Synthesis of some polycyclic noncondensed pyrimidine structures

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Methods for the synthesis of compounds containing two or more pyrimidine rings linked through aliphatic chains with different numbers of carbon atoms are described.

Key words: hydroxy- and mercaptopyrimidines, uracils, dihaloalkanes, α,ω-bis(hydroxypyrimidinyl)alkanes.

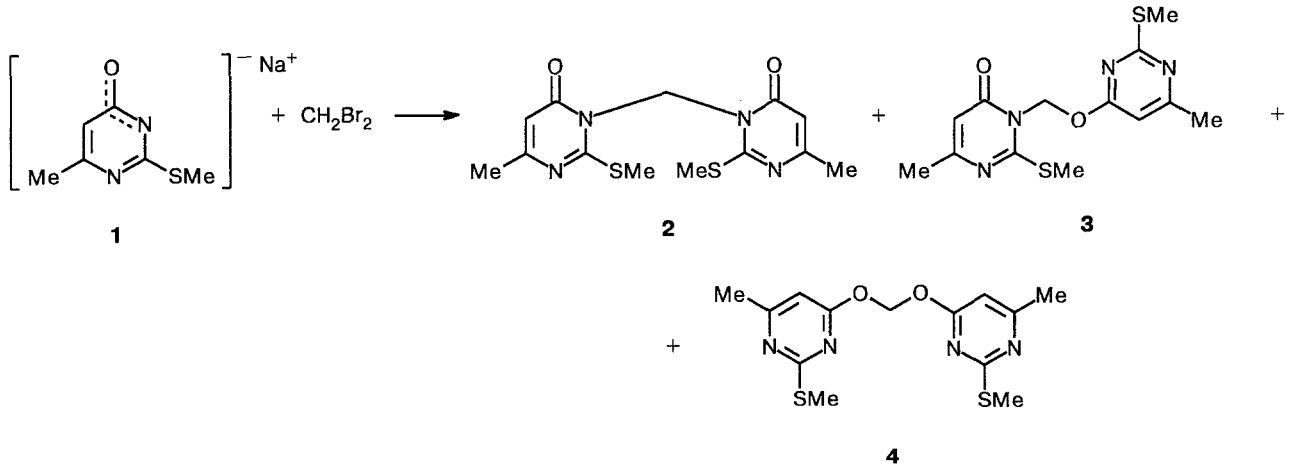
In a continuation of studies of reactions of the Na-salts of hydroxy- and mercaptopyrimidines with α,ω-dihaloalkanes, we synthesized compounds containing two or more pyrimidine rings linked through aliphatic chains with different numbers of carbon atoms (*n*). From them we also obtained ω-haloalkyl derivatives that can serve as the starting compounds for synthesizing compounds with various functional groups. We have previously reported[1] that the reactions of the Na-salts of uracils, which contain several nucleophilic centers, with dihaloalkanes result in oligomeric mixtures that are difficult to separate, especially in the case of the lowest dihaloalkanes ($n = 1 \div 3$). In this work we used two methods for obtaining the above compounds, namely, the reaction of dihaloalkanes with the salts of hydroxypyrimidines substituted at the nitrogen or sulfur atom, and reactions of uracil salts with authentic 3-(ω-bromoalkyl)-3,4-dihydro-6-methyl-2-methylthiopyrimidines.

We chose 4-hydroxy-6-methyl-2-methylthiopyrimidine (**1**) as one of the starting compounds for the synthesis according to the first method. However, in this case the reactions with dihaloalkanes can be expected to involve various types of binding of the two pyrimidine moieties to give N—C—N, N—C—O, and O—C—O isomers.

In fact, heating the Na-salt of **1** with dibromomethane (DBM) in the ratio 2 : 1 in *n*-butanol predominantly affords bis(3,4-dihydro-6-methyl-2-methylthio-4-oxopyrimidinyl-3)methane (**2**) and its N—C—O isomer, (3,4-dihydro-6-methyl-2-methylthiopyrimidinyloxy)methane (**3**), while the reaction in DMF gives additionally the O—C—O isomer, bis(6-methyl-2-methylthiopyrimidinyloxy)methane (**4**).

In agreement with the structure shown, none of the IR spectra of these compounds contain absorption bands (AB) in the ν(NH) and ν(OH) regions; compounds **2** and **3** display ν(C=O) absorption bands at 1700 and 1690 cm^{-1}, respectively. The region of the pyrimidine ring vibrations of compound **2** contains two AB at 1500 and 1580 cm^{-1}, and that of compound **3** contains three bands at 1500, 1555, and 1580 cm^{-1}. Compound **4** does not display any ν(C=O) band, while the ring vibrations manifest themselves as a group of bands at 1540—1575 cm^{-1}.

† Deceased.



