TRANSFORMATIONS OF 5-METHYL-6-CARBETHOXY-3,4-DIHYDROTHIENO-[2,3-d]PYRIMIDINE FOR SYNTHESIS OF 4-METHOXY-, 4-ALKYLAMINO-, AND OTHER DERIVATIVES OF THIENO[2,3-d]PYRIMIDINE

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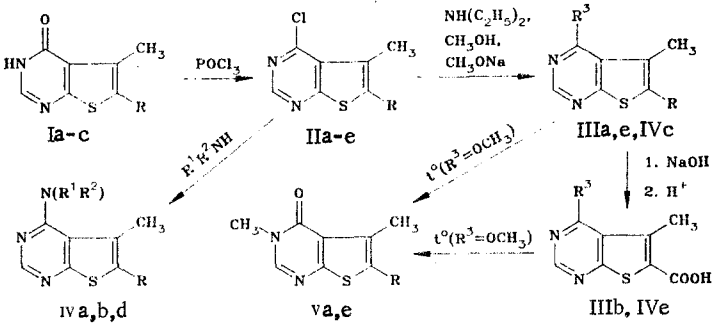
4-Chloro derivatives of thieno[2,3-d]pyrimidine are formed by the action of phosphorus oxychloride on 5-methyl- and 5-methyl-6-carbethoxythieno[2,3-d]pyrimidin-4-ones. Action of nucleophilic reagents (methanol, sodium methylate, primary and secondary amines) on these chloro derivatives gave 4-methoxy-, 4-alkylamino-, and 4-dialkylamino substituted thieno[2,3-d]pyrimidines. It was found that 4-methoxy derivatives of thieno[2,3-d]pyrimidines undergo a thermal rearrangement into 3-methyl-substituted thieno[2,3-d]pyrimid-4-ones. In the bromination of 5-methyl-4-chloro- and 5-methyl-4-methoxy-substituted thieno[2,3-d]pyrimidines by N-bromosuccinimide, 5-bromomethyl derivatives of thieno[2,3-d]pyrimidine are formed, from which, by the action of primary and secondary amines, 5-aminomethyl-substituted thieno[2,3-d]pyrimidines were obtained. A synthesis of 1,2,3,4-tetrahydro-1,3-diazepino[4a,10-d,e]thieno[2,3-d]pyrimidines was also carried out.

Various derivatives of thienopyrimidines have antiviral, antibacterial, and antiparasitic activity [1, 2]. However, studies in the series of thienopyrimidine derivatives containing an ethoxycarbonyl group in the 6-position, which may possibly be interesting from the point of view of the search for biologically active compounds, have not yet been developed. We therefore studied a series of transformations of 5-methyl-6-ethoxycarbonyl-3,4-dihydrothieno-[2,-d]pyrimid-4-one (Ia) [3]. By alkaline hydrolysis of the latter compound, 5-methylthieno-[2,3-d]pyrimid-4-one-6-carboxylic acid (Ib) was obtained, while decarboxylation gave the previously described [4], 5-methylthieno[2,3-d]pyrimid-4-one (Ie).

4-Chloro-substituted thieno[2,3-d]pyramidines are of definite interest as intermediates in the synthesis of other compounds, and most of all the amino derivatives of thieno[2,3-d]-pyrimidine, which can be regarded as antimetabolites of natural purine bases. 4-Chloro-derivatives of thieno[2,3-d]pyrimidine IIa,c were obtained by a conventional method, i.e., action of phosphorus oxychloride on compounds Ia,c. The reaction of the 4-chloro derivatives with nucleophilic reagents was studied. It is interesting to note that the presence of an electron-acceptor substituent in the 6-position in compound IIa, considerably enhances the tendency of chlorine in the 4-position to undergo nucleophilic substitution reactions, com-



Ia, IIa, IIIa, IVa, b, c Va R=$COOC_2H_5$; Ib R=COOH; Ic IIc, IIIc, IVd Vc R=H; IVa, b R^1=H; IV a R^2=CH_3; b R^2=C_4H_9; R^1=R^2=C_2H_5; IIIa, b, c R^3=OCH_3; IVc, e R^3=$N(C_2H_5)_2$

