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A REMARKABLE THIETANE FORMATION FROM A 6-MERCAPTOPURINE DERIVATIVE

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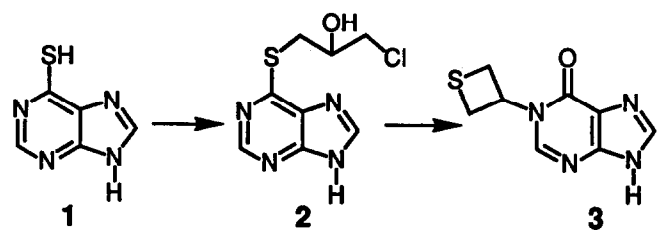
Summary: An unusual rearrangement/thietane ring formation results from the treatment of an 3-chloro-2-hydroxypropyl iminothioether with base. 6-Oxo-1-(thietan-3-yl)-purine (3) was characterized by spectral analysis and conversion to thientanyl 5-amino-4-carboxamidoimidazole (6) whose structure was confirmed by x-ray analysis.

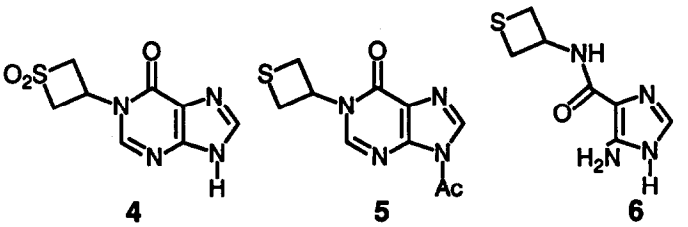
During the course of our investigations into the role of the adenosine receptor in the cardiovascular system[1], we became interested in derivatives of 6-mercaptopurine. In this report, we wish to communicate an unusual rearrangement and thietane ring formation that occured in this research. Reaction of 6-mercaptopurine (1) with sodium bicarbonate and epichlorohydrin (EtOH/7 days/room temperature) led to the expected chlorohydrin derivative 2.[2,3a] Surprisingly, when this compound was treated with 2 equivalents of sodium methoxide (MeOH/24 h/room temperature), the expected epoxide or methoxy containing derivatives were not isolated. Instead, 1-(3-thietanyl)-hypoxanthine 3 was the sole isolated product in 32% yield.[3b] (Scheme 1) Treatment of 2 with aqueous sodium hydroxide (2 equivalents) in methanol or sodium hydride (1 equivalent) in DMF gave similar results albeit in lower yields (2.5% and 6.7%, respectively). Thietane 3 is unchanged upon re-exposure to the reaction conditions. Presumably, the modest yields of 3 result from competing conversion of 2 to hypoxanthine which is lost during work-up.

SCHEME 1



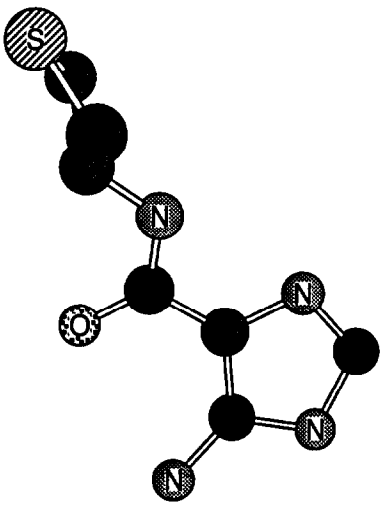
The structure of the thietane 3 was deduced both by analysis of NMR, IR and HRMS data[4] as well as conversion to the corresponding sulfone 4 (with potassium permanganate in aqueous sodium hydroxide) and N-acetyl derivative 5 (with acetic anhydride).[3c,d] Especially noteworthy for 3 were the strong infrared carbonyl absorption of 1698 cm^{-1} and ^{13}C nmr absorption of C-6 at 154.78 ppm characteristic of hypoxanthine derivatives.[5] Treatment of 3 with 2N sodium hydroxide (water/5 h/reflux) caused the ring-opening[6] formation of the thietanyl substituted 5-amino-4-carboxamidoimidazole 6 which was fully characterized and confirmed by x-ray crystallographic analysis.[3d,7] (Figure 1) The x-ray structure of 6 suggests that one of the 5-amine protons forms a

hydrogen bond with the amide carbonyl and that the amide proton forms a hydrogen bond with the imidazole nitrogen.



