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Reactions of 6-Benzyl-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one with Aliphatic and Aliphatic-Aromatic Amines

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Abstract—The rules were investigated of the regioselective synthesis of N^2-substituted derivatives of 2-amino-6-benzyl-5-methylpyrimidin-4(3*H*)-one from 6-benzyl-5-methyl-2-(methylsulfanyl) pyrimidin-4(3*H*)-one.

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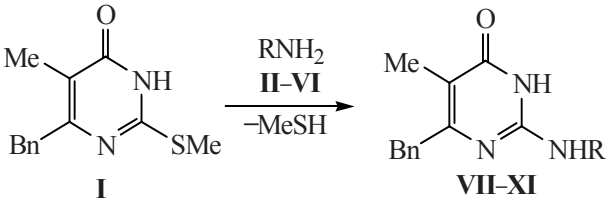
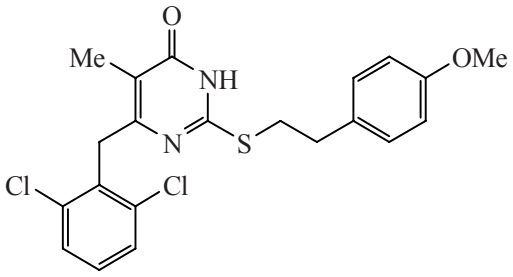
Derivatives of 5-alkyl-2-amino-6-(arylmethyl)-pyrimidin-4(3*H*)-one alkylated at the exocyclic nitrogen atom are promising antiviral agents of high activity with respect to a wide range of AIDS-1 strains [1–3]. Therefore the developments of new approaches to the synthesis of these compounds is a topical problem of organic and bioorganic chemistry. We studied the reaction of 6-benzyl-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (**I**) with a series of aliphatic and aliphatic-aromatic amines: 2-phenethylamine (**II**), 2-(4-methoxyphenyl)ethylamine (**III**), 2-(1-adamantyl)ethylamine (**IV**), 2-(1-adamantyl)propyl-2-amine (**V**), (1-adamantyl)methylamine (**VI**).



I **VII–XI**

R = $PhCH_2CH_2$ (**II, VII**), 4-$MeOC_6H_4CH_2CH_2$ (**III, VIII**), 1-$AdCH_2CH_2$ (**IV, IX**), 1-$AdCH_2CH(Me)$ (**V, X**), 1-$AdCH_2$ (**VI, XI**).

The choice of amines for this reaction should ensure the formation of derivatives which would be bioisosteric analogs of 2-{[2-(4-methoxyphenyl)ethyl]sulfanyl}-5-methyl-6-(2,6-dichlorobenzyl)pyrimidin-4(3*H*)-one (S-DABO) [4] that is now one of the most active anti-AIDS-1 agents.



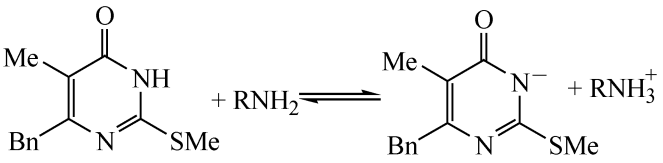
The reaction between compound **I** and amines **II–VI** was carried out under various conditions: without solvent, in excess amine; in ethylene glycol with 5–20-fold excess of amine; in cellosolve (2-ethoxyethanol) with 5–20-fold excess of amine; in carbitol [2-(2-ethoxyethoxy)ethanol] with 2–5-fold excess of amine; at heating from 135 to 200°C.

The reaction without solvent proceeded very slowly with considerable tarring and giving a complex mixture of products containing the initial compound alongside a small amount of the target compounds and a number of impurities. Although the reaction in ethylene glycol did not lead to strong tarring, it still resulted in a complex mixture of products with the prevalence of initial compound **I**, the target aminolysis product, and 6-benzyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione. In reaction in

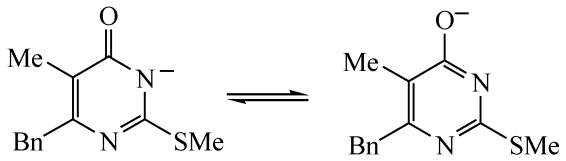
cellosolve the composition of the reaction mixture (TLC monitoring, eluent $CHCl_3$– MeOH, 19:1) was practically similar to the above, but the reaction time considerably increased because of the temperature conditions (cellosolve bp 135°C); at the same time somewhat increased the selectivity of the process. In the general case it should be stated that the reaction carried out above 160°C afforded a significant amount of side products. The performance of the reaction below 150°C resulted in a significant decrease in the aminolysis rate. It is also important, that the formation of the side products during the aminolysis is favored by amine excess over 5-fold.