1 **2** **3** **4**

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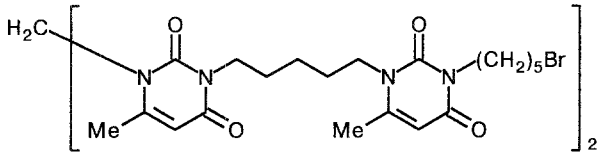
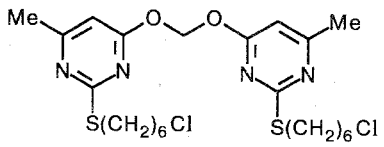
When compound **2** is refluxed in dilute HCl, the methylthio groups undergo hydrolysis to give bis(3,4-dihydro-2-hydroxy-6-methyl-4-oxopyrimidinyl-3)methane (**5**), which confirms the structure of the former compound. Compound **5** is infusible and insoluble in water and normal organic solvents. Its IR spectrum is typical of monosubstituted 6-methyluracils, *i.e.*, it contains two ν(C=O) AB at 1660 and 1710 cm^{-1} and shows ν(NH) absorption at 3090 cm^{-1} with a shoulder at 3230 cm^{-1}. The maximum of the long-wave band in the UV spectrum of compound **5** is shifted bathochromically from 266 to 285 nm when the medium changes from acid to alkaline pH. This fact also confirms structures **2** and **5**.

Attempts to obtain the corresponding mono- and bis(ω-haloalkyl) derivatives of compound **5** by the reactions of its disodium salt with α,ω-dihaloalkanes failed due to the formation of multicomponent mixtures that were difficult to separate. On the other hand, an analog of the ω-bromopentyl derivative of **5**, bis[(1-(ω-bromopentyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-3)]methane (**6**), was obtained in a satisfactory yield, *e.g.*, by the reaction of 1-(ω-bromopentyl)uracil (**7**) with DBM (in 1 : 2 ratio) in dry DMF. The presence of two ν(C=O) absorption bands at 1660 and 1705 cm^{-1} and the absence of absorption in the region corresponding to ν(NH) and ν(OH) confirm the structure of **6**. The reactions of DBM with 6-methyl-(ω-chlorohexyl)uracil (**8**) and 3-(ω-bromopentyl)quinazoline-2,4-dione (**9**) occur similarly to give bis[2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-3-(ω-chlorohexyl)-1-pyrimidinyl]methane (**10**) and bis[3-(ω-bromopentyl)-2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-1-quinazolinyl]methane (**11**), respectively. On the other hand, the reaction of 3-(ω-bromopentyl)-6-methyluracil (**12**) with DBM, under conditions similar to those used for obtaining compounds **10** and **11**, results predominantly in a compound containing four pyrimidine rings, bis{2,4-dioxo-6-methyl-3-[3′-(ω-bromopentyl)-2′,4′-dioxo-6′-methyl-1′,2′,3′,4′-tetrahydro-1′-pyrimidinyl]pentyl-1,2,3,4-tetrahydro-1-pyrimidinyl}methane (**13**).



13

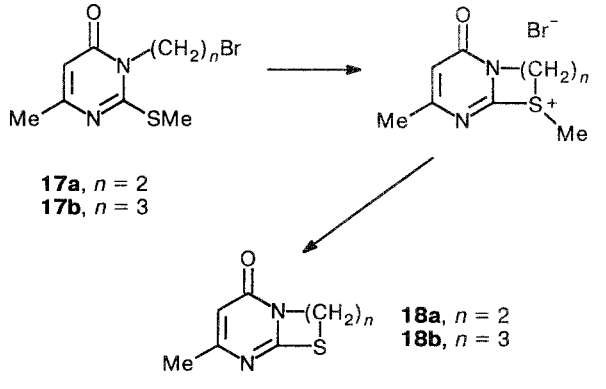
The reaction of the Na-salt of 6-methyl-4-hydroxy-2-(ω-chlorohexylthio)pyrimidine (**14**) with DBM could be expected to result in a compound analogous to that obtained from the reaction between **1** and DMB. However, this reaction gave the O—C—O isomer, bis[6-methyl-2-(ω-chlorohexylthio)pyrimidinyloxy]methane (**15**).



15

It is likely that the chlorohexyl substituent at the sulfur atom is a steric hindrance to attack on the ring nitrogen atom. The structure of compound **15** is confirmed by the absence of ν(C=O), (NH), and (OH) absorption bands in the IR spectrum and the presence of intense bands of pyrimidine ring vibrations at 1500, 1560, and 1585 cm^{-1}.

