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SYNTHESIS OF DERIVATIVES OF 7,8-DIHYDROTHIAZOLO[2,3-*i*]PURINE BY HALOCYCLIZATION OF 6-ALLYLTHIOPURINE

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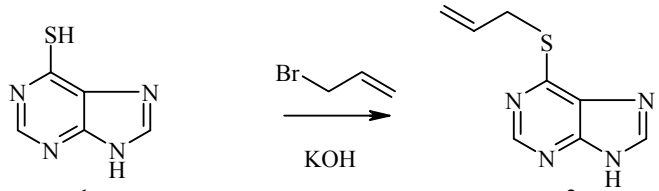
7-Halomethyl-7,8-dihydrothiazolo[2,3-i]purines were synthesized by the reaction of bromine and iodine with 6-allylthiopurine.

Keywords: 6-allylthiopurine, 7-bromomethyl-7,8-dihydrothiazolo[2,3-*i*]purine, 7-iodomethyl-7,8-dihydrothiazolo[2,3-*i*]purine, halocyclization.

7,8-Dihydrothiazolo[2,3-*i*]purine and its derivatives were obtained by the reaction of 6-mercaptopurine (**1**) and substituted 6-mercaptopurines with 1,2-dibromoethane [1, 2] and also by the interaction of 6-(2-hydroxyalkyl)thiopurines with $SOCl_2$ [3], and by treatment of 6-(2-aminoethyl)thiopurines with hydrochloric acid [4].

We have developed a new preparative synthesis of 7-substituted 7,8-dihydrothiazolo[2,3-*i*]purine by the halocyclization of 6-allylthiopurine (**2**). The sulfide **2** was obtained by allylation of purine **1** with allyl bromide in HMPA in the presence of alkali at room temperature. According to [5], alkylation of purine occurs primarily at the sulfur atom.



1 **2**

The structure of sulfide **2** was confirmed by ^{1}H NMR and chromato-mass spectroscopy. The molecular ion M^+ (*m/z* 192) and the maximum peak Φ_2 with *m/z* 177, corresponding to the elimination of a methyl radical are present in the mass spectrum. Apparently the molecular ion-radical cyclizes to give the ion radical Φ_1, which loses the methyl radical to form the aromatic thiazolo[2,3-*i*]purine cation Φ_2 (Scheme 1).

When compound **2** reacted with bromine or iodine in chloroform compounds are formed containing approximately 2 mol of halogen to 1 mol of substrate. Apparently they are trihalides of 7-halomethyl-7,8-dihydrothiazolo[2,3-*i*]purine **3a,b**. The tribromide **3a** gave 7-bromomethyl-7,8-dihydrothiazolo[2,3-*i*]purine (**4a**) on treatment with acetone, while the triiodide **3b** gave 7-iodomethyl-7,8-dihydrothiazolo[2,3-*i*]purine (**4b**) on treatment with sodium iodide in acetone (Scheme 2).

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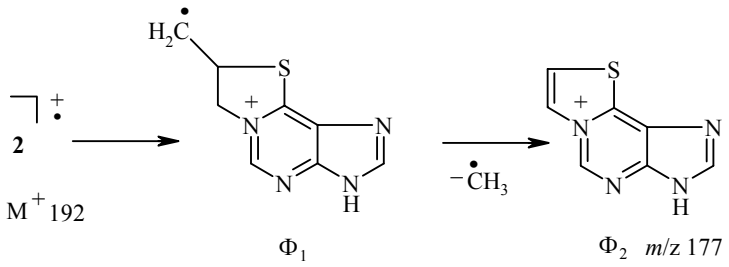
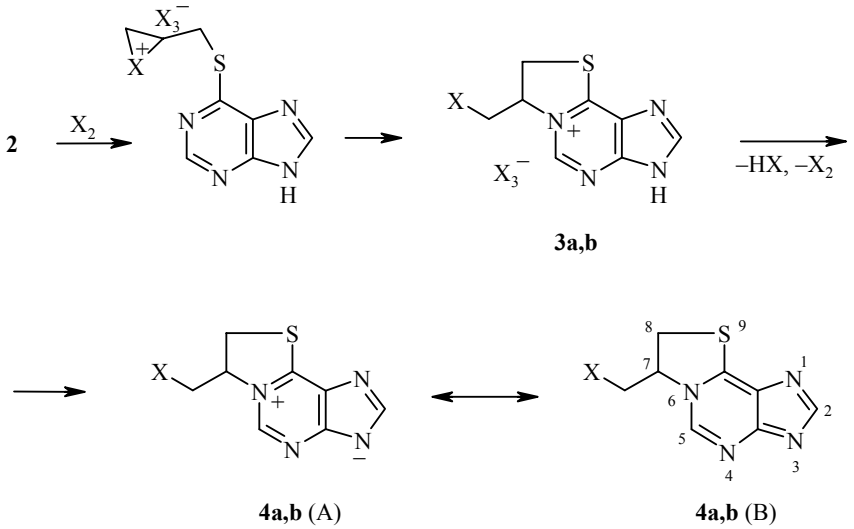
Scheme 1



Scheme 2



3, 4 a X = Br; **b** X = I

It should be noted that in the ^{1}H NMR spectra the signals of the protons of the purine ring (H-2 and H-5) in the halocyclization products **4a,b** resonate at weaker field than the corresponding protons (H-2 and H-8) in the allylsulfide **2**. This evidently indicates that these compounds exist in the bipolar form **4a,b** (A).

