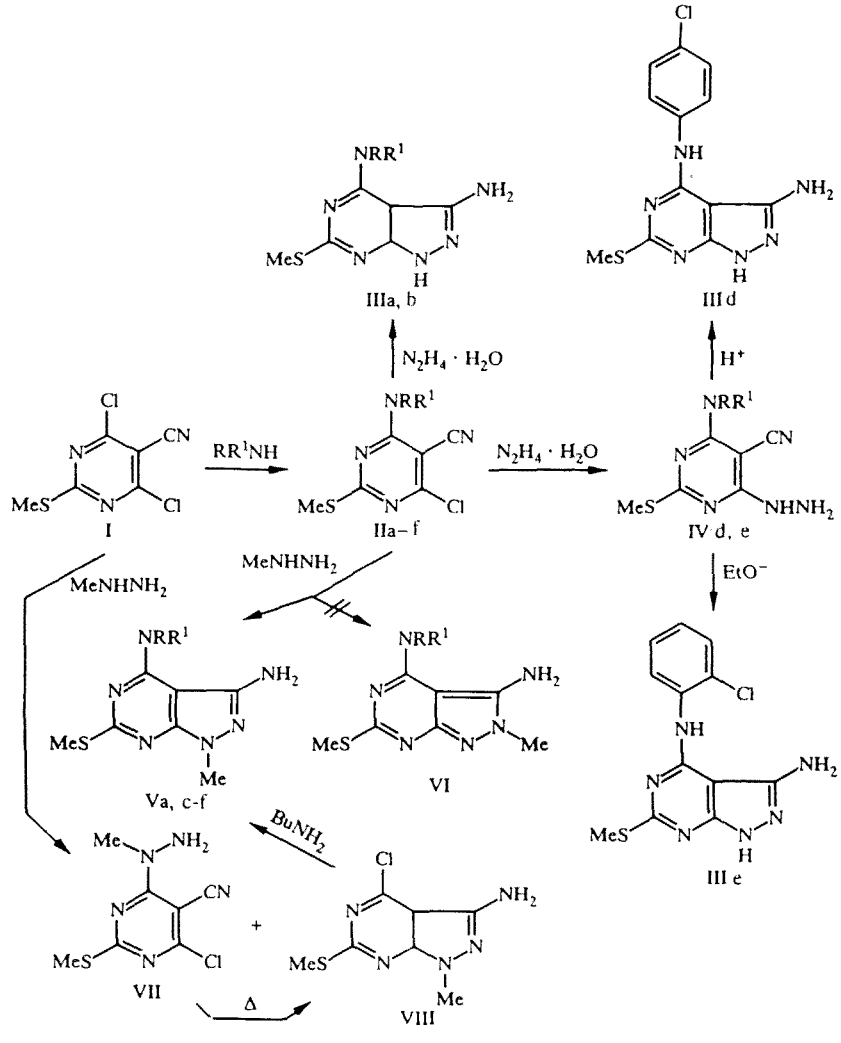
of the temperature system of the reaction, its duration, the solvents (dioxane, methanol, water), and the reagent ratio, only the pyrazolopyrimidine was isolated in all cases. Then the interaction of 2-methylthio-4,6-dichloropyrimidine-5-carbonitrile (I) with methylhydrazine was studied. It was established that conducting the reaction at room temperature leads to the formation of 4-(1-methylhydrazino)-2-methylthio-6-chloropyrimidine-5-carbonitrile (VII). The structure of compound VII was confirmed by the spectral data (Table 1). The IR spectrum has an absorption band of the cyano group at 2208 cm^{-1}, and a singlet of the amino group at 4.12 ppm was observed in the ^1H NMR spectrum together with the singlets of CH_3S and the CH_3N groups, indicating that replacement of the chlorine atom involves the substituted nitrogen atom of methylhydrazine. In an attempt to purify compound VII by crystallization, it was noted that it is converted to the pyrazolopyrimidine VIII, which was also obtained with a yield of 56% by heating compound VII in dioxane solution for 6 h. The IR spectrum of compound VIII does not contain the absorption band of the cyano group, while the signals of the CH_3N and NH_2 groups in the ^1H NMR spectrum are shifted 0.3 ppm in the weak-field direction in comparison with those of the hydrazinopyrimidine VII. We should mention that carrying out the reaction between the carbonitrile I and methylhydrazine at 65°C (10 min) leads to the formation of a mixture of compounds VII and VIII in a 2:3 ratio (according to the data of the ^1H NMR spectra).