Unlike DBM, 1,2-dibromoethane (DBE) reacts with compound **1** in a 1 : 2 ratio in dry DMF to give, predominantly, the N—C—O isomer, (3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)(6-methyl-2-methylthiopyrimidinyloxy)ethane (**16**), *i.e.*, an analog of compound **3**. The structure of compound **16** was confirmed by the results of its hydrolysis. Boiling it in dilute HCl gave the previously known 6-methyluracil, 6-methyl-3-(β-hydroxyethyl)uracil,[2] and 6-methyl-3-(β-chloroethyl)uracil.[3] The reaction of compound **1** with a tenfold excess of DBE in dry DMF at 25—30 °C gave, instead of bispyrimidinethanes, 3-(β-bromoethyl)-3,4-dihydro-6-methyl-2-methylthio-4-oxopyrimidine (**17a**) and the product of its intramolecular cyclization at the sulfur atom followed by the elimination of the methyl group from the resulting sulfonium salt, 5-methyl-7-oxo-2,3,4,7-tetrahydrothiazolo[3,2-*a*]pyrimidine (**18a**). Despite the apparent similarity of the electron structures of compounds **17a** and **18a**, their IR spectra in the 1500—1700 cm^{-1} region differ significantly. The spectrum of compound **17a** contains absorption bands at 1500, 1590 (ring vibrations), and 1690 cm^{-1} (ν(C=O)), while that of compound **18a** contains bands at 1500, 1540, 1590 (ring vibrations), and 1660 cm^{-1} (ν(C=O)). The low-frequency shift of ν(C=O) and the appearance of AB at 1540 cm^{-1} can be related to the formation of a five-membered hydrogenated thiazole side ring.



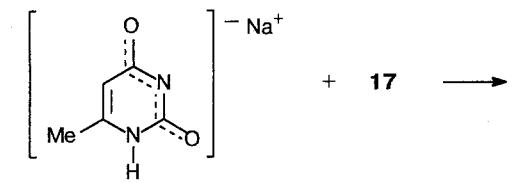
17a, $n = 2$
17b, $n = 3$

18a, $n = 2$
18b, $n = 3$

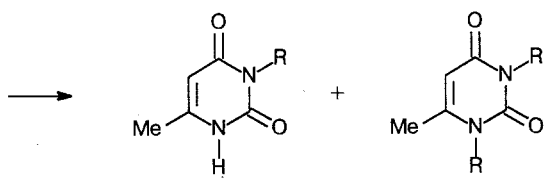
The structure of compound **18a** was confirmed by comparison with an authentic sample.[4]

Similarly, the reaction of compound **1** with 1,3-dibromopropane (DBPr) results in 3-(γ-bromopropyl)-3,4-dihydro-6-methyl-2-methylthio-4-oxopyrimidine (**17b**) and 8-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-pyrimido[2,1-*b*]thiazine (**18b**).[4] The ν(C=O) band in the IR spectrum of compound **18b**, like in the spectrum of **18a**, is shifted downfield to appear as a doublet at 1640 and 1670 cm^{-1}, while the band at 1540 cm^{-1} is absent (conversely, it appears in the spectrum of compound **17b**). In addition, the structure of compound **18b** was confirmed by X-ray diffraction analysis.

To implement the second synthetic pathway, the resulting compounds, **17a** and **17b**, were used for the alkylation of the sodium salts of 6-methyl- (**19**) and 5-methyl- (**20**) uracils. The reaction of mono-Na salt **19** with compounds **17a** and **17b** results in a mixture of mono- (at the N(3) atom) and bisalkylated derivatives of **19**, 3-[ω-(3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)]alkyl-6-methyluracils (**21a**, n = 2 and **21b**, n = 3) and 1,3-bis[ω-(3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)]alkyl-6-methyluracils (**22a**, n = 2 and **22b**, n = 3).



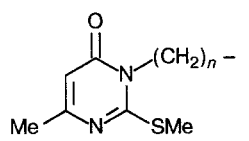
19 + **17** →



21a, n = 2
21b, n = 3

22a, n = 2
22b, n = 3

R =



Mono-Na salt **20** also reacts with compound **17b** to give a mixture of products of mono- and bisalkylation, 1-[γ-(3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)]propyl-5-methyluracil (**23**) and 1,3-bis[γ-(3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)]propyl-5-methyluracil (**24**).