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TABLE 1. Characteristics of Compounds I-XI

Compound	Mp*, °C	Found, %					Empirical formula	Calculated, %					Yield, %
		C	H	Cl (Br)	N	S		C	H	Cl (Br)	N	S	
Ib	300	45,7	2,9	—	13,3	15,3	$C_8H_6N_2O_3S$	45,7	2,9	—	13,3	15,3	82
IIa	114—115	46,8	3,5	13,9	11,0	12,4	$C_{10}H_9ClN_2O_2S$	46,8	3,5	13,8	10,9	12,5	46
IIIa	137—138	52,4	4,9	—	11,2	12,1	$C_{11}H_{12}N_2O_3S$	52,4	4,8	—	11,1	12,1	67
IIIb	267—268	48,3	3,7	—	12,4	14,3	$C_9H_8N_2O_3S$	48,2	3,6	—	12,5	14,3	50
IVa	229—230	45,9	5,0	12,2	14,7	11,2	$C_{11}H_{13}N_3O_2S \cdot HCl$	45,9	4,9	12,3	14,6	11,1	40
IVb	89—90	57,4	6,5	—	14,4	11,1	$C_{14}H_{19}N_3O_2S$	57,3	6,5	—	14,3	11,0	40
IVc	207—208	51,1	6,2	10,8	12,8	9,7	$C_{14}H_{19}N_3O_2S \cdot HCl$	51,0	6,1	10,8	12,8	9,7	86
IVd	188—189	51,0	6,6	13,8	16,2	12,5	$C_{11}H_{16}N_3S \cdot HCl$	51,0	6,6	13,7	16,2	12,4	50
Va	171—172	52,3	4,8	—	11,1	12,1	$C_{11}H_{12}N_2O_3S$	52,1	4,7	—	11,2	12,0	70
VI	89—90	40,0	3,3	(24,0)	8,4	9,7	$C_{11}H_{11}BrN_2O_3S$	39,9	3,3	(24,1)	8,4	9,7	80
VII	134—135	53,0	5,8	—	14,1	11,1	$C_{13}H_{17}N_3O_3S$	52,9	5,8	—	14,2	11,0	51
VIII	208—209	45,4	5,1	10,9	13,3	10,2	$C_{12}H_{15}N_2O_3S \cdot HCl$	45,4	5,1	11,0	13,2	10,1	60
IX	92—93	35,9	2,4	10,5 (23,7)	8,4	10,4	$C_9H_8BrClN_2O_2S$	35,8	2,4	10,6 (23,8)	8,4	10,5	96
Xa	204—205	51,4	5,7	—	20,0	11,4	$C_{12}H_{16}N_4O_2S$	51,4	5,7	—	20,0	11,4	60
Xb	79—80	66,7	5,6	—	13,0	7,3	$C_{24}H_{24}N_4O_2S$	66,6	5,6	—	13,0	7,4	40
Xc	178—179	49,3	6,9	16,3	12,9	7,3	$C_{18}H_{28}N_4O_2S \cdot 2HCl$	49,3	6,9	16,2	12,9	7,3	54
Xd	186—187	49,5	6,8	16,3	13,0	7,3	$C_{18}H_{28}N_4O_2S \cdot 2HCl$	49,4	6,9	16,2	12,8	7,3	40
XIa	119—120	53,5	5,5	—	19,3	10,8	$C_{13}H_{16}N_4O_2S$	53,4	5,5	—	19,2	10,9	39
XIb	134—135	67,4	5,3	—	12,5	7,1	$C_{26}H_{24}N_4O_2S$	67,5	5,4	—	12,6	7,2	45

*Compounds Ib, IIIb, and Va were recrystallized from dioxane, IIa from a chloroform—hexane 1:1 mixture, and the remaining compounds from alcohol.

pared with the chlorine atom at the same position in compound IIc. Thus, by the action of methanol on compound IIa, the chlorine atom is completely substituted for the methoxy group after only brief heating, and by the reaction with primary and secondary amines, aminoalkyl derivatives IVa-d are formed at room temperature, while chlorine in compound IIc is substituted for the methoxy group only by the action of sodium methylate [5], and for the diethylamino group, after a prolonged heating. Thus, by nucleophilic substitution reactions of the chlorine atom in compounds IIa,c, we obtained 4-methoxy- (IIIa), 4-alkylamino- and 4-dialkylamino derivatives (IVa-d).

