# Preparation and characterization of 2-alkylthio-4-(4-bromomethylbenzoyloxy)-6-methylpyrimidines

Z. NOVOTNÁ, M. KOÓŠ, and M. MATULOVÁ

*Institute of Chemistry, Slovak Academy of Sciences, CS-842 38 Bratislava*

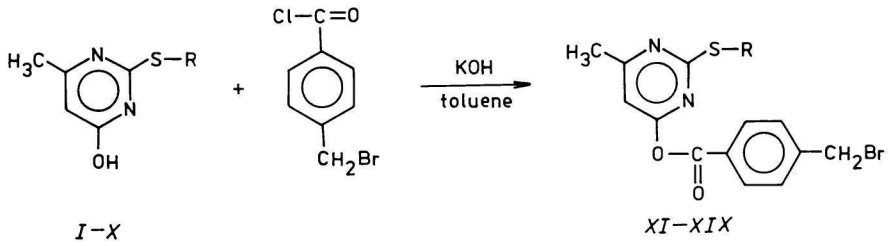
Received 30 August 1990

By the reaction of 2-alkylthio-4-hydroxy-6-methylpyrimidines with 4-bromomethylbenzoyl chloride, new 2-alkylthio-4-(4-bromomethylbenzoyloxy)-6-methylpyrimidines were prepared. The structure of the prepared compounds was determined on the basis of IR, NMR, and mass spectral data and elemental analysis.

Acylation of 4-hydroxypyrimidines, with regard to their possible keto-enol tautomerism, affords either *N*- or *O*-acylated derivatives. The direction of acylation depends as on the substituents of starting pyrimidine derivative as on the method of preparation. Uracil itself, resp. 5-alkoxy derivatives of uracil and thiouracil react with acetic anhydride or acyl halides under formation of 1-acyl or 1,3-diacyl derivatives [1, 2]. There are described other *N*-acylations in the case of unsubstituted 4-hydroxypyrimidine [3] and its derivatives having substituent with electron-withdrawing effect in the position 5 [4, 5].

In the case of 6-alkyl derivatives of 4-hydroxypyrimidines, acylations with halides of several types of acids (carbamoyl chlorides, dialkyl chlorophosphates or thiophosphates, acyl halides) were described. In all these cases, *O*-substituted derivative resulted [6—11]. Several methods of acylation using reaction between pyrimidine and acyl halide in polar organic solvent in the presence of carbonate or tertiary amine as hydrogen halide binding agent, are described. Reaction of alkaline salt of 4-hydroxypyrimidine derivative with acyl halides represents further possibility. *Botta et al.* [11, 12] in their works demonstrate that in the case of 6-alkylated derivatives, *N*-acylation is only very low yielding while *O*-acyl derivative is a predominant product. In the case of these compounds, substitution at nitrogen atom takes place only after preceding *O*-silylation.

In the present work, we focused our attention on the preparation of 2-alkylthio-4-(4-bromomethylbenzoyloxy)-6-methylpyrimidines with the aim to obtain intermediates for synthesis of biologically active compounds having tenside properties, where long alkyl chain of 2-alkylthio group should represent hydrophobic part of molecule. To prepare these compounds, acylation of dry alkaline salt in nonpolar solvent was used (Scheme 1). The results of elemental analysis, yields, and melting points of the prepared compounds are given in Table 1.




*I—X* *XI—XIX*

*Scheme 1*

Starting 2-alkylthio-4-hydroxy-6-methylpyrimidines *I—X* were prepared by the alkylation of 4-hydroxy-6-methyl-2-mercaptopyrimidine with corresponding alkyl halide in ethanolic solution of sodium hydroxide. This procedure is a modification of known methods utilizing alkylation in aqueous solutions of hydroxides [13, 14], in aqueous-alcoholic solutions of hydroxides [15] or in the medium of anhydrous alcoholate [16].

In the IR spectra of the prepared compounds *XI—XIX*, absorption bands in the region of $\tilde{\nu} = 1060—1083\,\mathrm{cm}^{-1}$ and $\tilde{\nu} = 1558—1579\,\mathrm{cm}^{-1}$ corresponding to the characteristic vibrations of pyrimidine ring, were observed. Stretching vibrations of ester group showed characteristic bands in the region of $\tilde{\nu} = 1739—1748\,\mathrm{cm}^{-1}$ and two bands in the region of $\tilde{\nu} = 1148—1160\,\mathrm{cm}^{-1}$ and $\tilde{\nu} = 1237—1246\,\mathrm{cm}^{-1}$