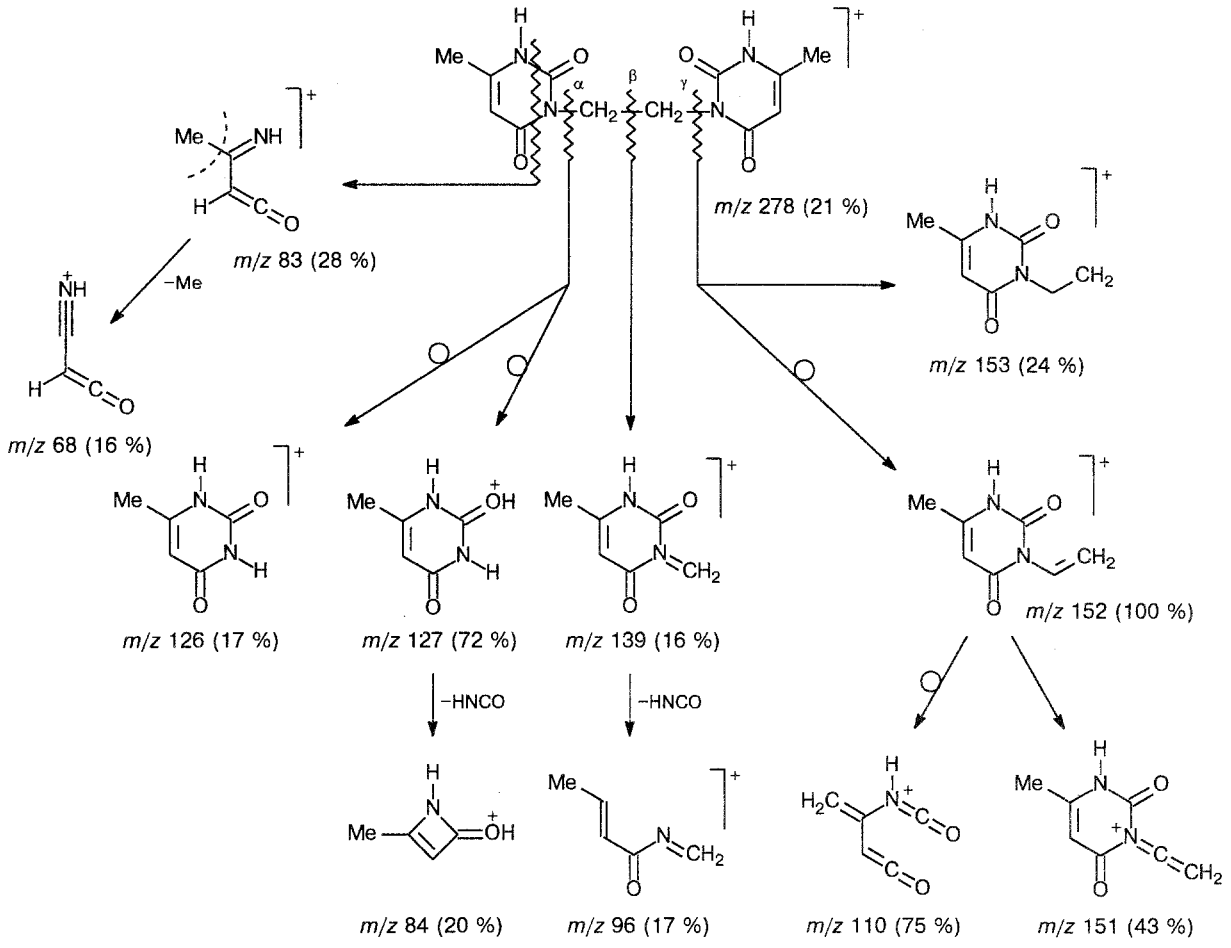
When compounds **21a,b** and **22a,b** are boiled in HCl, the methylthio groups undergo hydrolysis to give purely uracil derivatives, 3-[ω-(3,4-dihydro-6-methyl-2-hydroxy-4-oxo-3-pyrimidinyl)alkyl]-6-methyluracils (**25a**, n = 2 and **25b**, n = 3) and 1,3-bis[[ω-(3,4-dihydro-6-methyl-2-hydroxy-4-oxo-3-pyrimidinyl)-alkyl]-6-methyluracils (**26a**, n = 2 and **26b**, n = 3). The IR spectra of compounds **21a,b** and **22a,b** contain absorption bands corresponding to uracil ν(C=O) and to ring vibrations. These AB are typical of the methylthiopyrimidine moieties of the starting compounds, **17a** and **17b**. The latter bands disappear after hydrolysis, and only the AB in the region 1600—1720 cm^{-1} remain. The spectra of **25a** and **25b**, *i.e.*, of both compounds containing two rings, display only three absorption bands, namely, at 1610, 1645, and 1715 cm^{-1}, whereas those of compounds **26a** and **26b** display a group of five AB: at 1605, 1635, 1650, 1700, and 1720 cm^{-1}. The bathochromic shift of the long-wave absorption maximum in the UV spectra of **25a** and **25b** implies that the uracil rings are linked with each other through the N(3) atoms.

The reactions of the Na-salts of compounds **25a,b** and **26a,b** with 1,5-dibromopentane (DBP) gave their ω-bromopentyl derivatives. Compounds **25a** and **25b** afford mixtures of mono- and disubstituted derivatives. In particular, α,β-[1-(ω-bromopentyl)-2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-3-pyrimidinyl](3,4-dihydro-6-methyl-2-hydroxy-4-oxo-3-pyrimidinyl)ethane (**27a**) and α,β-bis-[1-(ω-bromopentyl)-2,4-dioxo-6-methyl-1,2,3,4-tetrahydropyrimidinyl-3]ethane (**28a**) result from the alkylation of compound **25a**, while the corresponding propanes are formed due to alkylation of **25b**. On the other hand, the reactions of DBP with compounds **26a** and **26b** give predominantly 1,3-bis{ω-[1-(ω-bromopentyl)-2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-3-pyrimidinyl]alkyl}-6-methyluracils (**29a**, n = 2 and **29b**, n = 3).

Unlike the starting compounds, **25a,b** and **26a,b**, whose IR spectra in the ν(C=O) region display a complicated pattern unusual for uracils, probably due to strong intra- and intermolecular interactions, the spectra of compounds **27a,b—29a,b** contain two ν(C=O) AB at 1655—1660 and 1695—1700 cm^{-1}, positions typical of substituted uracils. In addition, compounds **27a** and **27b** contain a ν(NH) absorption band in the 3080—3230 cm^{-1} region.