In the case of an alkaline hydrolysis of compounds IIIa and IVc, 4-methoxy- and 4-diethylamino-5-methylthieno[2,3-d]pyrimidine-6-carboxylic acids IIIb, IVe are formed. When acid IIIb is heated at a temperature of 350°C, not only decarboxylation, but also a rearrangement with the migration of methyl group is observed, and as a result the known 3,5-dimethylthieno[2,3-d]pyrimid-4-one (Vc) is formed, which was previously obtained by a method confirming its structure [5]. A similar rearrangement is observed on heating compounds IIIa,c and leads to N-methyl-substituted derivatives of thieno[2,3-d]pyrimid-4-one (Va,c). In the IR spectrum of compound IIIa there is one absorption band of the carbonyl group in the 1710 cm^{-1} region, while in the spectrum of compound Va, a second absorption band of the carbonyl group appears in the 1680 cm^{-1} region, which confirms the structure of compound Va.

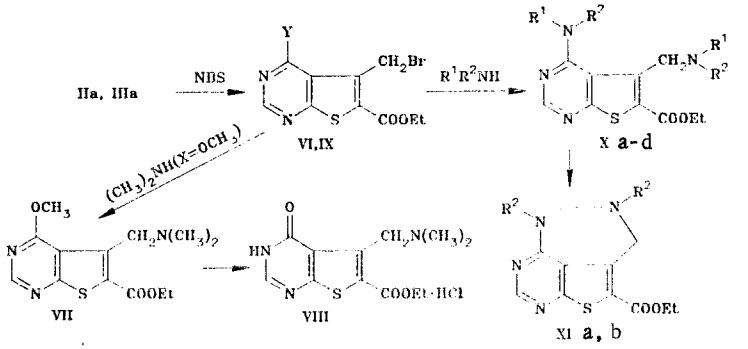
Bromination of thieno[2,3-d]pyrimidine derivatives IIa and IIIa by N-bromosuccinimide with illumination in the presence of benzoyl peroxide, gave 5-bromomethyl-substituted derivatives VI and IX, which by the action of primary and secondary amines convert into alkylamino and dialkylamino derivatives of thieno[2,3-d]pyrimidine VII and Xa-d. By treating 4-alkylamino-5-alkylaminomethyl-6-ethoxycarbonylthieno[2,3-d]pyrimidines (Xa,b) with formalin, as the result of intramolecular condensation, 1,3-dialkyl-9-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-diazepino[4a,10-d,e]thieno[2,3-d]pyrimidines (XIa,b) were obtained, representing a new heterocyclic system. Comparison with the IR spectra of compounds Xa,b and XIa,b showed that in the spectra of compounds XIa,b there is an absorption band of the carbonyl group in the 1710 cm^{-1} region, while the absorption band in the 3250 cm^{-1} region (NH) characteristic of the initial compounds Xa,b disappears, which confirms the structure of compounds XIa,b.

During the treatment of compound VII with hydrogen chloride at room temperature, a demethylation of the methoxy group in the 4-position is observed and 5-dimethylaminomethyl-6-ethoxycarbonyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one hydrochloride (VIII) is obtained, while in the IR spectrum of compound VII there is one absorption band of the carbonyl group in the 1700 cm^{-1} region, in the IR spectrum of compound VIII, there is a second absorption band of the carbonyl group in the 1660 cm^{-1} region, and an absorption band of the NH group in the 3165 cm^{-1} region are observed, which confirms the structure of compound VIII.

EXPERIMENTAL

The IR spectra were run on a Perkin-Elmer 599 spectrophotometer. The characteristics of the compounds synthesized are shown in Table 1.

