SYNTHESIS OF MONO- AND DIBROMOMETHYL DERIVATIVES OF THIENO[2,3-d] PYRIMIDINES

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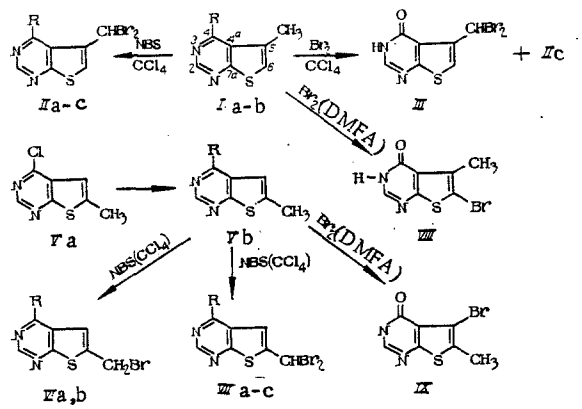
Halomethyl and dihalomethyl derivatives of aromatic, carbocyclic and heterocyclic compounds are convenient intermediates for introducing different functional groups and for various transformations in the synthesis of potential biologically active compounds.

In continuation of our investigations on the synthesis of polyfunctional derivatives of thieno[2,3-d]pyrimidines [2, 3], we studied the brominationof 4-chloro- and 4-methoxythieno-[2,3-d]pyrimidines (Ia, b) and (Va, b) containing a methyl group at the 5- or 6-position. It is known that bromination by molecular bromine of thieno[2,3-d]pyrimidines with no substituents at the 5- and 6-positions, or containing a methyl group at the 5-position, is directed in both cases to the 6-position, and thus no bromination products have been noticed in the side-chain [5, 6].

In order to bring about halogenation of the side chain, we studied the bromination of (Ia, b) and (Va, b) by N-bromosuccinimide in CCl_4 in the presence of benzoyl peroxide and using illumination. In the case of Va, b, we obtained fairly easily and in high yield the corresponding 6-bromomethyl derivatives (VIa, b). In bromination of the isomeric 5-methyl derivatives (Ia, b) [1] under the same conditions, the reaction does not stop at the monosubstitution stage, but proceeds up to the stage of formation of 5-dibromomethylthieno[2,3-d]-pyrimidines (IIa, b). With a double excess of N-bromosuccinimide, we obtained the corresponding 6- and 5-dibromomethyl-substituted derivatives VIIa,b and IIa,b from both Va,b and Ia,b. Further increase in the amount of the brominating agent leads to the formation of compounds IIc and VIIc, containing three bromine atoms per molecule: besides the substitution of two hydrogen atoms by bromine, the chlorine atom at the 4-position is also exchanged by bromine. The dibromide IIb can also be obtained by selective replacement of the chlorine atom at the 4-position of compound IIa by a methoxy group through the action of MeONa.



Ia, IIa, Va, VIa, VIIa: R = Cl; Ib, IIb, Vb, VIb, VIIb: R = OMe: IIc, VIIc: R = Br.

In the bromination of thienopyrimidine Ia by a triple excess of molecular bromine in CCl_4 with illumination, a mixture of products III and IIc was obtained in a 6:4 ratio, i.e., in this case the bromination is directed to the side chain with the formation of dibromethyl der-

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TABLE 1. Chemical Shifts of Protons (δ, ppm) in PMS Spectra of Thienopyrimidines Synthesized

Compound	H-2	H-5	H-6	Substituents at 4, 5, 6-positions	Solvent
Ia	8,81 s	—	7,23 quart	2,70 d	$CDCl_3$
IIa	8,91 s	8,33 s*	7,49 d**		$(CD_3)_2CO$
IIb	8,69 s	8,22 s*	7,52 d**	4,23 s	$CDCl_3$
IIc	8,91 s	8,33 s*	7,48 d**		$(CD_3)_2CO$
III	8,79 s	8,21 s*	7,64 d**		$(CD_3)_2CO$
Va	8,78 s	7,10 quart		2,66 d	$(CD_3)_2CO$
VIb	8,63 s	7,53 t	5,05 d***	4,13 s	$(CD_3)_2CO$
VIII	8,11 s	—	—	2,48 s	$(CD_3)_2CO$
IX	8,10 s	—	—	2,42 s	$(CD_3)_2CO$

*Chemical shift of a proton of $CHBr_2$ substituent, **J = 0.9-1.3 Hz. ***Chemical shift of methylene group of CH_2Br substituent.