We also obtained the electron impact mass spectra for some of the compounds. The most characteristic direction of the decomposition of the molecular ion for compounds **5**, **25a**, and **25b**, which contain CH_2, $(CH_2)_2$, and $(CH_2)_3$ bridging groups, respectively, involves the cleavage of these groups. For example, the cleavage of the C—N γ-bond in compound **25a** (Scheme 1) gives an ion peak at m/z 153 with an intensity of 24 %, while the cleavage of this bond that occurs with migration of the H atom gives an ion peak at m/z 152 with the highest intensity. The cleavage of the C—C β-bond gives an ion peak at m/z 139 (16 %), and the cleavage of the N—C α-bond results in an ion peak at m/z 127 (72 %) with migration of two H atoms to the charged fragment. The formation of an ion peak at m/z 126 (17 %) involves the cleavage of an α-bond with migration of one H atom.

Scheme 1



Thus, processes of the cleavage of the bridge system determine the main directions of the dissociative ionization to constitute more than 270 % as a whole. The migration of the H atoms is quite reasonable, since the migration of one H atom during the cleavage of an N—C α-bond results in the formation of a strong N—H bond, and the migration of the second H atom to the positively charged oxygen atom affords a strong $=O^+—H$ bond and saturates all valences in the ion.

The ion peak with *m/z* 110 (75 %) of composition $C_5H_4NO_2$ provides information on the position where the rings are linked through the bridge system, since this peak corresponds to the ring structure minus an —NH group, which is assumed to be eliminated together with the bridging group during the dissociative ionization. This assumption is consistent with the presence of a relatively intense peak of this ion in the mass spectra of compounds **25a**, **25b**, and **26a**, which possess a bridging system. The ion peaks at *m/z* 96 (17 %), 83 (28 %), and 68 (16 %) originate from the structure of the ring, and the corresponding structures can be assigned to these fragments.

The aforementioned features of the dissociative ionization of compound **25a** are also typical of compounds **5**, **25b**, and **26a**, the only difference being that the probabilities of the corresponding cleavage routes with or without hydrogen atom migration are somewhat different. This is an expected result, since the changes in the geometry of the molecules could change the energetic characteristics of these rearrangements. For example, cleavage at a σ-bond appears in the case of compound **25b**. The picture of the dissociative ionization of compound **26a** is nearly the same as that of **25a**, which could be predicted from the similarity of these structures.

We determined the exact molecular ion masses for compounds **6**, **10**, and **11** containing two ^{35}Cl (compound **10**), or ^{79}Br and ^{81}Br (compounds **6** and **11**). In addition, we determined the relative abundance of molecular ions containing different combinations of these isotopes.

Experimental

IR spectra were recorded on a Specord IR-75 spectrophotometer (solid samples were studied as suspensions in vaseline oil, and liquids as films between KBr plates). UV spectra were obtained on a Specord M-40 spectrophotometer. Mass spectra

