

SYNTHESES OF THE 7-*N*-OXIDES OF 6-MERCAPTOPURINE AND 6-METHYLTHIOPURINE

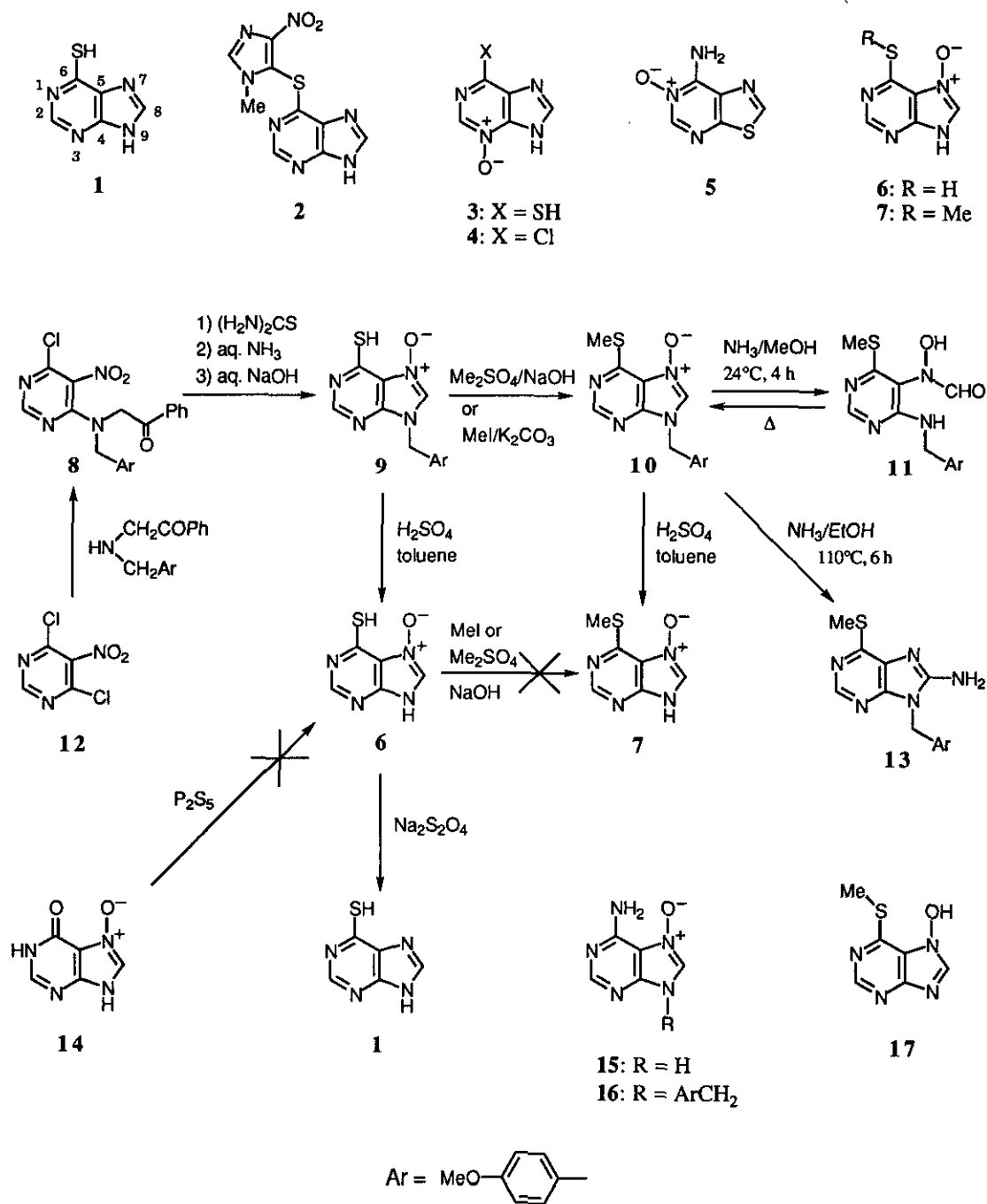
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Abstract—6-Mercaptopurine 7-*N*-oxide (**6**) has been synthesized for the first time from 4,6-dichloro-5-nitropyrimidine (**12**) by following a "phenacylamine route" through the intermediates (**8**) and (**9**). Methylation of **9** and removal of the *p*-methoxybenzyl group provided 6-methylthiopurine 7-*N*-oxide (**7**).