In the mass spectra ($U = 70\,\mathrm{eV}$) of all the prepared compounds, peaks corresponding to the molecular ions $M^{+\bullet}$, were observed. In the case of compounds *I—X*, their relative intensity ($I_r$/%) decreased with increasing length of alkyl chain R ($I_r = 100\,\%$ for R = $CH_3$ and $C_2H_5$; $I_r = 11\,\%$ for R = dodecyl). Maximum peak ($I_r = 100\,\%$) in the spectra of compounds *III—X* was registered at $m/z = 142$, corresponding to the ion of 4-hydroxy-2-mercapto-6-methylpyrimidine (loss of an alkyl radical and transfer of hydrogen atom to sulfur). By the loss of $^{\bullet}SCN$ radical from the ion at $m/z = 142$, further significant peak at $m/z = 84$ was formed. These, like then further observed fragmentations, were in agreement with those, published for compounds *II* and *III* [17]. In the case of compounds *XI—XIX*, no expressive dependence of $I_r$ on the length of alkyl chain R ($I_r = 3—12\,\%$) was observed. The base peaks of spectra of these compounds corresponded to the ions $BrCH_2C_6H_4CO^+$ Further significant peaks which confirm the structure of discussed compounds, were formed by the loss of $Br^{\bullet}$ radical or $BrCH_2C_6H_4CO^{\bullet}$ radical from molecular ion $M^{+\bullet}$

$^1$H NMR and $^{13}$C NMR spectral data are given in Experimental.

Testing of the final compounds *XI—XIX*, as well as starting pyrimidine derivatives *I—X*, revealed relatively low antimicrobial efficiency of these compounds. More detailed results in this field will be published elsewhere.

*Table 1*

Characterization of the prepared compounds *I*—*XIX*

| Compound | R | Formula | $M_r$ | $w_i$(calc.)/% $w_i$(found)/% | | | | | Yield | M.p. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S | Br | % | °C |
| *I* | Methyl | $C_6H_8N_2OS$ | 156.12 | 46.16 | 5.12 | 17.93 | 20.54 | — | 95 | 218—219 |
| | | | | 46.11 | 5.20 | 17.99 | 20.49 | | | |
| *II* | Ethyl | $C_7H_{10}N_2OS$ | 170.13 | 49.41 | 5.87 | 16.46 | 18.84 | — | 89 | 145—146 |
| | | | | 49.30 | 5.93 | 16.52 | 18.80 | | | |
| *III* | Propyl | $C_8H_{12}N_2OS$ | 184.14 | 52.17 | 6.52 | 15.21 | 17.41 | — | 90 | 121—123 |
| | | | | 52.03 | 6.59 | 15.29 | 17.34 | | | |
| *IV* | Butyl | $C_9H_{14}N_2OS$ | 198.15 | 54.54 | 7.06 | 14.13 | 16.18 | — | 90 | 85—87 |
| | | | | 54.40 | 7.14 | 14.09 | 16.14 | | | |
| *V* | Pentyl | $C_{10}H_{16}N_2OS$ | 212.16 | 56.60 | 7.54 | 13.20 | 15.11 | — | 92 | 91—92 |
| | | | | 56.49 | 7.60 | 13.29 | 15.04 | | | |
| *VI* | Hexyl | $C_{11}H_{18}N_2OS$ | 226.17 | 58.41 | 7.96 | 12.38 | 14.18 | — | 88 | 78—79 |
| | | | | 58.33 | 7.99 | 12.43 | 14.14 | | | |
| *VII* | Heptyl | $C_{12}H_{20}N_2OS$ | 240.18 | 60.00 | 8.33 | 11.66 | 13.35 | — | 96 | 88—89 |
| | | | | 59.93 | 8.38 | 11.70 | 13.34 | | | |
| *VIII* | Octyl | $C_{13}H_{22}N_2OS$ | 254.19 | 61.42 | 8.65 | 11.02 | 12.61 | — | 93 | 68—70 |
| | | | | 61.36 | 8.69 | 11.10 | 12.58 | | | |
| *IX* | Decyl | $C_{15}H_{26}N_2OS$ | 282.21 | 63.83 | 9.21 | 9.92 | 11.36 | — | 91 | 91—92 |
| | | | | 63.77 | 9.26 | 9.97 | 11.33 | | | |
| *X* | Dodecyl | $C_{17}H_{30}N_2OS$ | 310.23 | 65.81 | 9.67 | 9.03 | 10.33 | — | 90 | 92—93 |
| | | | | 65.77 | 9.70 | 9.07 | 10.29 | | | |
| *XI* | Ethyl | $C_{15}H_{15}BrN_2O_2S$ | 367.12 | 49.07 | 4.08 | 7.63 | 8.73 | 21.77 | 84 | 80—81 |
| | | | | 49.01 | 4.11 | 7.67 | 8.70 | 21.68 | | |
| *XII* | Propyl | $C_{16}H_{17}BrN_2O_2S$ | 381.13 | 50.42 | 4.46 | 7.35 | 8.41 | 20.97 | 84 | 58—60 |
| | | | | 50.31 | 4.49 | 7.40 | 8.37 | 20.90 | | |
| *XIII* | Butyl | $C_{17}H_{19}BrN_2O_2S$ | 395.14 | 51.67 | 4.81 | 7.09 | 8.11 | 20.22 | 80 | 49—50 |
| | | | | 51.61 | 4.86 | 7.14 | 8.08 | 20.17 | | |