II, III, V a R = H, R^1 = Me, b *i*-Pr, c *n*-Bu, d *p*-ClC_6H_4, e *o*-ClC_6H_4, f R = R^1 = Me

When the pyrazolopyrimidine VIII was heated with an excess of butylamine, 3-amino-4-butylamino-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidine (Vc) was isolated; in its physical characteristics and ^1H NMR and IR spectral data it is identical with the compound obtained by the reaction of the carbonitrile IIIc with methylhydrazine. These data permit us to conclude that the formation of 3,4-diamino-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines in the reaction of the corresponding 6-chloropyrimidine-5-carbonitriles with methylhydrazine proceeds through intermediate 4-(2-methylhydrazino)pyrimidine-5-carbonitriles.

TABLE 1. IR and ^1H NMR Spectra of Compounds IId,f, IIIa,b,d,e, IVd,e, Va,c-f, VII, and VIII

Compound	mp, °C (solvent)	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm*	Yield, %
IId	217...218 (Chloroform)	3288 (NH), 2224 (CN)	1,61 (1H, br. s, NH), 2,50 (3H, s, SMe), 7,36 (2H, d, arom. protons), 7,5 (2H, d, arom. protons)	73
IIf	150...152 (Methanol)	2208 (CN)	2,5 (3H, s, SMe), 3,38 (6H, s, NMe_2)	80
IIIa	263...264 (Methanol)	3392, 3352, 3160 (NH, NH_2)	2,56 (3H, s, SMe), 2,93 (3H, d, NMe), 6,42 (4H, br. s, 2NH, NH_2)	69
IIIb	226...228 (Ethyl acetate)	3400, 3352, 3128 (NH, NH_2)	1,0 (6H, d, 2Me), 2,56 (3H, s, SMe), 4,6 (1H, q, NCH), 6,46 (4H, br. s, NH, NH_2)	64
IIId	290 (разл.) (Dioxane)	3320, 3184 (NH, NH_2)	2,49 (3H, s, SMe), 7,25 (5H, m, NH, NH_2, arom. protons), 7,96 (2H, d, arom. protons)	78
IIIe	275...277 (Ethanol)	3360, 3300, 3120 (NH, NH_2)	2,49 (3H, s, SMe), 5,0 (2H, br. s, NH_2), 7,2 (3H, m, arom. protons), 8,6 (1H, d, arom. protons), 8,85 (1H, br. s, NH), 13,85 (1H, br. s, NH)	83
IVd	285 (dec.) (Dioxane)	3304, 3230 (NH, NH_2), 2200 (CN)	2,40 (3H, s, SMe), 5,20 (3H, br. s, NH, NH_2), 7,32 (2H, d, arom. protons), 7,64 (2H, d, arom. protons), 9,97 (1H, s, NH)	90
IVe	260...263 (2-Propanol)	3360, 3328, 3232 (NH, NH_2), 2192 (CN)	2,31 (3H, s, SMe), 5,12 (3H, br. s, NH, NH_2), 7,2 (2H, m, arom. protons), 8,05 (1H, d, arom. protons), 8,6 (1H, d, arom. protons), 9,3 (1H, br. s, NH)	58
Va	214...216 (Methanol)	3376, 3304 (NH, NH_2)	2,57 (3H, s, SMe), 3,11 (3H, d, NMe), 3,75 (3H, s, NMe), 5,4 (3H, br. s, NH, NH_2)	85
Vc	106...108 (Ethyl acetate)	3248 (NH, NH_2)	0,95 (3H, t, Me), 1,5 (4H, m, $2CH_2$), 2,55 (3H, s, SMe), 3,05 (2H, br. s, NH_2), 3,55 (3H, s, NMe), 5,41 (1H, br. s, NH)	72
Vd	180...182 (Methanol)	3280, 3168 (NH, NH_2)	2,53 (3H, s, SMe), 3,74 (3H, s, NMe), 5,53 (2H, br. s, NH_2), 7,28 (2H, d, arom. protons), 7,61 (2H, d, arom. protons), 9,02 (1H, s, NH)	89
Ve	206...208 (Dioxane)	3336, 3200 (NH, NH_2)	2,48 (3H, s, SMe), 3,73 (3H, s, NMe), 5,43 (2H, br. s, NH_2), 7,25 (3H, m, arom. protons), 8,43 (1H, d, arom. protons), 8,85 (1H, br. s, NH)	87
Vf	175...177 (Methanol)	3384, 3184 (NH_2)	2,53 (3H, s, SMe), 3,13 (6H, s, NMe_2), 3,71 (3H, s, NMe), 5,28 (2H, s, NH_2)	83
VII	†	3328 (NH_2), 2208 (CN)	2,49 (3H, s, SMe), 3,47 (3H, s, NMe), 4,12 (2H, s, NH_2)	86
VIII	190...192 (Dioxane)	3408 (NH_2)	2,59 (3H, s, SMe), 3,79 (3H, s, NMe), 4,40 (2H, s, NH_2)	56

