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Unified Synthetic Approach to 2-Substituted 6-Methylisocytosines and Their 5-Bromo Derivatives

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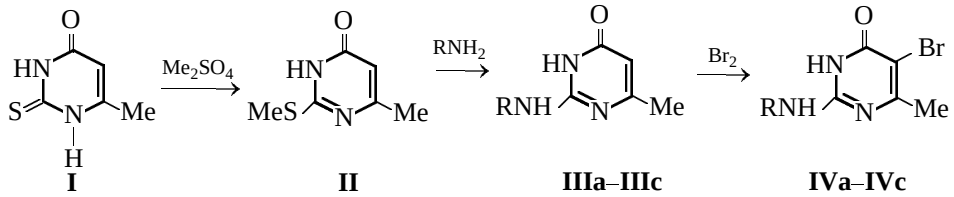
Abstract — 6-Methyl-4(3*H*)-pyrimidinones containing 2-alkyl-, 2-cycloalkyl-, and 2-arylalkylamino groups were synthesized and brominated to obtain 5-bromo derivatives.

The interest in isocytosines is due to the fact that some representatives of this series have exhibited pronounced antiviral properties [1]. Among them is bromopyrimine [2-amino-5-bromo-6-phenyl-4(3*H*)-pyrimidinone], an inhibitor of the replicative cycle of herpes virus. At the same time, multiple side effects (hyperthermia, diuresis, tachycardia, etc.) produced by bropyrimine in vivo [2] stimulates search for its less toxic analogs.

To this end, in the present work, starting from 6-methyl-2-thiouracil (**I**) and the intermediate 6-methyl-2-methylthio-4(3*H*)-pyrimidinone (**II**), we synthesized 2-amino-6-methyl-4(3*H*)-pyrimidinones **IIIa**–**IIIc** and 2-amino-5-bromo-6-methyl-4(3*H*)-pyrimidinones **IVa**–**IVc** (Tables 1, 2), potential antiviral agents, according to the following scheme.



I **II** **IIIa**–**IIIc** **IVa**–**IVc**

R = Bu (**a**), *cyclo*-C_6H_{11} (**b**), $PhCH_2$ (**c**).

S-Methylation of thioxoketone **I** with dimethyl sulfate gives thioether **II** which reacts with amines in rigid conditions, affording secondary amines **IIIa**–**IIIc**. Treatment of the latter with bromine yields compounds **IVa**–**IVc**.

The starting thioxoketone was obtained by condensation of thiourea with acetoacetic ester in ethanol in the presence of sodium ethylate by a modified method [3].

Owing to the high reactivity of the thiolactam

Table 1. Yields, melting points, and elemental analyses of 6-methyl- (**IIIa**–**IIIc**) and 5-bromo-6-methylisocytosines (**IVa**–**IVc**)

Comp. no.	Yield, %[a]	mp, °C	R_f (eluent)	Found N, %	Formula	Calculated N, %
IIIa[b]	39	207	0.55 (A)	19.05	$C_9H_{15}N_3O \cdot HCl$	19.31
IIIb[b]	40	200	0.63 (A)	17.56	$C_{11}H_{17}N_3O \cdot HCl$	17.24
IIIc[b]	46	214	0.56 (A)	16.61	$C_{12}H_{13}N_3O \cdot HCl$	16.70
IVa	40	189	0.82 (B)	16.52	$C_9H_{14}BrN_3O$	16.15
IVb	66	205	0.86 (B)	13.92	$C_{11}H_{16}BrN_3O$	14.69
IVc	49	216	0.78 (B)	13.83	$C_{12}H_{12}BrN_3O$	14.29

[a] Per starting thioether **II**. [b] Isolated as hydrogen chloride.

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Table 2. UV, IR, and ^{1}H NMR spectra of 6-methyl- (**IIIa**–**IIIc**)- and 5-bromo-6-methylisocytosines (**IVa**–**IVc**)

Comp. no.	UV spectrum, λ_{max} (log ε) (solvent)	IR spectrum, ν(C=O), cm^{-1}	^{1}H NMR spectrum, δ, ppm[a]
IIIa	265 (3.67) (H_2O)	1705	2.41 s (3H, Me), 5.77 s (1H, CH), 8.96 s (1H, NH_e), 12.58 br.s (1H, NH)
IIIb	267 (3.70) (H_2O)	1710	2.39 s (3H, Me), 5.75 s (1H, CH), 9.01 (1H, NH_a), 12.80 br.s (1H, NH)
IIIc	266 (3.75) (H_2O)	1710	2.65 s (3H, Me), 5.88 s (1H, CH), 7.45 m (5H, Ph), 9.00 br.s (2H, NH + NH_a)
IVa	277 (3.92) (0.1 N HCl)	1655	2.11 s (3H, Me), 6.57 br.s (2H, NH + NH_a)
IVb	280 (3.67) (0.1 N HCl)	1655	2.40 s (3H, Me), 7.80 br.s (2H, NH + NH_a)
IVc	277 (3.82) (0.1 N HCl)	1650	2.32 s (3H, Me), 7.43 m (5H, Ph), 8.35 s (1H, NH_a), 11.15 br.s (1H, NH)

[a] Chemical shift of the pyrimidine methyl proton signal is given.

group, thiouracils are preferentially alkylated by the sulfur atom [4].