4 5 6

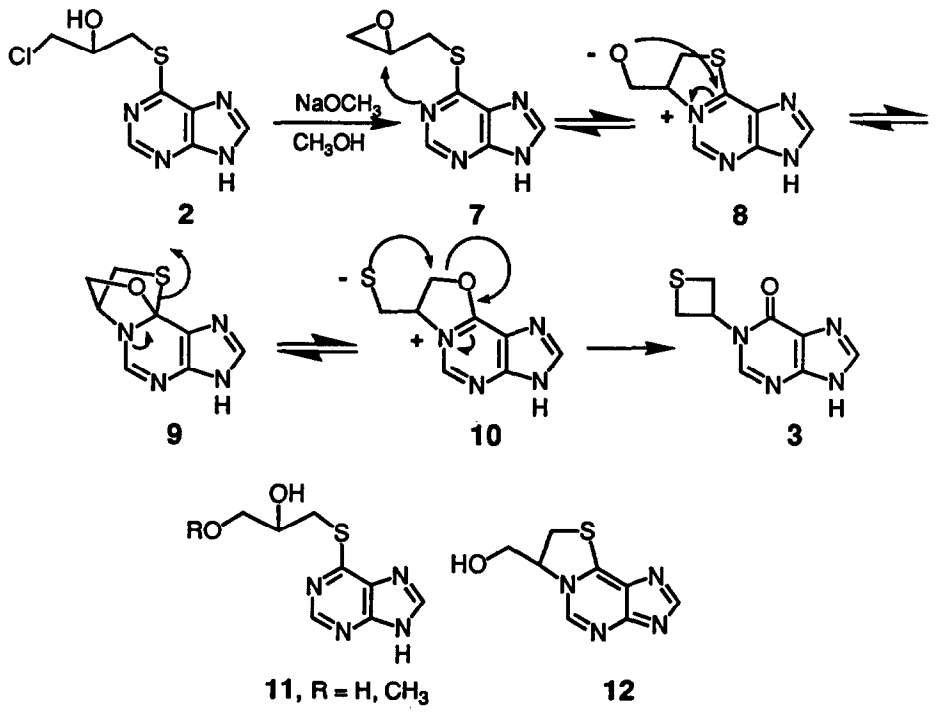
Figure 1. ORTEP drawing of **6** showing positions of heteroatoms.



A possible mechanism to account for this novel rearrangement is depicted in Scheme 2. Base-induced epoxide formation gives **7** which may close in a 5-exo-trig manner[8] with alkylation of the N-1 nitrogen of the purine ring to give **8**.[9] Intramolecular alkoxide attack at C-6 (activated by the charged N-1 nitrogen) gives bicyclic intermediate **9**. Opening of the bicyclic intermediate forms the isomeric mercaptide anion **10** which attacks the oxygen-bearing methylene to generate the stable hypoxanthine system and the thietane ring of product **3**. It is particularly interesting that, while oxygen anion **8** either does not form an oxetane or the oxetane forms and re-opens, the analogous mercaptide of **10** closes irreversibly. Presumably, formation of the thietane occurs in preference to oxetane as a consequence of the enhanced nucleophilicity of sulfur as well as the fact that the longer S-C bond allows a better trajectory for this presumed S_N2 process. The irreversible thietane ring formation drives the reaction after the series of facile equilibria. Intermediacy of a hemithioketal seems unlikely since treatment of glycol **11** (R = H) or its methyl ether (R = CH_3) under the same conditions (sodium methoxide in methanol) causes no change to **11**. Supporting the

proposed mechanism, dihydrothiazole **12**,[10] the tautomer of intermediate **8**, was isolated from reaction of **1** with epichlorohydrin and 1 equivalent of aqueous sodium hydroxide (MeOH/24 h/room temperature) and could be converted to **3** in 94% yield upon exposure to sodium methoxide (MeOH/24 h/room temperature).

SCHEME 2



We are examining solvent and base effects on the course of the reaction as well as various other heterocycles in order to further define the generality of this rearrangement. The remarkable formation of N-thietanyl substituted lactams such as **3** from easily preparable chlorohydrin derivatives represents a simple entry into this relatively unknown class of compounds[11] and is the subject of a future report from these laboratories.[12]

ACKNOWLEDGMENT

We thank Drs. Kevin Fachine and David Burinsky for determination of NMR and MS data. JBP also thanks Dr. David Wustrow for enlightening discussions during the course of this work.

SUPPLEMENTARY MATERIAL AVAILABLE:

Tables of atomic coordinates and thermal parameters for **6**.

