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

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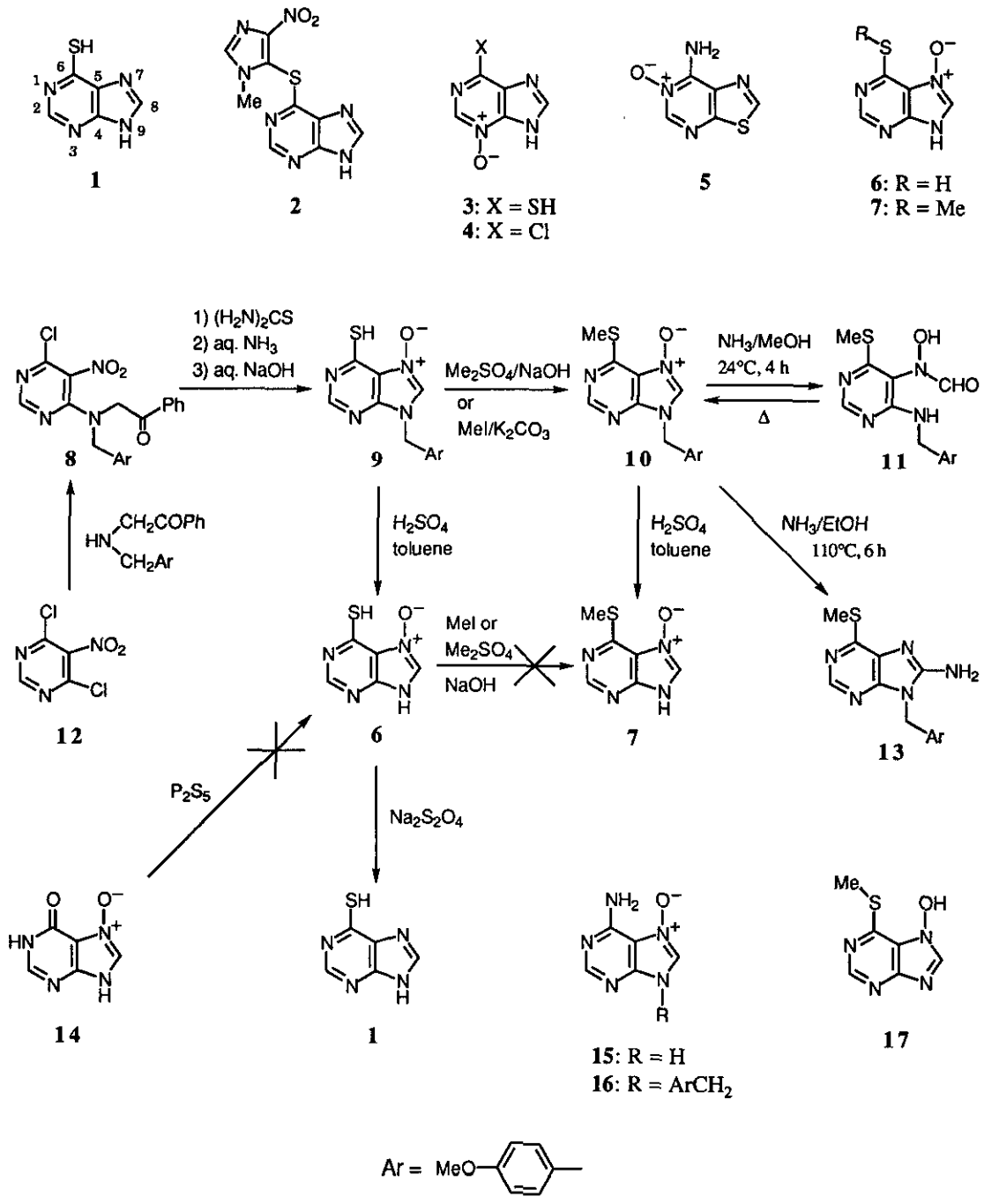
Abstract——6-Mercaptopurine 7-*N*-oxide (**6**) has been synthesized for the first time from 4,6-dichloro-5-nitropyrimidine (**12**) by following a "phenacylamine route" through the intermediates (**8**) and (**9**). Methylation of **9** and removal of the *p*-methoxybenzyl group provided 6-methylthiopurine 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*-oxides[2] of 6-MP, only the 3-oxide (**3**) is hitherto known: it has been synthesized from 6-chloropurine 3-oxide (**4**) and ammonium dithiocarbamate[3] 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 success[5] 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**) ($CHCl_3$, 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


1
2
3: X = SH
4: X = Cl
5
6: R = H
7: R = Me
1) $(H_2N)_2CS$
2) aq. NH_3
3) aq. NaOH
Me_2SO_4/NaOH
or
MeI/K_2CO_3
NH_3/MeOH
24°C, 4 h
Δ
8
9
10
11
H_2SO_4
toluene
NH_3/EtOH
110°C, 6 h
12
6
7
13
MeI or
Me_2SO_4
NaOH
P_2S_5
$Na_2S_2O_4$
14
1
15: R = H
16: R = $ArCH_2$
17
Ar = MeO

Scheme 1

successively by conc. aqueous NH_3 and 2 N aqueous NaOH (0°C, 5 min) gave the *N*-oxide (**9**) [mp 161–163°C (decomp.) for **9**·2/5H_2O] 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°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°C) inferred to be 8-mercaptohypoxanthine.[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 195–205°C (decomp.)] in 52% yield. Methylation of **9** with methyl iodide (K_2CO_3/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 220–223°C (decomp.)][10] in 90% yield. On recrystallization from MeOH–H_2O (3 : 1, v/v), **7** gave a monohydrate, which was shown to exist in the N(7)-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 C(6)-SMe group in the anionic species of **7**. On the other hand, treatment of the N(9)-arylmethyl derivative (**10**) with 16% methanolic NH_3 (24°C, 4 h) afforded an unstable crude compound [mp 154–155°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 C(8)-amino derivative (**13**) (mp 180–181°C) in 18% yield. In either case, the desired adenine derivative (**16**) could not be obtained, and the observed reactivity of **10** at the C(8) atom toward nucleophiles is interpretable in terms of the N(7)-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 $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 18300), 329 (19800); $\lambda_{max}^{H_2O}$ (pH 1) 329 (19800); $\lambda_{max}^{H_2O}$ (pH 7) 230 (sh) (11700), 291 (sh) (8000), 319 (sh) (12100), 333 (13100); $\lambda_{max}^{H_2O}$ (pH 13) 228 (17200), 291 (6800), 329 (13400); ^{1}H nmr (Me_2SO-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 Me_2SO-d_6.
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10. Selected spectral data for **7**: uv $\lambda_{max}^{95\%\ aq.\ EtOH}$ 222 nm (ε 11900), 262 (sh) (4600), 297 (13300); $\lambda_{max}^{H_2O}$ (pH 1) 224 (10100), 306 (14200); $\lambda_{max}^{H_2O}$ (pH 7) 230 (18100), 260 (7700), 280 (8800), 318 (5800); $\lambda_{max}^{H_2O}$ (pH 13) 230 (18100), 260 (7700), 280 (8800), 318 (5800); ^{1}H nmr (Me_2SO-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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