*Table 1* (Continued)

| Compound | R | Formula | $M_r$ | $w_i$(calc.)/% $w_i$(found)/% | | | | | Yield | M.p. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S | Br | % | °C |
| *XIV* | Pentyl | $C_{18}H_{21}BrN_2O_2S$ | 409.15 | 52.84 | 5.13 | 6.84 | 7.82 | 19.53 | 81 | 42—43 |
| | | | | 52.80 | 5.17 | 6.90 | 7.80 | 19.49 | | |
| *XV* | Hexyl | $C_{19}H_{23}BrN_2O_2S$ | 423.16 | 53.93 | 5.44 | 6.62 | 7.58 | 18.88 | 80 | 80—81 |
| | | | | 53.99 | 5.48 | 6.68 | 7.55 | 18.82 | | |
| *XVI* | Heptyl | $C_{20}H_{25}BrN_2O_2S$ | 437.17 | 54.94 | 5.72 | 6.40 | 7.33 | 18.28 | 85 | 47—48 |
| | | | | 54.88 | 5.78 | 6.43 | 7.29 | 18.21 | | |
| *XVII* | Octyl | $C_{21}H_{27}BrN_2O_2S$ | 451.18 | 55.90 | 5.98 | 6.21 | 7.11 | 17.71 | 83 | 38—39 |
| | | | | 55.80 | 5.99 | 6.26 | 7.07 | 17.65 | | |
| *XVIII* | Decyl | $C_{23}H_{31}BrN_2O_2S$ | 479.20 | 57.64 | 6.47 | 5.84 | 6.69 | 16.68 | 85 | 48—49 |
| | | | | 57.56 | 6.50 | 5.86 | 6.66 | 16.62 | | |
| *XIX* | Dodecyl | $C_{25}H_{35}BrN_2O_2S$ | 507.22 | 59.19 | 6.90 | 5.52 | 6.32 | 15.45 | 84 | 55—56 |
| | | | | 59.11 | 6.94 | 5.55 | 6.31 | 15.40 | | |

## Experimental

4-Bromomethylbenzoyl chloride was prepared according to the known method [18]. The other used chemicals were commercial products (Lachema, Brno; Fluka, Buchs; Merck, Darmstadt).

Melting points were determined on a Kofler hot-stage. IR spectra (in KBr pellets) were obtained using Perkin—Elmer G-983 instrument. Mass spectra (70 eV) were measured on a JMS-100D spectrometer at an emission current of 300 μA, applying direct sample-introduction technique. $^1$H NMR and $^{13}$C NMR spectra were recorded on an FT-NMR Bruker AM-300 spectrometer operating with 300.13 MHz resp. 75.46 MHz working frequencies in $CDCl_3$ solutions with TMS as an internal standard. For the assignment of signals in $^{13}$C NMR spectra, DEPT and semiselective INEPT techniques were used. Elemental analyses were performed on a Perkin—Elmer 240 analyzer.

### *2-Alkylthio-4-hydroxy-6-methylpyrimidines I—X*

To a stirred solution of sodium hydroxide (0.1 mol) in ethanol (96 %, 200 cm$^3$), 4-hydroxy-2-mercapto-6-methylpyrimidine (0.1 mol) was added. To the formed suspension, corresponding alkyl halide (0.1 mol) was added and the reaction mixture was heated under reflux for 4 h. After cooling, separated salt was filtered off, solvent evaporated under diminished pressure and obtained crude product was recrystallized from ethanol.