5-Methyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one-6-carboxylic acid (Ib). The reaction mixture consisting of 2.38 g (10 mmoles) of ester Ia, 0.8 g (20 mmoles) of sodium hydroxide in 7 ml of water is boiled for 1.5 h, then poured into water, and acidified by 36% HCl. The precipitate is filtered off.



Xa, b, c, R^1=H; Xa, XIa R^2=CH_3; Xb, XIb, R^2=$CH_2C_6H_5$; X c R^2=C_4H_9; Xd R^1=R^2=C_2H_5;
VI Y=OCH_3; IX Y=Cl

Acids IIIb and IVe are obtained in a similar way by hydrolysis of esters IIIa and IVc, respectively.

5-Methyl-4-chloro-6-ethoxycarbonylthieno[2,3-d]pyrimidine (IIa). A reaction mixture consisting of 2.38 g (10 mmoles) of compound Ia and 5 ml of phosphorus oxychloride, is boiled for 1.5 h. The mixture is cooled, the precipitate that separates is filtered, washed with hexane, dried, and recrystallized.

5-Methyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one (Ic). A 2.1 g portion of acid Ib is heated at temperature of 350°C for 15 min. The mixture is cooled and the solidified mass is recrystallized.

Compounds Va,c and IVd are obtained under the same conditions from compounds IIIa,c and IVe, respectively.

5-Bromomethyl-4-methoxy-6-ethoxycarbonylthieno[2,3-d]pyrimidine (VI). A reaction mixture consisting of 2.52 g (10 mmoles) of compound IIIa, 1.78 g (10 mmoles) of N-bromosuccinimide, 15 ml of absolute CCl_4 and catalytic amounts of benzoyl peroxide is boiled for 30 min under illumination, then is washed with water, and the solvent is evaporated. Compound IX is obtained in a similar way by bromination of the chloro derivative IIa.

5-Dimethylaminomethyl-4-methoxy-6-ethoxycarbonylthieno[2,3-d]pyrimidine (VII). A solution consisting of 3.31 g (10 mmoles) of bromide VI, 30 ml of benzene, 4.5 ml (20 mmoles) of a 20% solution of dimethylamine in benzene is allowed to stand for 18 h at 20°C, then it is washed with water, and the solvent is evaporated.

Amino derivatives IVa-c are obtained in a similar way from compound IIa. To prepare the amino derivative IVd from IIc, the reaction mixture is boiled for 10 h.

5-Dimethylaminomethyl-6-ethoxycarbonyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one (VIII). A solution of 2.95 g (10 mmoles) of the amino derivative VII in 30 ml of acetone is treated at the temperature of 5°C with a solution of hydrogen chloride in ether to an acid reaction. The precipitate isfiltered and crystallized from alcohol.

4-Methylamino-5-methylaminomethyl-6-ethoxycarbonylthieno[2,3-d]pyrimidine (Xa). A 30 ml portion (60 mmoles) of an 8% solution of methylamine in benzene is added to a solution of 5 g (15 mmoles) of compound IX. The mixture is left to stand overnight at room temperature, washed with water, and the solvent is distilled off.

Compounds Xb-d are obtained in a similar way.

1,3-Dimethyl-9-ethoxycarbonyl-1,2,3,4-tetrahydro-1,3-diazepino[4a,10-d,e]-thieno[2,3-d]-pyrimidine (XIa). A solution of 2.8 g (10 mmoles) of diamine Xa, 0.72 ml (10 mmoles) of formalin, and 20 ml of alcohol is boiled for 5 h, and the solvent is distilled off.

Compound XIb is obtained in a similar way.

LITERATURE CITED

1. US Patent No. 3,981,951; Chem. Abstr., 77, 1266 (1972).
2. West German Patent Application No. 2,060,968; Chem. Abstr., 75, 88,638 (1971).
3. V. I. Shvedov, A. N. Grinev, and V. K. Ryzhkova, Khim. Geterotsikl. Soed., No. 3, 459 (1967).
4. Dissert. Abstr., No. 26(7), 3627 (1966).
5. M. Robba, J. M. Lecomte, and M. Gugnon de Sevricourt, C. R. Acad. Sci., Ser. C., Paris, No. 266, 1706 (1968).