In carbitol in a sealed ampoule in the presence of 2–5-fold molar excess of amine at 150–160°C the reaction occurred selectively leading to the formation virtually of the target aminolysis products containing only trace impurities. Moreover, the purity of isolated compounds was without additional recrystallization no worse than 90%.

To get an understanding of this phenomenon we considered two probable mechanisms of the reaction: The "addition-elimination" mechanism (Scheme 1) and the mechanism of *ipso*-substitution (Scheme 2). In both cases the reaction starts by the establishment of a dynamic equilibrium.

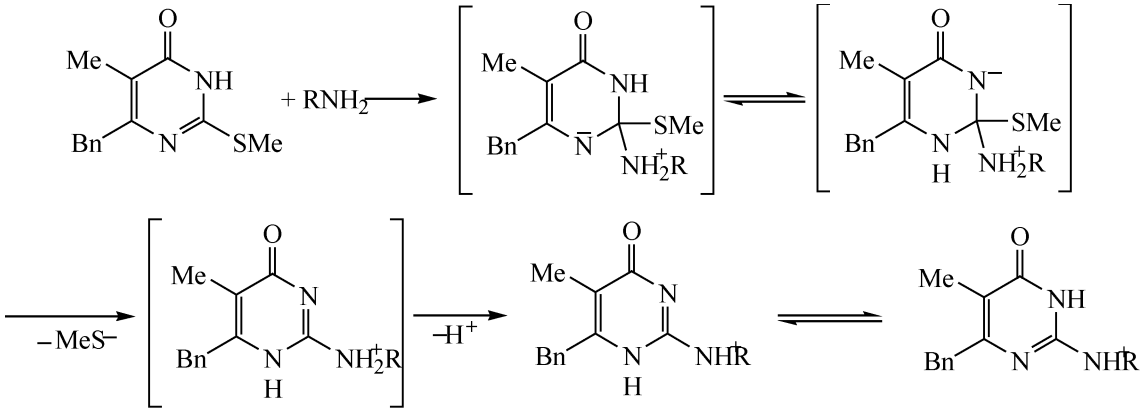


Whereas the nonionized form of compound **I** exists materially exclusively as a nonaromatic tautomer, the anion of compound **I** is present as a mixture of aromatic and nonaromatic tautomers.

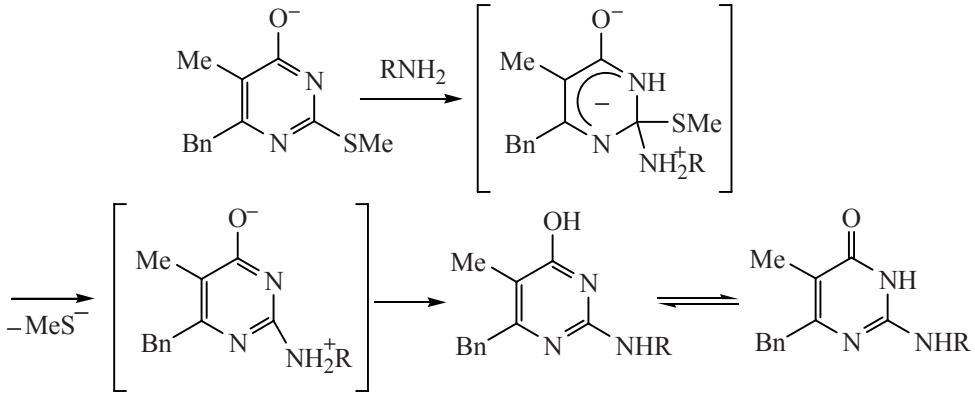


The "addition-elimination" involves the nonaromatic form, and the *ipso*-substitution occurs only with the

Scheme 1.



Scheme 2.



aromatic tautomer. The proceeding of the "addition-elimination" is favored for the nonionized form. This is due to the occurrence of the first reaction stage as a nucleophilic attack by the amine on the electron-deficient C^2 atom of the pyrimidine ring, and the nucleophilic attack on the same atom in the anionic form of compound **I** is hampered (Scheme 1).

In the anionic form of compound **I** the sequence of the transformations is retained.

We presume that the reason of the catalytic effect of carbitol and of its ability to increase the regioselectivity of this reaction is caused by the fact of carbitol being a shortened analog of podandes (open-chain analogs of crown ethers). Therefore it apparently is able to coordinate with the small cationic sites of the molecule thus stabilizing the transition state of the reaction.

All target compounds were obtained in nearly quantitative yields. At the same time the yield of some products was decreased by the high solubility and large losses at the recrystallization.