Table 1. Characteristics of the compounds synthesized

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula
			C	H	N	Hal	
2	85	121—123	48.14	4.73	17.58	19.64*	$C_{13}H_{16}N_4O_2S_2$
			48.13	4.97	17.27	19.76	
3	7	**	48.27	4.67	17.43	19.59*	$C_{13}H_{16}N_4O_2S_2$
			48.13	4.97	17.27	19.76	
4	2	114—115	48.31	4.77	17.39	19.83*	$C_{13}H_{16}N_4O_2S_2$
			48.13	4.97	17.27	19.76	
5	70	> 400	49.66	4.85	21.10		$C_{11}H_{12}N_4O_4$
			50.00	4.57	21.21		
6	69	**	42.77	4.98	10.35	29.72	$C_{19}H_{26}Br_2N_4O_4$
			42.72	4.90	10.49	29.91	
10	52	140—142	55.10	6.51	10.87	14.38	$C_{23}H_{34}Cl_2N_4O_4$
			55.09	6.83	11.18	14.14	
11	50	203—206	50.90	4.67	9.19	25.02	$C_{27}H_{30}Br_2N_4O_4$
			51.12	4.76	8.83	25.19	
13	85	**	51.71	5.97	11.58	16.96	$C_{41}H_{58}Br_2N_8O_8$
			51.76	6.10	11.78	16.79	
15	64	**	51.73	6.65	10.32	13.61	$C_{23}H_{34}Cl_2N_4O_2S_2$
			51.77	6.42	10.50	13.28	
16	82	115—116	49.26	5.30	16.38	18.72*	$C_{14}H_{18}N_4O_2S_2$
			49.68	5.36	16.55	18.94	
17a	45	64—65	36.10	3.96	10.66	30.16	$C_8H_{11}BrN_2OS$
			36.51	4.21	10.65	30.36	
17b	46	38—39	39.28	4.68	10.14	28.91	$C_9H_{13}BrN_2OS$
			39.00	4.73	10.11	28.82	
18a	48	122—124	49.26	5.21	16.38	19.26*	$C_7H_8N_2OS$
			50.00	4.79	16.65	19.05	
18b	15.5	119—121	53.10	5.68	15.72	17.19*	$C_8H_{10}N_2OS$
			52.72	5.53	15.37	17.59	
21a	15	243—246	50.91	5.37	18.42	10.65*	$C_{13}H_{16}N_4O_3S$
			50.63	5.23	18.17	10.40	
21b	18	167—170	52.32	5.72	17.61	9.98*	$C_{14}H_{18}N_4O_3S$
			52.16	5.63	17.38	9.94	
22a	15	211—213	51.54	5.61	17.31	12.98*	$C_{21}H_{26}N_6O_4S_2$
			51.41	5.34	17.13	13.06	
22b	17	141—143	53.30	5.65	16.49	12.68*	$C_{23}H_{30}N_6O_4S_2$
			53.26	5.83	16.21	12.36	
23	26.5	173—174	52.24	5.76	17.50	10.33*	$C_{14}H_{18}N_4O_3S$
			52.16	5.63	17.38	9.94	
24	38	168—169	53.67	5.97	16.37	12.69*	$C_{23}H_{30}N_6O_4S_2$
			53.26	5.83	16.21	12.36	
25a	63	> 360	52.19	5.40	19.83		$C_{12}H_{14}N_4O_4$
			51.79	5.07	20.14		
25b	79	353—355	53.54	5.84	18.79		$C_{13}H_{16}N_4O_4$
			53.42	5.52	19.17		
26a	57	322—324	53.17	5.30	19.21		$C_{19}H_{22}N_6O_6$
			53.02	5.15	19.53		
26b	80	249—251	54.93	5.78	18.65		$C_{21}H_{26}N_6O_6$
			55.01	5.72	18.33		
27a	46	129—131	47.96	5.73	13.16	18.60	$C_{17}H_{23}BrN_4O_4$
			47.78	5.42	13.11	18.70	
27b	23	102—105	49.36	5.89	12.60	18.17	$C_{18}H_{25}BrN_4O_4$
			48.98	5.71	12.70	18.10	
28a	21	**	45.68	5.53	9.87	27.91	$C_{22}H_{32}Br_2N_4O_4$
			45.85	5.60	9.72	27.72	
28b	23	**	46.96	5.84	9.24	27.14	$C_{23}H_{34}Br_2N_4O_4$
			46.79	5.80	9.49	27.07	
29a	45	75—77	47.68	5.85	11.58	21.78	$C_{29}H_{40}Br_2N_6O_6$
			47.81	5.53	11.54	21.93	
29b	68	**	49.56	5.78	10.87	20.81	$C_{31}H_{44}Br_2N_6O_6$
			49.21	5.86	11.11	21.12	

* An analysis for sulfur was carried out. ** Oil.

were obtained on an MX-1310 mass spectrometer (direct injection; ionizing voltage, 60 V; current in the ion source, 30 μA; R = 15000 with high-precision determination of ion masses).

Column chromatography was carried out on neutral Al_2O_3 (activity grade II), and TLC was performed on Silufol UV-254 plates. To obtain the Na-salts of hydroxypyrimidines, a calculated amount of sodium was dissolved in an optimum amount of *n*-butanol, the corresponding hydroxypyrimidine was added, and the mixture was refluxed if required. Subsequent reactions of the resulting salts were either performed in the same butanol solution (method **A**), or the butanol was distilled off *in vacuo*, the remaining alcohol was removed by azeotropic distillation with toluene, and the salt was dried *in vacuo* (method **B**). In the case of haloalkyl derivatives of hydroxypyrimidines, the salt was obtained without heating, precipitated with a hexane—ether mixture, filtered off, and dried *in vacuo* (method **C**). The salts of polycyclic compounds **25—26a** were obtained using aqueous NaOH (method **D**). The reactions of the dry Na-salts by methods **B**, **C**, and **D** were carried out in dry DMF.

The constants of the compounds synthesized are presented in Table 1.

The reaction of 1 with DBM. Method A. Compound **1** (31.2 g) was added at 55—60 °C to a solution of Na (4.6 g) in *n*-butanol (300 mL). When the salt dissolved, DBM (17.4 g) was added. The mixture was refluxed until pH 7 was attained. After cooling, NaBr was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, NaBr and compound **1** (9 g) were filtered off, and the filtrate was concentrated and chromatographed. Work-up of the hexane fractions gave 6 g of compound **3**, R_f 0.46 (ether). Work-up of the ether and benzene fractions gave 15.6 g of compound **2**.

Method B. The reaction was carried out in DMF. Repeated chromatography of the residue from the hexane fractions gave 5 g of compound **3** and 2.3 g of **4**, R_f 0.38 (hexane—ether, 1 : 1).