ivatives. In this case the reaction is complicated by the replacement of chlorine at the 4-position by hydroxyl and the formation of compound III. Treatment of the latter by phosphorus oxychloride leads to the formation of dibromide IIa. However, when polar solvents, such as AcOH or DMFA, are used, the bromination of Ib and Vb by N-bromosuccinimide, even with illumination, proceeds by an electrophilic substitution mechanism and leads to the formation of 5(6)-bromo-6(5)-methyl derivatives VIII, IX. Thus, conditions were found for controlled bromination, under which bromomethyl, dibromomethyl and bromo derivatives of thieno[2,3-d]pyrimidines can be obtained.

The structure of the compounds obtained was confirmed by the ^1H (Table 1) and ^{13}C NMR spectra. In the spectrum of compound VIb, the signal of the methyl group at the 6-position is absent, and a doublet of the methylene group is observed at δ 5.05 ppm. In the ^1H NMR spectra of compounds IIa-c, III, in addition to the singlet of a proton at the 2-position (8.69-8.91 ppm), and a doublet (J = 0.9-1.3 Hz) of a proton at the 6-position (7.48-7.64 ppm), a broadened signal (8.21-8.33 ppm) is observed, which was assigned to the proton of the $CHBr_2$ substituent. The broadening of the signal of this proton, masking its splitting with the proton at the 6-position, can be caused by the following factors: the influence of neighboring bromine atoms, having a considerable quadrupole moment and also possible inhibited rotation of the $CHBr_2$ substituent with respect to the ordinary bond. In the ^1H double resonance NMR spectrum of compound IIc, the interaction with proton of the $CHBr_2$ substituent is suppressed and a signal of a proton at the 6-position is observed in the form of a singlet. The appreciable shift of the proton of the $CHBr_2$ substituent to the weak field region is possibly due to an acceptor effect of two neighboring bromine atoms on the one hand, and, on the other hand, the preference for such a conformation of the substituent at which the proton is located in the field of influence of the ring currents of the molecule.

The structure of compounds IIc and VIIa was confirmed by ^{13}C NMR spectra. The signal of the carbon atom of the $CHBr_2$ substituent in the spectrum taken in a regime without suppression of the interaction with protons has the form of a doublet (J = 180 Hz), each component of which is additionally split due to the interaction with a proton at the 6-position.

The structure of compounds VIII and IX, brominated in the nucleus of thienopyrimidine has been established from the ^1H NMR spectra, in which, compared with the spectra of the initial compounds, the signal of a proton at the 6(5)-position is absent, and the signals of the methyl group (2.42, 2.48 ppm), respectively, are retained.

EXPERIMENTAL CHEMICAL

The PMR spectra were run on a XI-200 spectrometer from the firm Varian (USA).

The starting 6-methylthieno[2,3-d]pyrimidine Va,b, used in the present investigation, were obtained from 6-methylthieno[2,3-d]pyrimid-4-one (IV), followed by treatment with phosphorus oxychloride and sodium methylate.

The characteristics of the compounds synthesized are listed in Tables 1 and 2.

5-Dibromomethyl-4-chlorothieno[2,3-d]pyrimidine (IIa). A mixture of 3.6 g (0.02 mole) of 5-methyl-4-chlorothieno[2,3-d]pyrimidine, 7.12 g (0.04 mole) of N-bromosuccinimide, 0.01 g of benzoyl peroxide in 30 ml of CCl_4 is boiled for 30 min. The reaction mixture is washed with water and the solvent is removed in vacuum. The residue is recrystallized from CH_2Cl_2.

The dibromo derivatives IIb, VIIa,b are obtained in a similar way from compounds Ib, Va,b, respectively. ^{13}C NMR spectrum of compound VIIIa, $CDCl_3$, δ, ppm: 153.5 d (C_2, J = 210 Hz), 168.4 (C_4), 147.7 (C_{4a}), 118.0 (C_5), 129.0 d (C_6, J = 190 Hz), 153.3 (C_{7a}), 31.1 d (CH_2Br, J = 180 Hz).

4-Bromo-5-dibromomethylthieno[2,3-d]pyrimidine (IIc). A mixture of 1.84 g (0.01 mole) of compound Ia, 5.54 g (0.03 mole) of N-bromosuccinimide, and 0.005 g of benzoyl peroxide in 40 ml of CCl_4 is boiled for 40 min. The reaction mixture is washed with water, the solvent is evaporated, and the residue is recrystallized from CH_2Cl_2. The 4-bromo derivative VIIc was obtained in a similar way from compound Va.