*The ^1H NMR spectra of compounds IId,f, Va,c, VII, and VIII were recorded in $CDCl_3$, those of the remaining compounds in C_5D_5N.

†Compound VII begins to change color at 138°C and melts at 189-191°C; it could not be isolated in analytically pure form.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / calculated, %		
		C	H	N
IId	$C_{12}H_8Cl_2N_4S$	46.02 46,31	2.7 2,59	18.35 18,01
IIf	$C_8H_9ClN_4S$	42.12 42,01	4.06 3,97	24.35 24,5
IIIa	$C_7H_{10}N_6S$	40.21 39,99	4.52 4,79	39.81 39,97
IIIb	$C_9H_{14}N_6S$	45.24 45,36	6.06 5,92	35.29 35,26
IIId	$C_{12}H_{11}ClN_6S$	47.17 46,98	3.52 3,61	27.21 27,39
IIIe	$C_{12}H_{11}ClN_6S$	46.75 46,98	3.55 3,61	27.19 27,39
IVd	$C_{12}H_{11}ClN_6S$	46.13 46,98	3.67 3,61	27.55 27,39
IVe	$C_{12}H_{11}ClN_6S$	46.82 46,98	3.71 3,61	27.21 27,39
Va	$C_8H_{12}N_6S$	42.65 42,84	5.21 5,39	37.33 37,47
Vc	$C_{11}H_{18}N_6S$	49.75 49,6	6.53 6,81	31.66 31,55
Vd	$C_{13}H_{13}ClN_6S$	48.83 48,67	3.98 4,08	26.21 26,2
Ve	$C_{13}H_{13}ClN_6S$	48.88 48,67	4.31 4,08	26.41 26,2
Vf	$C_9H_{14}N_6S$	45.39 45,36	5.83 5,92	35.45 35,27
VIII	$C_7H_8ClN_5S$	36.82 36,6	3.59 3,51	30.34 30,49

EXPERIMENTAL

The IR spectra were recorded in liquid petrolatum on a Specord M-80 instrument. The ^1H NMR spectra were obtained on a Tesla BS-587 A spectrometer (80 MHz), internal standard TMS. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography on DC Alufolien Alluminiumoxid 150 F 254 neutral (Typ T) plates; development with UV light.

2-Methylthio-4,6-dichloropyrimidine-5-carbonitrile (I) was produced according to the procedure described in [21]. Compounds IIa-c,e were synthesized according to the procedures that we had developed earlier [11, 12].

The characteristics of the compounds synthesized are presented in Table 2.