### *2-Alkylthio-4-(4-bromomethylbenzoyloxy)-6-methylpyrimidines XI—XIX*

To a solution of 2-alkylthio-4-hydroxy-6-methylpyrimidine (0.1 mol) in toluene (500 cm$^3$), potassium hydroxide (0.1 mol) was added and under stirring, water was removed from the reaction mixture using an adapter for azeotropic water removal. 4-Bromomethylbenzoyl chloride (0.1 mol) was added to the formed suspension of potassium salt of hydroxypyrimidine and the reaction mixture was heated under reflux for 2 h. After cooling, separated salt was filtered off, toluene solution was washed with water and dried over $Na_2SO_4$. After removing of solvent under diminished pressure, crude product was recrystallized from n-heptane.

$^1$H NMR spectrum ($CDCl_3$), $\delta$: 6.73—6.78 (s, 1H, H-5), 2.36—2.50 (s, 3H, $CH_3$ at C-6), 8.06—8.18 (d, 2H, $H_{arom}$-$\alpha$), 7.44—7.55 (d, 2H, $H_{arom}$-$\beta$), 4.45—4.51 (s, 2H, $CH_2Br$), 3.13 (t, 2H, S—$CH_2$), 1.73 (m, 2H, $CH_2$—$CH_3$), 1.40 (t, 3H, terminal $CH_3$), 1.20—1.50 (m, remaining $CH_2$ of alkyl chain). $^{13}$C NMR spectrum ($CDCl_3$), $\delta$: 172.6—172.9 (C-2), 164.6—164.8 (C-4), 107.2—107.3 (C-5), 170.3—170.5 (C-6), 24.0—24.2 ($CH_3$ at C-6), 162.7—163.0 (C=O), 128.2—128.4 (C-1′), 130.9 ($C_{arom}$-$\alpha$), 128.3 ($C_{arom}$-$\beta$), 144.0 (C-4′), 31.9 ($CH_2Br$), 22.7 ($CH_2$—$CH_3$), 14.1 (terminal $CH_3$), 28.0—31.0 (remaining $CH_2$ of alkyl chain).

*Acknowledgements. The authors thank RNDr. M. Kačuráková, A. Gembická, and K. Paule (Institute of Chemistry, Slovak Academy of Sciences, Bratislava) for measurements of IR and mass spectra and for elemental analyses.*

## References

1. Spector, L. B. and Keller, B., *J. Biol. Chem. 232,* 185 (1958).
2. Nováček, A. and Hedrlín, I., *Collect. Czechoslov. Chem. Commun. 32,* 1045 (1967).
3. Prystaš, M. and Šorm, F., *Collect. Czechoslov. Chem. Commun. 32,* 1298 (1967).
4. Bredereck, H., Gompper, R., and Herlinger, H., *Chem. Ber. 91,* 2833 (1958).
5. Ozaki, S. and Mizuno, H., *Jpn. Kokai* 7785179 (1977); *Chem. Abstr. 88,* 22966p (1978).
6. Margot, A. and Gysin, H., *Helv. Chim. Acta 40,* 1562 (1957).
7. Gysin, H. and Margot, A., *J. Agric. Food Chem. 6,* 900 (1958).
8. Gysin, H., Margot, A., and Simon, Ch., *U.S.* 2694717 (1954); *Chem. Abstr. 49,* 8333f (1955).
9. Müller, P. H., *Naturwiss. Bdsch. 14,* 215 (1961).
10. Gysin, H., *Chimia 8,* 205 (1954).
11. Botta, M., De Angelis, F., and Nicoletti, R., *Tetrahedron Lett. 1988,* 2741.
12. Botta, M., De Angelis, F., Finizia, G., Nicoletti, R., and Delfini, M., *Tetrahedron Lett. 1985,* 3345.
13. Koppel, H. C., Springer, R. H., Robins, R. K., and Cheng, C. C., *J. Org. Chem. 26,* 792 (1961).
14. Wyrzykiewicz, E., Stobiecki, M., and Golankiewicz, K., *Rocz. Chem. 51,* 1227 (1977).
15. Barrett, H. W., Goodman, I., and Dittmer, K., *J. Am. Chem. Soc. 70,* 1753 (1948).
16. Yangibaev, S., Yun, L. M., Abdullaev, N. D., and Shakhidoyatov, Kh. M., *Dokl. Akad. Nauk Uzb. SSR 11,* 37 (1984).
17. Wyrzykiewicz, E., Stobiecki, M., and Golankiewicz, K., *Pol. J. Chem. 52,* 1697 (1978).
18. Pillai, V. N. R. and Mutter, M., *J. Org. Chem. 45,* 5364 (1980).

Translated by M. Koóš