^{13}C NMR spectrum of compound IIc, $CDCl_3$, δ, ppm: 152.2 d ($C_{(2)}$, J = 210 Hz), 169.6 ($C_{(4)}$, 133.9 ($C_{(4)}$, 129.4$_{(5)}$), 131.4 d ($C_{(6)}$, J = 190 Hz), 153.9 ($C_{(7)}$), 32.4 d (CH_2Br, J = 180 Hz).

5-Dibromomethyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one (III). An 8.3 ml portion (0.15 mole) of bromine in 50 ml of CCl_4 is added at the boiling point to a solution containing 10 g (0.054 mole) of 4-chloro substituted compound Ia and 0.01 of benzoyl peroxide in 750 ml of CCl_4, up to complete decoloration of the reaction mixture (40 h). The precipitate of compound III that separates is filtered, and recrystallized from a 1:1 mixture of ethanol and dioxane. The filtrate is evaporated, and 5-dibromomethyl derivative IIa is obtained. The ratio of the products obtained is 6:4.

6-Methylthieno[2,3-d]pyrimid-4-one (IV). A 3.7 g portion of 2-amino-3-ethoxycarbonyl-5-methylthiophene [4] and 20 ml of formamide are boiled for 2 h, then the mixture is cooled, the precipitate is filtered, and crystallized from dioxane. Yield 2.42 g (73%) of IV.

6-Methyl-4-chlorothieno[2,3-d]pyrimidine (Va). A reaction mixture consisting of 5 g (0.03 mole) of 6-methyl-3,4-dihydrothieno[2,3-d]pyrimid-4-one, 3 ml (0.032 mole) of phosphorus oxychloride, 2.4 ml (0.034 mole) of DMFA and 60 ml of dry dichloroethane is boiled with stirring for 1.5 h.

The solution is cooled, washed with water and then with aqueous solution of sodium acetate to pH 7. The solvent is evaporated. The residue is recrystallized from methanol.

6-Methyl-4-methoxy[2,3-d]pyrimidine (Vb). a). A 2.3 ml portion (0.01 mole) of sodium methylate (0.23 g of Na in 2.3 ml of MeOH) is added with cooling to a solution of 1.84 g (0.01 mole) 4-chloro-substituted compound Va in 30 ml of CCl_4. After 40 min, the NaCl precipitate that separates is filtered, the solvent is evaporated, and the residue is recrystallized from methanol.

b) A solution of 1.84 g of Va and catalytic amounts of HCl in 30 ml of MeOH is boiled for 30 min, then cooled, and the precipitate that separates is filtered.

6-Bromomethyl-4-chlorothieno[2,3-d]pyrimidine (VIa). A mixture containg 1.84 g (0.01 mole) of 4-chloro-derivative Va, 1.78 g (0.01 mole) of N-bromosuccinimide, 0.005 g of benzoyl peroxide in 40 ml of CCl_4 is boiled for 1.5 h. The reaction mixture is washed with water, the solvent is evaporated in vacuo, and the residue is recrystallized from ethanol.

6-Bromomethyl derivative VIb is obtained in a similar way from compound Vb.

6-Bromo-5-methyl-4-methoxythieno[2,3-d]pyrimidine (VIII). A mixture containing 1.84 g (0.01 mole) of compound Ib and 0.75 ml (0.02 mole) of bromine in 35 ml of DMFA is held for 1.5 h at 60°C, The mixture is cooled, poured into water, the precipitate that separates is filtered, washed with water and crystallized from alcohol. The bromo derivative IX is obtained in a similar way from Vb.

EXPERIMENTAL BIOLOGICAL

The antiviral action of compounds IIb, Va,b VIb was studied with respect to examples of DNA viruses (The Herpes simplex I viruses of the antigenic type, strain L_2) and RNA viruses: the A_0 influenza virus.

The investigation was carried out in a primarily trypsinized culture of chicken embryo fibroblasts. Compounds in maximally endurable and lower concentrations were introduced 1 h after the infection of the cellular single layer by the virus. The results were evaluated according to the ability of the virus to prevent cytopathic action of the virus on the cells.