Thioether **II** was synthesized by reaction of equimolar amounts of thioxoketone **I** and dimethyl sulfate in 10% aqueous sodium hydroxide at 80°C and subsequent acidification of the reaction mixture with dilute hydrochloric acid. Methyl thioether **II** is the most convenient substrate for ammonolysis. With longer chain alkyl thioethers, the rate of ammonolysis is much lower [5].

Thioxoketone **I** could not be S-methylated by the method [6] that presupposes using equimolar amounts of thiopyrimidine and caustic alkali, since it is poorly soluble in highly dilute alkalis even under heating.

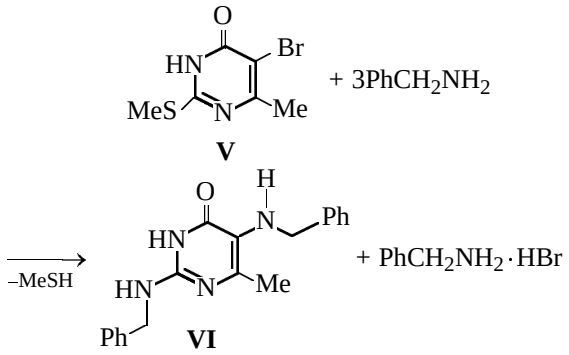
Along with the synthesis of isocytosine derivatives from iminoureas and appropriate three-carbon fragments [7], of great preparative importance is ammonolysis of 2-methylthio-4(3*H*)-pyrimidinones, since the latter are more accessible compared with corresponding halopyrimidines. Less suitable for this purpose are amination of 2-methoxy-4(3*H*)-pyrimidinones, in view of its multistage nature [8], and *trans*-ammonolysis of 6-methylisocytosine. The latter reaction is nonselective, and its direction is much dependent of the basicity of the aminating agent and the nature of the solvent [9].

Accoridng to [10, 11], ether **II** can be aminated in excess amine at 170–190°C with subsequent crystallization of the reaction product from from methanol [10] or alcohol–acetone or alcohol–benzene mixtures [11]. Unfortunately, the reported procedures could be reproduced only partially. By chromatography we found in the reaction mixture a number of unidentified products but failed to isolate them by crystallization from methanol and proposed solvents mixtures, as well as from other solvents (water, ethanol, 2-propanol, acetone, chloroform, diethyl ether, C_5–C_7 hydrocarbons) and some of their mixtures (chloroform–hexane). At the same time, taking account of the fact that the basicity of pyrimidines increases with decreasing number of oxo substituents in their nucleus [5], we isolated the target products as hydrogen chlorides obtained by passing dry hydrogen chloride through a solution of the reaction residue in absolute 2-propanol. The resulting hydrochlorides of compounds **IIIa**–**IIIc** are colorless crystals. The UV spectra of aqueous solutions of the hydrochlorides contain an absorption band at 265–267 nm, whose low intensity by the protonation of the pyrimidine ring by the nitrogen atom. The IR spectra display a strong absorption band at 1710–1705 cm^{-1}, corresponding stretching vibrations of the carbonyl group and implying that the target compounds are present in the lactam form. The ^{1}H NMR spectra of the hydrochlorides of 6-methylisocytosines **IIIa**–**IIIc** contain characteristic aminomethylene carbon signals at 3.0–5.0 ppm (Table 2).

5-Bromo derivatives **IVa**–**IVc** can be prepared either by ammonolysis of 5-bromo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone [12] (method *a*), or by bromination of 2-amino-6-methyl-4(3*H*)-pyrimidinones [13] (method *b*).

The required 5-bromo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone (**V**) was obtained by treatment of thioether **II** with bromine in glacial acetic acid by a modified method [12].

The reaction performed by method *a* gave umbiguous results. Thus, heating compound **V** with excess benzylamine at 130°C for 10 h resulted in substitution not only of the methylthio group, but also of the bromine atom. As a result, a mixture of 2,5-dibenzylamino-6-methyl-4(3*H*)-pyrimidinone (**VI**) and benzylamine hydrochloride formed and was crystallized by addition of diethyl ether. The composition of



the mixture was determined from its ^{1}H NMR spectrum which showed signals of the methyl, methylene, phenyl, and amino groups with an integral intensity ratio of 3:6:15:6. Note that if benzylamine was replaced by a weaker base, 4-chloroaniline, and the reaction was performed in 2-ethoxyethanol under reflux, the bromine atom in compound **V** was not touched on [12].