6-Mercaptopurine (6-MP) (**1**) and its *S*-(1-methyl-4-nitro-1*H*-imidazol-5-yl) derivative, azathioprine (Imuran®) (**2**), are antileukemic and immunosuppressive agents, respectively, of longstanding clinical usefulness.¹ The latter compound acts as a pro-drug for 6-MP.^{1a} Among the four possible *N*-oxides² of 6-MP, only the 3-oxide (**3**) is hitherto known: it has been synthesized from 6-chloropurine 3-oxide (**4**) and ammonium dithiocarbamate³ or from 7-aminothiazolo[5,4-*d*]pyrimidine 6-*N*-oxide (**5**) by rearrangement,⁴ and a comparison of the *N*-oxide (**3**) with the parent 6-MP has been made in several biological systems.⁴ Our recent interest and success⁵ in the synthesis of purine 7-*N*-oxides led us to synthesize 6-mercaptopurine 7-*N*-oxide (**6**) and its *S*-methyl derivative (**7**), a simple model for the 7-*N*-oxide of azathioprine (**2**), in the present study.

In reaching the target *N*-oxides (**6**) and (**7**), direct oxidations of 6-MP and its *S*-methyl derivative would provide the shortest synthetic routes. However, they require protection of the sulfur atom from oxidation, a favorable regioselectivity in oxidation, and selective deprotection of the sulfur atom, which seem difficult to solve immediately. We therefore decided to adopt a dichloropyrimidine version of our favorite "phenacylamine route", which had worked well for the syntheses of the antitumor antibiotic guanine 7-oxide,^{5a} its 8-methyl derivative,^{5c} and hypoxanthine 7-*N*-oxide (**14**).^{5b} Thus, condensation of *N*-(4-methoxybenzyl)phenacylamine, generated from its hydrochloride salt^{5a} (2 molar equiv.), with 4,6-dichloro-5-nitropyrimidine (**12**) (CHCl₃, 0–5°C, 1 h) furnished the phenacylaminopyrimidine (**8**) (mp 107–109°C)⁶ in 75% yield (Scheme 1). Treatment of **8** with thiourea (boiling EtOH, 5 min), followed



Scheme 1

successively by conc. aqueous NH_3 and 2 N aqueous NaOH (0°C , 5 min) gave the *N*-oxide (**9**) [mp $161\text{--}163^\circ\text{C}$ (decomp.) for $9\cdot 2/5\text{H}_2\text{O}$] in 76% yield. Removal of the *p*-methoxybenzyl group from **9** was then effected in conc. H_2SO_4 in the presence of toluene (23°C , 2 h),⁷ affording the target 6-mercaptopurine 7-*N*-oxide (**6**) [mp $> 300^\circ\text{C}$ (decomp.)]⁸ in 75% yield. On treatment with sodium dithionite [boiling 50% (v/v) aqueous MeOH , 1.5 h], **6** provided 6-MP (**1**) in 37% yield.