As a result of the investigation we found that compounds Va and Vb have a virus inhibiting action on the reproduction of Herpes simplex virus, in a concentration of 5 μg/ml, low-

TABLE 2. Physicochemical Properties of Synthesized Compounds

Compound	mp, °C (solvent*)	Found, % C	H	Cl (Br)	N	S	Empirical formula	Calculated, % C	H	Cl (Br)	N	S	Yield, %
IIa	81—2	24,5	0,9	10,2 (46,7)	8,2	9,4	$C_7H_4Br_2ClNS$	24,5	0,8	10,3 (46,7)	8,2	9,4	75
IIb	76—7	28,6	1,8	(47,3)	8,2	9,6	$C_9H_6Br_2N_2OS$	28,4	1,8	(47,3)	8,3	9,5	85
IIc	95—6	21,6	0,7	(61,9)	7,3	8,2	$C_7H_3Br_3N_2S$	21,7	0,7	(62,0)	7,2	8,3	80
III	214 (dec.)	25,7	1,0	(50,0)	8,7	9,8	$C_7H_4Br_2N_2OS$	25,9	1,2	(49,3)	8,6	9,9	60
IV	241—2	50,6	9,6	—	16,8	19,3	$C_7H_8N_2OS$	50,5	9,7		16,7	19,3	73
Va	86—7	45,4	2,6	19,1	15,1	17,3	$C_7H_5ClN_2S$	45,5	2,7	19,2	15,2	17,3	82
Vb	75—6	53,3	4,4	—	15,6	17,8	$C_9H_8N_2OS$	53,3	4,5	—	15,5	17,8	90
VIb	134—5	37,0	2,6	(30,9)	11,0	12,2	$C_9H_7BrN_2OS$	37,0	2,7	(30,8)	10,8	12,3	79
VIa	69—70	32,0	1,6	13,2 (30,4)	10,7	12,2	$C_7H_4BrN_2S$	31,9	1,5	13,4 (30,3)	10,6	12,1	55
VIIa	65—6 (dec.)	25,5	0,9	10,2 (46,7)	8,2	9,4	$C_7H_4Br_2ClNS$	24,5	0,88	10,3 (46,7)	8,2	9,4	60
VIIb	56—7	28,6	1,8	(47,3)	8,2	9,6	$C_9H_6Br_2N_2OS$	28,4	1,8	(47,3)	8,3	9,5	55
VIIc	(oil)	21,7	0,7	(61,9)	7,3	8,3	$C_7H_3Br_3N_2S$	21,7	0,7	(62,0)	7,2	8,3	50
IX	287—8	34,2	2,0	(32,7)	11,4	13,0	$C_7H_5BrN_2OS$	34,3	2,0	(32,6)	11,4	13,1	57
VIII	243—4	34,3	2,0	(32,6)	11,3	13,0	$C_7H_5BrN_2OS$	34,3	2,0	(32,6)	11,4	13,1	65

*The compounds are crystallized from a 1:1 mixture of hexane and CH_2Cl_2.

ering the infection titer of the virus, as compared with control, by 1.0 log TCD_{50}. Compounds IIb and VIb had no activity with respect to the Herpes simplex viruses. All the compounds studied had no influence on the reproduction of the A_0 influenza virus.

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CHEMICAL CONVERSIONS OF COMPLEXES OF PLATINUM METALS WITH 3-AMINOCOUMARIN AND BIOLOGICAL ACTIVITY OF THE COMPOUNDS FORMED

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Earlier we described complex compounds of Pt(2+) and Pd(2+) with 3-aminocoumarin (3-AMC) [7], which possess high biological and catalytic activity [5, 6]. Taking into consideration the fact that chelating ligands promote an increase in biological activity, while phosphorus-containing compounds increase their stability [3], we carried out the reaction of complexes of vis-$[M(3\text{-AMC})_2Cl_2]$, where M = Pt (2+) (I), Pd (2+) (II), with ethylenediamine (En) and triphenylphosphine (Ph_3P). The complex compounds obtained as a result of the reaction were studied for antimicrobial and antiphagal activity.

In the reaction of solutions of complexes of cis-$[M(3\text{-AMC})_2Cl_2]$ in DMFA with an aqueous solution of En in a 1:1 ratio, complex compounds with the composition $[M(3\text{-AMC})_2En]Cl_2$ (III, IV) were obtained. According to the values of the molar electric conductivity (Table 1), the compounds are triionic electrolytes.

A comparison of the IR spectra (Table 2) of the complexes obtained with the spectra of the original compounds and En shows a certain change in the high-frequency region, where two broad absorption bands are observed (3400-3200 cm^{-1}) on account of interference of the

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