Boiling bromopyrimidine **V** with excess benzylamine in ethyl cellosolve gives a mixture of unidentified oily compounds.

At the same time, as follows from published data [13], isocytosines are readily brominated in acetic acid already at room temperature. In our case, however, this procedure is difficult to realize, since isocytosines **IIIa**–**IIIc** should be isolated as free bases. Moreover, halogenation of some representatives of this group, specifically compound **IIIc**, may theoretically involve protons both at the pyrimidine and phenyl carbon atoms. To go around these difficulties, we performed bromination of isocytosines **IIIa**–**IIIc** *in situ* in glacial acetic acid at a temperature of no higher than 40°C (method *b*).

Thus obtained bromo derivatives **IVa**–**IVc** are colorless crystals. The UV spectra of their hydrochloric acid solutions show an absorption band at 277–280 nm, shifted red from the respective band of 6-methylisocytosines due to the presence in the former compounds of the electron-acceptor halogen substituent. The IR spectra contain a strong band at 1655–1650 cm^{-1} due to stretching vibrations of the carbonyl group and indicative of the lactam form of the target compounds. The ^{1}H NMR spectra of bromo derivatives **IVa**–**IVc** lack C^{5}H proton signal near 6 ppm (Table 2). The selective bromination of amine **IIIc** at the 5 position of the pyrimidine ring is also confirmed by the presence of a five-proton multiplet of phenyl protons at 7–8 ppm.

EXPERIMENTAL

The UV spectra were recorded on an SF-26 spectrophotometer for 10^{-4} M solutions in water and in 0.1 N hydrochloric acid. The IR spectra were taken on a UR-20 instrument in mineral oil. The ^{1}H NMR spectra were obtained on a Bruker AC-300 spectrometer (300.13 MHz) in DMSO-d_6.

The purity of the obtained compounds was proved by TLC on Silufol UV254 plates in the systems acetone–hexane–acetic acid, 2:1:1 (A), and acetone–hexane, 2:1 (B).

Analysis for nitrogen was performed by the Dumas method.

6-Methyl-2-thiouracil (I). Freshly distilled acetoacetic ester, 36.4 g, was added to a solution of sodium ethylate, prepared from 6.5 g of sodium and 100 ml of 96% ethanol. The resulting mixture was heated to 60°C, and 21.6 g of crystalline thiourea was added in portions with vigorous stirring (in [3], ethanolic thiourea was used). The suspension that formed was heated under reflux for 3 h and then cooled. The precipitate was filtered off, dissolved in 200 ml of water, and the solution was acidified with concentrated hydrochloric acid to pH 2. The precipitate was filtered off, washed with cold water, and dried at 100°C for 6 h. Yield 20.5 g (51%), R_f 0.54 (B), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, Me), 5.60 s (1H, CH), 12.15 s (2H, NH).

6-Methyl-2-methylthio-4(3*H*)-pyrimidinone (II). Dimethyl sulfate, 7.1 g, was added to a solution of 8.0 g of thioxoketone **I** in 45 ml of water, containing 5 g of sodium hydroxide. The mixture was heated on a boiling water bath for 3 h, after which it was cooled to room temperature and acidified with dilute (1:1) hydrochloric acid to a stable weakly acidic reaction. The precipitate that formed was filtered off and purified by reprecipitation with dilute (1:1) hydrochloric acid from 10% aqueous sodium hydroxide. The precipitate was washed with water and dried in a vacuum dessicator with phosphorus pentoxide. Yield 7.2 g (82%), R_f 0.47 (B), mp 228°C (mp 225°C [14]).

2-Butylamino-6-methyl-4(3*H*)-pyrimidinone (IIIa). A mixture of 1.56 g thioether **II** and 1.46 g of freshly distilled butylamine was heated in a sealed ampule at 160°C for 5 h. After cooling to room temperature, the ampule was unsealed, the oily material was diluted with 10 ml of absolute 2-propanol, and dry hydrogen chloride was passed through the solution until saturation. The resulting suspension was kept at 0°C for 1 h, the precipitate was filtered off, recrystallized from 2-propanol, and dried over phos-

phorus pentoxide in a vacuum dessicator. Compound **IIIa** was obtained as hydrochloride.

2-Cyclohexylamino-6-methyl-4(3*H*)-pyrimidinone (**IIIb**) was prepared in a similar way.