FOOTNOTES and REFERENCES

1. See for example Shamim, M. T.; Ukena, D.; Padgett, W. L.; Daly, J. W. *J. Med. Chem.*, **1988**, *31*, 613 and references contained therein.
2. S-alkylation of 6-mercoptopurine has been well defined; see, for example, Skinner, C. G.; Shive, W.; Ham, R. G.; Fitzgerald, Jr., D. C.; Eakin, R. E. *J. Amer. Chem. soc.*, **1956**, *78*, 5097.
3. All compounds were fully characterized with satisfactory combustion analysis.
   a) 6-(1-Chloro-2-hydroxy-3-propanylthio)purine (**2**), mp 143-145°C.
   b) 6-Oxo-1-(thietan-3-yl)purine (**3**), mp 258-260°C (dec).
   c) 6-Oxo-1-(1,1-dioxythietan-3-yl)purine (**4**), mp 278 - 280°C (dec).
   d) 9-Acetyl-6-oxo-1-(thietan-3-yl)purine (**5**), mp 175-178°C (dec).
   e) 5-Amino-4-(thietan-3-ylaminocarbonyl)imidazole (**6**), mp 173 - 176°C (dec).
4. HRMS was particularly informative since the $C_7H_5N_4O$ parent (208.0505) lost C_3H_3S to give a hypoxanthine base peak at 137.0450 (137.0449 $C_5H_5N_4O$ calcd).
5. Hypoxanthine has a strong carbonyl absorption at 1685cm^{-1}, C-6 ^{13}C nmr absorption at 155.12 ppm and proton absorptions at d 8.12 and 7.98. In contrast, 6-methoxypurine has medium intensity absorptions centered about 1600 cm^{-1} in the infrared, a C-6 absorption at 159.35 ppm and proton absorptions at δ 8.55 and 8.23.
6. For inosines, see, for example, Witkowski, J. T.; Kreishman, G. P.; Schweizer, M. P.; Robins, R. K. *J. Org. Chem.*, **1973**, *38*, 180. Similar ring opening is presumed to be an intermediate in the Dimroth rearrangement of purines; Brooks, P.; Lawley, P. D. *J. Chem. Soc.*, **1960**, 539.
7. X-ray analysis was performed by Oneida Research Services, Whitesboro, New York. Crystals of **6** were of the monoclinic space group $P2_1/n$ with a =12.920 (11) Å, b = 9.700 (3) Å, c = 15.229 (7) Å, b = 112.32 (4)°, V = 1766 (3) Å^3 and Z = 8. Room temperature data collection gave 2926 reflections of which 2253 were unique. The structure was solved by direct methods and refined in full-matrix least-squares. The final reliability index R = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$ was 0.108.
8. Baldwin, J. E. *J. Org. Chem.*, **1977**, *42*, 3826.
9. Balsiger, R. W.; Fikes, A. L.; Johnston, T. P.; Montgomery, J. A. *J. Org. Chem.*, **1961**, *26*, 3446 proved unambiguously that a similar ring closure of 6-(2-chloroethylthio)purine occurs at N-1 rather than N-7.
10. 8-Hydroxymethyl-7,8-dihydrothiazolo[2,3-i]purine (**12**) was obtained in ≈90% purity as judged by ^1H NMR and the hydroxymethylene structure was supported by the loss of CH_2OH in MS; mp >300°C. HRMS : $C_8H_8N_4OS$ (M^+) 208.0418 (208.0419 calcd); $C_7H_5N_4S$ (M-CH_2OH) 177.0236 (177.0235 calcd); $C_5H_5N_4O$ (M-C_3H_3S) 137.0468 (137.0463 calcd); 100 Mc ^1H NMR (DMSO-d_6) δ: 8.9 (s,1H), 8.3 (s,1H), 5.5 (m, 1H), 4.6 (m, 2H), 3.6-3.9 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 161.0 (C-2, methine), 159.1 (C-6, quat), 150.0 (C-5, quat), 141.59 (C-8, methine), 129.7 (C-3, quat), 68.0 (C-8, CHN), 60.9 (CH_2OH), 32.0 (CH_2S); C-order determined by DEPT experiment.
11. 3-Aminothietanes have been prepared by amine nucleophilic addition to thiete sulfones and LAH reduction, see Dittmer, D. C.; Christy, M. E. *J. Amer. Chem. Soc.*, **1962**, *84*, 399; or by 2+2 cycloadditon of enamines with sulfenes, see Dittmer, D. C.; Chang, R. L.-F.; Davis, F. A. Iwanami, M.; Stamos, I. K.; Takahashi, K. *J. Org. Chem.*, **1972**, *37*, 1111.
12. Press, J. B.; Hajos, Z. G.; Sawyers, R. A., manuscript in preparation.

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