The homogeneity of all compounds obtained was confirmed by TLC, and their structure, by IR, NMR, and mass spectra..

Hence we investigated the aminolysis of 6-benzyl-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one and established that the preferred solvent for this reaction was carbitol ensuring the high level of the reaction regioselectivity. The hypothetic mechanism was assumed to provide an understanding of this phenomenon.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian Mercury 300BB from solutions in $CDCl_3$, internal reference HMDS. IR spectra were recorded on a Fourier IR spectrophotometer Nicolet-6700. Mass spectra were obtained on an instrument Varian MAT 111, electron impact 70 eV, the direct sample admission into the ion source. The product homogeneity was checked and the reactions progress was monitored by TLC on high-efficiency plates Alugram NanoSil G/UV_{254} in the systems chloroform–methanol, 19:1 (A), and petroleum ether of bp 40–70°C –ethyl acetate– methanol, 12:3:1 (B). The melting points were measured on a Cole-Palmer instrument and are reported with correction.

6-Benzyl-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (I) was obtained by procedure [5]. Yield 84%, mp 205–206°C (MeCN) (mp 199–200°C [6]).

6-Benzyl-5-methyl-2-[(2-phenylethyl)amino]-pyrimidin-4(3*H*)-one (VII). A mixture of 2 g (8.12 mmol) of reagent **I**, 5 ml (4.82 g, 39.78 mmol) of 2-phenethylamine (**II**), and 20 ml of carbitol was heated for 50 h at 150–160°C in a sealed ampoule, cooled to room temperature, and evaporated in a vacuum. The residue was dissolved in 150 ml of toluene and the solution was washed with 250 ml of 10% aqueous citric acid. Then the organic layer was washed with water and dried by aseotropic distillation of water. The solvent was distilled off in a vacuum, the residue was recrystallized from acetonitrile. Yield after recrystallization 2.3 g (89%), mp 146–148°C (MeCN), R_f 0.21 (A), 0.16 (B). IR spectrum, ν, cm^{-1}: 3416, 3026, 2630 (NH), 1667 (C=O), 1609 (C_6H_5, C=N, NH), 1538 (NH), 1494 (C_6H_5, C=N), 1473 (CH_2), 1322, 1454, 1392, 1375, 1240 (C_6H_5, CH_2), 1178, 1101, 1027, 929 (C–O), 779 (NH), 758 (NH), 744 (NH), 696, 614, 591, 566 (NH). ^{1}H NMR spectrum, δ, ppm: 1.77 s (3H, CH_3), 2.78 t (2H, CH_2, *J* 7.33 Hz), 3.52 m (2H, CH_2), 3.76 s (2H, CH_2), 6.33 br.s (1H, NH), 7.15 m (10H, $2C_6H_5$), 11.55 br.s (1H, NH). Found, %: C 75.61; H 6.23; N 13.56. M^+ 319. $C_{20}H_{21}N_3O$. Calculated, %: C 75.21; H 6.63; N 13.16. *M* 319.40.

Likewise were obtained compounds **VIII–XI**.

6-Benzyl-5-methyl-2-{[2-(4-methoxyphenyl)-ethyl]amino}pyrimidin-4(3*H*)-one (VIII). Yield 63%, mp 156–157°C (MeCN), R_f 0.28 (A), 0.17 (B). IR spectrum, ν, cm^{-1}: 3418, 2687 (NH), 1670 (C=O), 1610 (C_6H_5, CN, NH), 1513 (CN, NH), 1494 (C_6H_5, CN), 1472, 1393, 1325, 1299, 1250 (CH_2), 1174 (C–O), 1101, 1029, 918 (CH in 1,4-C_6H_4), 814 (CH in 1,4-C_6H_4), 761 (NH), 778 (NH), 702, 609, 568, 522 (NH), . ^{1}H NMR spectrum, δ, ppm: 1.79 s (3H, CH_3), 2.72 m (2H, CH_2), 3.49 m (2H, CH_2), 3.69 s (3H, CH_3), 3.77 s (2H, CH_2), 6.20 s (1H, NH), 6.73 d (2H, C_6H_4, *J* 8.79 Hz), 7.01 d (2H, C_6H_4, *J* 8.79 Hz), 7.15 m (1H, C_6H_5), 7.21 m (4H, C_6H_5), 11.56 s (1H, NH). Found, %: C 72.58; H 6.33; N 12.43. M^+ 349. $C_{21}H_{23}N_3O_2$. Calculated, %: C 72.18; H 6.63; N 12.03. *M* 349.43.