2-Benzylamino-6-methyl-4(3*H*)-pyrimidinone (IIIc). Freshly distilled benzylamine, 2.14 g, was added to 1.56 g of thioether **II**. The mixture was heated on an oil bath with stirring at 160°C (bath temperature) for 5 h and then cooled to room temperature and diluted with 15 ml of absolute 2-propanol. Dry hydrogen chloride was passed through the solution until saturation. The precipitate that formed was filtered off, recrystallized from 2-propanol, and dried over phosphorus pentoxide in a vacuum dessicator. Compound **IIIc** was obtained as hydrochloride.

5-Bromo-2-butylamino-6-methyl-4(3*H*)-pyrimidinone (IVa). A mixture of 1.56 g of thioether **II** and 1.46 g of freshly distilled butylamine was heated in a sealed ampule at 160°C for 5 h. After cooling, the ampule was unsealed, and its content was diluted with 10 ml of glacial acetic acid. Bromine, 1.6 g, was added dropwise with stirring to the resulting solution. The precipitate that formed was filtered off, washed with acetic acid, reprecipitated with dilute (1 : 1) hydrochloric acid from 10% aqueous sodium hydroxide, washed with cold water, and dried over phosphorus pentoxide in a vacuum dessicator.

5-Bromo-2-cyclohexylamino-6-methyl-4(3*H*)-pyrimidinone (**IVb**) was obtained in a similar way.

5-Bromo-2-benzylamino-6-methyl-4(3*H*)-pyrimidinone (IVc). Freshly prepared benzylamine, 2.14 g, was added to 1.56 g of thioether **II**. The mixture was heated on an oil bath with stirring at 160°C (bath temperature) for 5 h. After cooling to 40°C, the reaction mixture was diluted with 10 ml of glacial acetic acid, and, maintaining this temperature, 1.6 g of bromine was added dropwise with stirring. The precipitate that formed was filtered off, washed with acetic acid, reprecipitated with dilute (1 : 1) hydrochloric acid from 10% aqueous sodium hydroxide, washed with cold water, and dried over phosphorus pentoxide in a vacuum dessicator.

5-Bromo-6-methyl-2-methylthio-4(3*H*)-pyrimidinone (V). Bromine, 0.8 g, was added with stirring at room temperature to a solution of 0.78 g of thioether **II** in 15 ml of glacial acetic acid. The resulting suspension was filtered off, the precipitate was washed with acetic acid, reprecipitated with dilute (1 : 1) hydrochloric acid from 10% aqueous sodium hydroxide (in [12], recrystallization from 2-ethoxyethanol was used), washed with cold water, and dried in a vacuum dessicator over phosphorus pentoxide. Yield 0.75 g (63%), R_f 0.88 (B), mp 250°C (decomp.) {mp 254–256°C (decomp.) [12]}.

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REFERENCES

1. Wierenga, W., Skulnick, H.I., Stringfellow, D.A., Weed, S.D., Renis, H.E., and Eidson, E.E., *J. Med. Chem.*, 1980, vol. 23, no. 3, p. 237.
2. Shimada, A., Iizuka, H., Takada, K., Susuki, S., Hirata, M., and Yanagita, T., *Jitchuken Zenrinsho Kenkyuho*, 1993, vol. 19, no. 1, p. 35, *Chem. Abstr.*, 1993, vol. 119, 195132 a.
3. List, R., *Justus Liebigs Ann. Chem.*, 1886, vol. 236, no. 1, p. 1.
4. Wyrzykiewicz, E., Stobieski, M., and Golankiewicz, K., Roczn. *Chem.*, 1977, vol. 51, no. 6, p. 1227.
5. Brown, D.J., *The Pyrimidines*, Suppl. I, New York: Wiley, 1970.
6. Kuliev, F.A., Galstyan, K.A., and Babakhanov, R.A., *Dokl. Akad. Nauk Azerb. SSR*, 1985, vol. 51, no. 6, p. 27.
7. Majima, R., *Ber.*, 1908, vol. 41, no. 2, p. 176.
8. Botta, M., De Angelis, F., Finizia, G., Gambacorta, A., and Nicoletti, R., *Synth. Commun.*, 1985, vol. 15, no. 1, p. 27.
9. Akhmerov, M.A., Reznik, V.S., Shagidullin, R.R., and Shvetsov, Yu.S., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1992, no. 1, p. 169.
10. Matsukawa, T. and Shirakawa, K., *J. Pharm. Soc. Jpn.*, 1951, vol. 71, no. 9, p. 943.
11. Sen, A.B. and Gupta, S.K., *J. Indian Chem. Soc.*, 1962, vol. 39, no. 2, p. 129.
12. Curd, F.H.S., Richardson, D.N., and Rose, F.L., *J. Chem. Soc.*, 1946, no. 5, p. 378.
13. Roth, B. and Schlomer, L.A., *J. Org. Chem.*, 1963, vol. 28, no. 10, p. 2659.
14. Simon, I.B. and Kovtunovskaya, I.I., *Zh. Obshch. Khim.*, 1951, vol. 21, no. 4, p. 760.