Compound 6: Similarly, the reaction starting from 6.2 g of the Na-salt of **7** and 3 g of DBM (method **C**) gave 4 g of compound **6** (from the $CHCl_3$—MeOH fractions, 10 : 1), oil, R_f 0.53 ($CHCl_3$—MeOH, 10 : 1); MS (EI, 60 eV), m/z (I_{rel} (%)): 536 (0.3), 534 [$C_{19}H_{26}{}^{79}Br^{81}BrN_4O_4$, M^+] (0.6), 532 (0.3).

Compound 13: The reaction starting from 6.5 g of the Na-salt of **12** and 5 g of DBM (method **C**) gave 4 g of compound **13** (from the $CHCl_3$—MeOH fraction, 20 : 1, oil, R_f 0.77 ($CHCl_3$—MeOH, 10 : 1)).

Compound 15 (method **B**): The reaction starting from 10.8 g of the Na-salt of compound **14** and 7 g of DBM gave 6.5 g of compound **15** (after repeated chromatography of the ethereal fraction, oil, R_f 0.59 (hexane—ether, 1 : 1)).

Compounds 17b, 18b: The reaction starting from 107.8 g of the Na-salt of compound **1** (method **B**) and 600 g of DBPr gave 77.7 g of compound **17b** (from the hexane fraction, R_f 0.42 (hexane—ether, 1 : 2)) and 17 g of **18b** (from benzene and $CHCl_3$, R_f 0.76 ($CHCl_3$—MeOH, 5 : 1)).

Compounds 21a, 22a: The reaction starting from 13 g of the Na-salt of **19** (method **B**) and 37.5 g of **17a** gave 5.6 g of **22a** (from the first $CHCl_3$ fraction, R_f 0.8 ($CHCl_3$—MeOH, 10 : 1)) and 4.5 g of **21a** (from the third and fourth $CHCl_3$ fractions).

Compounds 21b, 22b: The reaction starting from 20 g of the Na-salt of compound **19** (method **B**) and 37.5 g of **17a** gave 12 g of compound **22b** (from the $CHCl_3$ fraction, R_f 0.33 ($CHCl_3$—MeOH, 20 : 1)) and 8 g of **21b** (from the $CHCl_3$—MeOH fraction, 20 : 1, R_f 0.54 ($CHCl_3$—MeOH, 10 : 1)).

Compounds 23, 24: The reaction starting from 3.3 g of the Na-salt of compound **20** (method **B**) and 11 g of **17a** gave 3.9 g of compound **24** (from $CHCl_3$, R_f 0.42 ($CHCl_3$—MeOH, 20 : 1)) and 1.6 g of **23** (from the $CHCl_3$—MeOH fraction, 20 : 1, R_f 0.57 ($CHCl_3$—MeOH, 10 : 1)).

Compounds 27a, 28a: The reaction starting from 3.8 g of the Na-salt of compound **25a** (method **D**) and 25 g of DBP gave 0.65 g of compound **28a** (from $CHCl_3$, R_f 0.56 ($CHCl_3$—MeOH, 10 : 1)) and 1.1 g of **27a** (from MeOH, R_f 0.43 ($CHCl_3$—MeOH, 10 : 1)).

Compounds 27b, 28b: The reaction starting from 1.8 g of the Na-salt of compound **25b** (method **D**) and 16 g of DBP gave 0.7 g of **28b** (from $CHCl_3$, R_f 0.65 ($CHCl_3$—MeOH, 10 : 1)) and 0.5 g of **27b** (from the $CHCl_3$—MeOH fraction, 20 : 1, R_f 0.38 ($CHCl_3$—MeOH, 10 : 1));

Compound 29a: The reaction starting from 2.7 g of the Na-salt of **26a** (method **D**) and 14 g DBP gave 2.4 g of **29a** (from the $CHCl_3$—MeOH fraction, 15 : 1, R_f 0.47 ($CHCl_3$—MeOH, 10 : 1)).

Preparation of compound 10. The Na-salt of compound **8** (4.6 g) (method **C**) and DBM (10 g) in dry DMF were heated at 50—60 °C until pH 7 was attained. The solution was filtered, and the filtrate was concentrated *in vacuo*. The residue was worked-up with $CHCl_3$, filtered, and concentrated. The residue was worked-up with ether, and the precipitate was filtered off and crystallized from an isooctane—toluene mixture (4 : 1) to give 2.5 g of compound **10** (R_f 0.78, $CHCl_3$—MeOH, 10 : 1). MS (EI, 60 eV), m/z (I_{rel} (%)): 504 (0.7), 502 (4.2), 500 [$C_{23}H_{34}Cl_2N_4O_4$, M^+] (6.0).

Similarly, the reaction of the Na-salt of compound **9** (2.7 g) (method **C**) and DBM (10 g) gave 1.6 g of compound **11** (ether—benzene, 1 : 3), R_f 0.5 ($CHCl_3$). MS (EI, 60 eV), m/z (I_{rel} (%)): 636 (2.5), 634 [$C_{27}H_{30}{}^{79}Br^{81}BrN_4O_4$, M^+] (5.2), 632 (2.5).