EXPERIMENTAL

^{1}H NMR spectra in $(CD_3)_2SO$ were recorded with a Bruker WP-250 (250 MHz) spectrometer and ^{13}C NMR spectra in $(CD_3)_2SO$ were recorded with a Bruker AM-300 (75 MHz) spectrometer with TMS as internal standard. Mass spectra were recorded on a GC/MS instrument consisting of a HP-5890 chromatograph and a HP-5972 mass selective detector.

6-Allylthiopurine (2). Allyl bromide (0.29 ml, 3.2 mmol) was added to a solution of KOH (0.180 g, 3.2 mmol) and 6-mercaptopurine (0.510 g, 3.0 mmol) in HMPA (2 ml). The reaction mixture was stirred at room temperature for 1.5 h, after which it was diluted to 45 ml with water. Calcium chloride (3 g) was added to the solution which was then kept for 6 h. The precipitate was filtered off and washed with water to give compound **2**, 0.290 g (50%); mp 153°C. ^{1}HNMR spectrum, δ, ppm (*J*, Hz): 4.03 (2H, d, ^3J =6.9, SCH_2); 5.11 (1H, dd, CH=C$\underline{H}_2$); 5.34 (1H, dd, CH=C$\underline{H}_2$); 5.97 (1H, m, $\underline{CH}$=CH_2); 8.23 (1H, s, H-8); 8.58 (1H, s, H-2); 13.30 (1H, br. s, NH). Found, %: C 49.45; H 4.43; S 16.35. $C_8H_8N_4S$. Calculated, %: C 49.98; H 4.19; S 16.68.

3-Bromomethyl-2,3-dihydrothiazolo[2,3-*i*]purine (4a). A solution of bromine (0.052 ml, 1 mmol) in chloroform (4 ml) was added dropwise to a solution of 6-allylthiopurine (0.100 g, 0.5 mmol) in chloroform (6 ml). A precipitate formed was separated, treated with acetone and filtered off to give **4a** (0.120 g, 88%); mp 191°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.96 (1H, dd, SCH_2); 4.19 (1H, dd, SCH_2); 4.34 (2H, m, CH_2Br); 6.15 (1H, m, H-7); 8.89 (1H, s, H-2); 9.61 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 33 (CH_2Br), 133 (C-2), 108 (C-3a), 162 (C-5), 64 (C-7), 33 (C-8), 168 (C-9a). Found, %: Br 29.56; S 11.38. $C_8H_7BrN_4S$. Calculated, %: Br 29.47; S 11.83.

3-Iodomethyl-2,3-dihydrothiazolo[2,3-*i*]purine (4b). A solution of 6-allylthiopurine (0.100 g, 0.5 mmol) in chloroform (5 ml) was added to a solution of iodine (0.254 g, 1.0 mmol) in chloroform (3 ml). A deep-red precipitate which separated over 48 h was treated with a saturated solution of NaI in acetone (6 ml). The yellow precipitate was filtered off and washed with acetone to give compound **4b** (0.154 g, 93%); mp 204°C (dec.). ^{1}H NMR spectrum, δ, ppm: 3.86 (1H, dd, SCH_2); 3.97 (2H, m,CH_2I); 4.25 (1H, dd, SCH_2); 5.84 (1H, m, H-7); 8.87 (1H, s, H-2); 9.47 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 7 (CH_2I), 146 (C-3a), 68 (C-7), 38 (C-8), 158 (C-9), 151 (C-9b). Found, %: I 39.01; S 9.86. $C_8H_7IN_4S$. Calculated, %: I 39.89; S 10.08.

REFERENCES

1. R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.,* **26**, 3446 (1961).
2. J. A. Montgomery, R. W. Balsiger, A. L. Fikes, and T. P. Johnston, *J. Org. Chem.,* **27**, 3446 (1962).
3. P. M. Kochergin, E. V. Aleksandrova, and E. V. Rusinova, *Khim. Geterotsikl. Soedin.,* 1434 (1993).
4. T. P. Johnston and A. Gallagher, *J. Org. Chem.,* **28**, 1305 (1963).
5. G. W. Grigg, Y. Iwai, D. J. Brown, K. N. McAndrew, T. Nagamatsu, and R. Heeswyck, *Austral. J. Chem.,* **32**, 2713 (1979).