2-Methylthio-4-(p-chlorophenylamino)-6-chloropyrimidine-5-carbonitrile (IId). To a solution of 0.72 g (3.3 mmoles) of compound I in 10 ml of ethanol, a solution of 0.83 g (6.5 mmoles) p-chloroaniline in 8 ml of diethyl ether was added dropwise at room temperature. The reaction mixture was mixed at 40°C for 1 h and cooled to 5°C. The precipitate was filtered off, washed with water, and recrystallized.

4-Dimethylamino-2-methylthio-6-chloropyrimidine-5-carbonitrile (IIf). Compound IIf was produced from 2 g (9 mmoles) of compound I and 4.1 ml of a 33% aqueous solution of dimethylamine according to the procedure described for the carbonitrile IId. The reaction took 1 h.

3-Amino-4-(substituted amino)-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines (IIIa,b). A mixture of 3.3 mmoles of the corresponding compounds IIa,b, 10 ml of methanol, and 0.45 ml (9 mmoles) of 99% hydrazine hydrate was boiled for 3 h, cooled to −10°C, and the precipitate was filtered off and recrystallized.

3-Amino-6-methylthio-4-(p-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidine (IIId). To a hot solution of 0.52 g (1.7 mmoles) of compound IVd in 40 ml of dioxane we added 3 drops of conc. hydrochloric acid. After the reaction mixture was cooled to room temperature, the precipitate was filtered off and recrystallized.

3-Amino-6-methylthio-4-(o-chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidine (IIIe). To a boiling suspension of 0.52 g (1.7 mmoles) of compound IVe, 6 ml of 0.1 M solution of sodium ethylate in ethanol was added with mixing. The reaction mixture was boiled for 10 min and cooled to room temperature. The precipitate was filtered off and recrystallized.

4-(Substituted amino)-6-hydrazino-2-methylthiopyrimidine-5-carbonitrile (IVd,e). A mixture of 2.6 mmoles of compound IId,e, 10 ml of methanol, 5 ml of dioxane, and 0.5 g (10 mmoles) of hydrazine hydrate was boiled for 1.5 h. It was cooled to room temperature, and the precipitate was filtered off and recrystallized.

3-Amino-4-(substituted amino)-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidines (Va,c-f). To a hot solution of 4 moles of the corresponding compound IIa,c-f in 20 ml of methanol (compounds IId,e were dissolved in a mixture of 20 ml of methanol and 10 ml of dioxane) we added 0.46 g (10 mmoles) of methylhydrazine. The reaction mixture was boiled with mixing for 1-2 h and cooled to room temperature. To isolate compounds Va,c we added 40 ml of water. The precipitate was filtered off and recrystallized.

3-Amino-4-butylamino-1-methyl-6-methylthio-1H-pyrazolo[3,4-d]pyrimidine (Vc). A mixture of 0.25 g (1.1 mmoles) of compound VIII and 1.1 g (15 mmoles) of butylamine was boiled for 2 h. Then the hot reaction mixture was filtered, and 20 ml of water was added to the filtrate. After cooling to room temperature, the precipitate was filtered off, recrystallized, and 0.18 g (62%) of compound Vc was obtained. The spectral data and melting point of the substance obtained are in full agreement with the data for compound Vc obtained according to the procedure described above.

4-(1-Methylhydrazino)-2-methylthio-6-chloropyrimidine-5-carbonitrile (VII). To a solution of 0.5 g (2 mmoles) of compound I in 10 ml of ethanol, 0.22 g (5 mmoles) of methylhydrazine was added dropwise with mixing at room temperature. The reaction mixture was mixed at room temperature for 5 min. The precipitate was filtered off and dried at room temperature. Compound VII was used for the synthesis of compound VIII without further purification.

3-Amino-1-methyl-6-methylthio-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (VIII). A solution of 1.15 g (5 mmoles) of compound VII in 15 ml of dioxane was boiled for 6 h. Then it was cooled, and the precipitate was filtered off and recrystallized.

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