The reaction of the Na-salt of compound 1 with DBE (1 : 10). Dry DMF (400 mL) and DBE (620 g) were added to the Na-salt of compound **1** (method **B**) prepared from **1** (52 g) and Na (7.7 g) in *n*-butanol (400 mL). Dry DMF (400 mL) and DBE (620 g) were added, and the mixture was heated at 30—35 °C until pH 7 was attained. The solution was filtered off, and the filtrate was concentrated *in vacuo*. The residue was worked-up with benzene, the precipitate was filtered off, and the filtrate was concentrated. The residue was worked-up with a hexane—ether mixture (7 : 1), and the precipitate was filtered off to give 39 g of compound **1**. The filtrate was concentrated to give 26 g of compound **11**. Fractional crystallization of compounds **1** and **11** from hexane—ether and hexane—benzene mixtures gave 30 g of compound **18a** (R_f 0.25, hexane—ether, 1 : 3) and 23 g of compound **17** (R_f 0.37, hexane—ether, 1 : 2).

In a similar way, 53.5 g of compound **16** (hexane—benzene, 1 : 1) was obtained from 75 g of compound **1** and 46 g of DBE (2 : 1).

Hydrolysis of compound 2. Compound **2** (8.3 g) was refluxed for 4 h in a mixture of H_2O (150 mL) and concentrated HCl (30 mL). The precipitate was filtered off and reprecipitated with dilute AcOH from NaOH. The precipitate was filtered off and washed with H_2O and acetone to give 5.5 g of compound **5**. MS (EI, 60 eV), m/z (I_{rel} (%)): 265 (8), 264 [$C_{11}H_{12}N_4O_4$, M^+] (55), 249 [$C_{10}H_9N_4O_4$] (3), 221 [$C_{10}H_{11}N_3O_3$] (5), 178 [$C_9H_{10}N_2O_2$] (24), 140 (13.4), 139 [$C_6H_7N_2O_2$] (82), 138 (49), 127 [$C_5H_7N_2O_2$] (48), 126 ($C_5H_6N_2O_2$] (66), 111 (9), 110 [$C_5H_6N_2O$] (10), 97 (12), 96 [C_5H_6NO] (39), 95 [C_5H_5NO] (49), 84 [C_4H_6NO] (12), 83 [C_4H_5NO] (47), 70 (28), 68 [C_3H_2NO] (64), 67 (29), 42 [C_2H_4N] (100).

In a similar way, 3.4 g of compound **25a** was obtained from compound **21a** (6 g). The mass spectrum is presented in the Scheme.

Compound 25b (5.3 g) was obtained from compound **21b** (7.4 g); MS (EI, 60 eV), *m/z* (I_{rel} (%)): 293 (7), 292 [$C_{13}H_{16}N_4O_4$, M^+] (49), 167 [$C_8H_{11}N_2O_2$] (21), 166 [$C_8H_{10}N_2O_2$] (47), 165 (9), 154 (9), 153 [$C_7H_9N_2O_2$] (10), 152 (5), 151 [$C_7H_7N_2O_2$] (65), 140 [$C_6H_8N_2O_2$] (52), 139 (8), 127 [$C_5H_7N_2O_2$] (43), 126 [$C_5H_6N_2O_2$] (9), 111 (8), 110 [$C_5H_4NO_2$] (64), 96 [C_5H_6NO] (11), 84 [C_4H_6NO] (48), 83 [C_4H_5NO] (31), 68 [C_3H_2NO] (20);

Compound 26a (4.8 g) was obtained from compound **22a** (9.6 g); MS (EI, 60 eV), *m/z* (I_{rel} (%)): 431 (3), 430 [$C_{19}H_{22}N_6O_6$, M^+] (12), 305 [$C_{14}H_{17}N_4O_4$] (7), 304 [$C_{14}H_{16}N_4O_4$] (11), 279 [$C_{12}H_{15}N_4O_4$] (9), 278 [$C_{12}H_{14}N_4O_4$] (14), 178 [$C_9H_{10}N_2O_2$] (14), 153 [$C_7H_9N_2O_2$] (49), 152 (100), 151 (30), 139 [$C_6H_7N_2O_2$] (11), 127 [$C_5H_7N_2O_2$] (45), 110 [$C_5H_4NO_2$] (53), 96 [C_5H_6NO] (25), 84 [C_4H_6NO] (19), 83 [C_4H_5NO] (14), 68 [C_3H_2NO] (12);

Compound 26b (5.6 g) was obtained from compound **22b** (8 g).

References

1. V. S. Reznik, I. Sh. Salikhov, Yu. S. Shvetsov, and B. E. Ivanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 2568 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1980, **29**, 1824 (Engl. Transl.)].
2. V. S. Reznik and N. G. Pashkurov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 1327 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1968, **17** (Engl. Transl.)].
3. V. S. Reznik, Yu. S. Shvetsov, and N. G. Pashkurov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, 2811 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1968, **17**, *N* 12 (Engl. Transl.)].
4. N. G. Pashkurov and V. S. Reznik, *Khim. Geterotsikl. Soedin.*, 1968, 918 [*Chem. Heterocycl. Compd.*, 1968 (Engl. Transl.)].

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