In an alternative synthetic approach to **6**, hypoxanthine 7-*N*-oxide (**14**)^{5b} was treated with P_2S_5 in boiling pyridine for 3 h. However, we were unable to obtain **6** but a compound (20% yield; mp $> 300^\circ\text{C}$) inferred to be 8-mercaptophypoxanthine.⁹

For the synthesis of the second target (**7**), **9** was methylated with dimethyl sulfate (1 N aqueous NaOH/MeOH , room temp., 1 h) to give the 6-methylthio derivative (**10**) [mp $195\text{--}205^\circ\text{C}$ (decomp.)] in 52% yield. Methylation of **9** with methyl iodide ($\text{K}_2\text{CO}_3/\text{MeOH}$, room temp., 1 h) also produced **10** in 63% yield. For removal of the *p*-methoxybenzyl group, **10** was treated with conc. H_2SO_4 (toluene, 25°C , 1 h),⁷ furnishing the desired *N*-oxide (**7**) [mp $220\text{--}223^\circ\text{C}$ (decomp.)]¹⁰ in 90% yield. On recrystallization from $\text{MeOH-H}_2\text{O}$ (3 : 1, v/v), **7** gave a monohydrate, which was shown to exist in the $\text{N}(7)\text{-OH}$ form (**17**) in the solid state by preliminary X-ray crystallographic analysis.¹¹ Methylation of **6** with methyl iodide or dimethyl sulfate in a mixture of MeOH and 1 N aqueous NaOH gave a complicated mixture of many products, from which we were unable to obtain the *S*-methyl derivative (**7**).

Finally, with a view to converting **7** into adenine 7-oxide (**15**),^{5d} amination of **7** with saturated methanolic NH_3 or conc. aqueous NH_3 was examined under a variety of reaction conditions. However, all attempts resulted in the recovery of **7**, suggesting the inertness of the $\text{C}(6)\text{-SMe}$ group in the anionic species of **7**. On the other hand, treatment of the $\text{N}(9)\text{-arylmethyl}$ derivative (**10**) with 16% methanolic NH_3 (24°C , 4 h) afforded an unstable crude compound [mp $154\text{--}155^\circ\text{C}$ (decomp.)] inferred to be the ring-opened product (**11**), which reverted to **10** on heating in EtOH . On heating in saturated ethanolic NH_3 using an autoclave (110°C , 6 h), **10** gave the $\text{C}(8)\text{-amino}$ derivative (**13**) (mp $180\text{--}181^\circ\text{C}$) in 18% yield. In either case, the desired adenine derivative (**16**) could not be obtained, and the observed reactivity of **10** at the $\text{C}(8)$ atom toward nucleophiles is interpretable in terms of the $\text{N}(7)\text{-oxide}$ structure.

In conclusion, the above results have established a multi-step synthetic route to the hitherto unknown 7-*N*-oxide at the 6-MP level. They also exemplifies the usefulness of our "phenacylamine route"⁵ for the synthesis of purine 7-*N*-oxides. The problem of the tautomeric forms of **6** and **7** will be discussed in a future full paper. Unfortunately, preliminary biological evaluation of **6** and **7** has revealed that both *N*-oxides have only very weak antileukemic activities against murine L5178Y cells.¹²

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6. Satisfactory analytical and/or spectroscopic data have been obtained for all of the new compounds reported herein.
7. See refs. 5a–d for similar debenzylations.
8. Selected spectral data: uv $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 235 nm (ϵ 18300), 329 (19800); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 329 (19800); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 230 (sh) (11700), 291 (sh) (8000), 319 (sh) (12100), 333 (13100); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 228 (17200), 291 (6800), 329 (13400); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 8.10 [1H, d, $J = 3.5$ Hz, C(2)-H], 8.54 [1H, s, C(8)-H], 12.40 and 13.61 (1H each, s, NH's). The appearance of the C(2)-H signal as a doublet suggests that this *N*-oxide exists in the 6-thioxo-1*H*-purine form rather than the 6-mercapto form (**6**) in $\text{Me}_2\text{SO}-d_6$.
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10. Selected spectral data for **7**: uv $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 222 nm (ϵ 11900), 262 (sh) (4600), 297 (13300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 224 (10100), 306 (14200); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 230 (18100), 260 (7700), 280 (8800), 318 (5800); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 230 (18100), 260 (7700), 280 (8800), 318 (5800); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 2.66 [3H, s, C(6)-SMe], 8.69 and 8.75 (1H each, s, purine protons), 12.70 [1H, s, N(9)-H or N(7)-OH].
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