

## Notizen

# Synthesis of Purine and Pyrimidine Substituted Nitroxides

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Purines, Pyrimidines, Nitroxides

Reaction of 6-hydrazinopurine and 2-hydrazinopyrimidine with 2,2,6,6-tetramethylpiperidone-1-oxyl gives 2,2,6,6-tetramethylpiperidone-1-oxyl-(6-purinyl)hydrazone (**3b**) and 2,2,6,6-tetramethylpiperidone-1-oxyl-(2-pyrimidinyl)hydrazone (**4b**) respectively. Compound **3b** is inactive even at high dose levels against TLX/5 lymphoma and **3b** and **4b** are both inactive in tests using the L1210 leukaemia system.

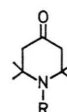
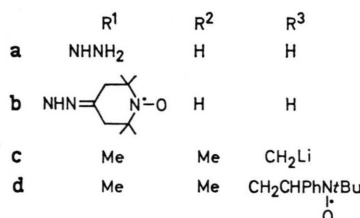
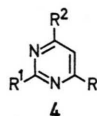
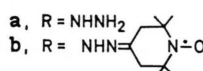
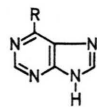
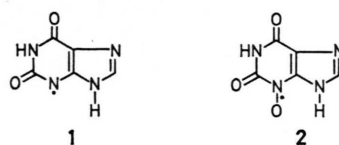
Considerable effort has been expended by Brown *et al.*<sup>1</sup> on the synthesis of purine N-oxides for evaluation in chemotherapy and oncogenesis assays. Recently they adduced chemical evidence<sup>2</sup> suggesting the intermediacy of a radical-anion in one solution decomposition mode of esters of the potent oncogen<sup>3</sup> 3-hydroxyxanthine. It is therefore desirable to synthesise and assay if possible free radicals bearing purinyl or pyrimidinyl substituents. Recently 3-hydroxyxanthine-derived radicals (**1**, **2**) have been generated<sup>4</sup> but cannot be isolated. We now report our preliminary studies on the synthesis and assay of stable nitroxide radicals containing purine and pyrimidine substituents.

Treatment of 6-hydrazinopurine<sup>5</sup> (**3a**) or 2-hydrazinopyrimidine<sup>6</sup> (**4a**) with 2,2,6,6-tetramethylpiperidone-1-oxyl<sup>7</sup> (**5a**) gave the desired free radicals<sup>8</sup> **3b** and **4b** as stable pale yellow and beige solids respectively. Approaches to nitroxides using the lithium derivative **4c** were less successful: when the free radical **5a** was allowed to react<sup>9</sup> with the lithium derivative **4c**<sup>10</sup>, only the hydroxylamine derivative **5b** was isolated. Treatment<sup>11</sup> of *tert*-butyl phenyl nitron with the lithium derivative **4c** followed by autoxidation of the ensuing anion resulted in a nitroxide **4d** as evidenced by ESR spectroscopy ( $a_N = 1.46$ ;  $a_H = 0.34$  mT) although no attempt was made to isolate this free radical.

## Antitumor Evaluation

The purine derivative **3b** was tested on TLX/5 lymphoma, but was found to be inactive even at high dose levels (288 mg/kg for 5 days). Compounds **3b** and **4b** were also inactive in tests using the L1210 leukaemia system.

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## Experimental Section

### 2,2,6,6-Tetramethylpiperidone-1-oxyl-(6-purinyl)-hydrazone **3b**

To a saturated solution of 6-hydrazinopurine<sup>5</sup> (0.45 g, 3 mmol) in a mixture of glacial acetic acid (1.6 ml) and water (11 ml) was added 2,2,6,6-tetramethylpiperidone-1-oxyl<sup>7</sup> (0.5 g, 3 mmol). The mixture was shaken for 15 min, cooled and extracted with chloroform. The extract was washed with water, dried (MgSO<sub>4</sub>) and evaporated to give a solid that was chromatographed (silica gel with CHCl<sub>3</sub>/EtOH 9:1 eluant) to give a pure pale yellow product (0.60 g, 66%), m. p. 207–208 °C (dec.). Found: C, 55.49; H, 6.62; N, 32.51%. C<sub>14</sub>H<sub>20</sub>N<sub>7</sub>O requires: C, 55.61; H, 6.67; N, 32.43%. IR (KBr) 3200, 2965, 2922, 1622, 1326 cm<sup>-1</sup>. UV  $\lambda_{max}^{EtOH}$  298 ( $\epsilon$ ,  $2.7 \times 10^4$ ), 224 ( $1.7 \times 10^4$ ). ESR. triplet,  $a_N = 1.425$  mT (in benzene).

### 2,2,6,6-Tetramethylpiperidone-1-oxyl-(2-pyrimidinyl)hydrazone (**4b**)

To a solution of 2-hydrazinopyrimidine<sup>6</sup> (1.8 g, 16 mmol) in a mixture of glacial acetic acid (0.3 ml) and water (2.2 ml) was added 2,2,6,6-tetramethylpiperidone-1-oxyl<sup>7</sup> (1.5 g, 9 mmol) and the mixture



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shaken for 20 min. The product was extracted with ether and the ensuing solid was purified by preparative scale tlc ( $\text{CHCl}_3 : \text{Et}_2\text{O}$  1 : 1 eluant with silica gel). The orange extract was washed with ether to give a pure product (1.6 g, 30%) m.p. 114–115 °C. Found: C, 59.25; H, 7.54; N, 26.49%.  $\text{C}_{13}\text{H}_{20}\text{N}_5\text{O}$  requires C, 59.52; H, 7.68; N, 26.70%.

IR (KBr) 3210, 2965, 2922, 1585, 1342, 1228  $\text{cm}^{-1}$ . UV  $\lambda_{\text{max}}^{\text{EtOH}}$  264 nm ( $\epsilon$   $2.3 \times 10^4$ ). ESR triplet,  $a_N = 1.50$  mT (in benzene).

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<sup>1</sup> G. B. Brown, *Prog. Nucleic Acid Res.* **8**, 209 [1968].

<sup>2</sup> N. J. M. Birdsall, J. C. Parham, V. Wölcke, and G. B. Brown, *Tetrahedron* **28**, 3 [1972].

<sup>3</sup> M. N. Teller, G. Stohr, and H. Dienst, *Cancer Res.* **30**, 179 [1970]; K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.* **30**, 184 [1970].

<sup>4</sup> J. C. Parham, I. Pullman, and G. B. Brown, *Tetrahedron* **29**, 3329 [1973].

<sup>5</sup> J. A. Montgomery and L. B. Holum, *J. Amer. Chem. Soc.* **79**, 2185 [1957].

<sup>6</sup> V. Vanderhaeghe and M. Claesen, *Bull. Soc. Chim. Belges* **68**, 30 [1959].

<sup>7</sup> E. G. Rozantsev, *Free Nitroxyl Radicals*, p. 213, Plenum Press, New York 1970.

<sup>8</sup> *cf.* The synthesis of a spin labelled dinucleotide: W. E. Trommer, H. Wenzel, and G. Pfeleiderer, *Liebigs Ann. Chem.* **1974**, 1357.

<sup>9</sup> *cf.* ref. 7, p. 64.

<sup>10</sup> J. C. Roberts, *J. Chem. Soc.* **1952**, 3065.

<sup>11</sup> *cf.* E. G. Janzen and B. J. Blackburn, *J. Amer. Chem. Soc.* **91**, 4481 [1969].