2-{[2-(1-Adamantyl)ethyl]amino}-6-benzyl-5-methylpyrimidin-4(3*H*)-one (IX). Yield 69%. 182–184°C (MeCN), R_f 0.30 (A), 0.24(A). IR spectrum, ν, cm^{-1}: 3319, 2897, 2844 (NH), 1612, 1575 (C_6H_5, CN, NH), 1495, 1451, 1395, 1328, 1302, 1236, 1093, 901 (C_6H_5, CN), 763 (NH), 701, 597, 567 (NH). ^{1}H NMR spectrum, δ, ppm: 1.23 q ($J_{1,2}$ 8.79 Hz, $J_{2,3}$ 7.32 Hz), 1.43 s, 1.59 q (15 H, 1-Ad, $J_{1,2}$ 11.72 Hz, $J_{2,3}$ 13.19 Hz), 1.87 br.s (2H, CH_2), 1.90 s (3H, CH_3), 3.29 m (2H, CH_2), 3.77 s (2H, CH_2), 5.92 s (1H, NH), 7.14 m (1H, C_6H_5),

7.21 m (4H, C_6H_5), 11.52 s (1H, NH). Found, %: C 76.00; H 8.00; N 11.13. M^+ 377. $C_{24}H_{31}N_3O$. Calculated, %: C 76.35; H 8.28; N 11.13. *M* 377.52.

2-{[1-(1-Adamantyl)prop-2-yl]amino}-6-benzyl-5-methylpyrimidin-4(3*H*)-one (X). Yield 38%, mp 167–168°C (petroleum ether bp 40–70°C). R_f 0.37 (A), 0.38 (B). IR spectrum, ν, cm^{-1}: 3273, 2895 (NH), 2846 (CH_2, CH_3), 1618 (C=O), 1569 (C=N, NH), 1493 (C=N, C_6H_5), 1449, 1391(CH_3), 1373, 1344, 1311, 1235, 1183, 1128, 1097, 1082, 1049, 1031, (CH_3), 855, 783 (NH), 758, 750 (NH), 706, 694, 597, 569, 517, 491, 478, 468, 461, 456 (NH). ^{1}H NMR spectrum, δ, ppm: 1.06 d (3H, CH_3, *J* 6.84 Hz), 1.12 d (*J* 3.42 Hz), 1.24 d.d ($J_{1,2}$ 8.55 Hz, $J_{2,3}$ 5.13 Hz), 1.35 br.s, 1.40 s, 1.52 q ($J_{1,2}$ 11.97 Hz, $J_{2,3}$ 17.10 Hz) (15H, 1-Ad), 1.80 br.s (3H, CH_3), 1.93 s (2H, CH_2), 3.78 q (2H, CH_2, $J_{1,2}$ 13.68 Hz, $J_{2,3}$ 3.42 Hz), 4.23 m (1H, CH), 5.87 d (1H, NH, *J* 8.55 Hz), 7.12 d (*J* 6.84 Hz), 7.16 s (1H, C_6H_5), 7.20 d (2H, C_6H_5, *J* 6.84 Hz), 7.25 d (2H, C_6H_5, *J* 6.84 Hz), 11.23 s (NH). Found, %: C 76.29; H 8.89; N 10.73. M^+ 391. $C_{25}H_{33}N_3O$. Calculated, %: C 76.69; H 8.49; N 10.73. *M* 391.55.

2-[(1-Adamantylmethyl)amino]-6-benzyl-5-methylpyrimidin-4(3*H*)-one (XI). Yield 78%, mp 228–229°C (MeCN). R_f 0.26 (A). IR spectrum, ν, cm^{-1}: 3322, 2898 (NH), 2846 (CH_2, CH_3), 1638 (C=N, C=O), 1609 (C=N, NH, C_6H_5), 1493 (C=N, C_6H_5), 1451 (CH_2), 1386, 1346, 1312, 1278, 1246, 1186, 1090, 819, 754 (CH_3), 700, 595, 569, 517, 489, 453 (NH). ^{1}H NMR spectrum, δ, ppm: 1.38 s, 1.56 q ($J_{1,2}$ 13.19, $J_{2,3}$ 17.33 Hz), 1.84 s (15H, 1-Ad), 1.88 s (3H, CH_3), 3.01 d (2H, CH_2, *J* 6.00 Hz), 3.75 s (2H, CH_2), 6.14 s (1H, NH), 7.12 m (1H, C_6H_5), 7.20 m (4H, C_6H_5), 11.48 s (1H, NH). Found, %: C 76.23; H 8.17; N 11.21. M^+ 363. $C_{23}H_{29}N_3O$. Calculated, %: C 76.00; H 8.04; N 11.56. *M* 363.50.

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