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Synthesis of Purine and Pyrimidine Substituted Nitroxides

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(Z. Naturforsch. **31 c**, 101–102 [1976]; received July 8/September 24, 1975)

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.*[1] on the synthesis of purine N-oxides for evaluation in chemotherapy and oncogenesis assays. Recently they adduced chemical evidence[2] suggesting the intermediacy of a radical-anion in one solution decomposition mode of esters of the potent oncogen[3] 3-hydroxyxanthine. It is therefore desirable to synthesise and assay if possible free radicals bearing purinyl or pyrimidinyl substituents. Recently 3-hydroxyanthine-derived radicals (**1**, **2**) have been generated[4] 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[5] (**3 a**) or 2-hydrazinopyrimidine[6] (**4 a**) with 2,2,6,6-tetramethylpiperidone-1-oxyl[7] (**5 a**) gave the desired free radicals[8] **3 b** and **4 b** as stable pale yellow and beige solids respectively. Approaches to nitroxides using the lithium derivative **4 c** were less successful: when the free radical **5 a** was allowed to react[9] with the lithium derivative **4 c**[10], only the hydroxylamine derivative **5 b** was isolated. Treatment[11] of *tert*-butyl phenyl nitrone with the lithium derivative **4 c** followed by autoxidation of the ensuing anion resulted in a nitroxide **4 d** as evidenced by ESR spectroscopy ($a_N = 1{\cdot}46$; $a_H = 0{\cdot}34$ mT) although no attempt was made to isolate this free radical.

Antitumor Evaluation

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

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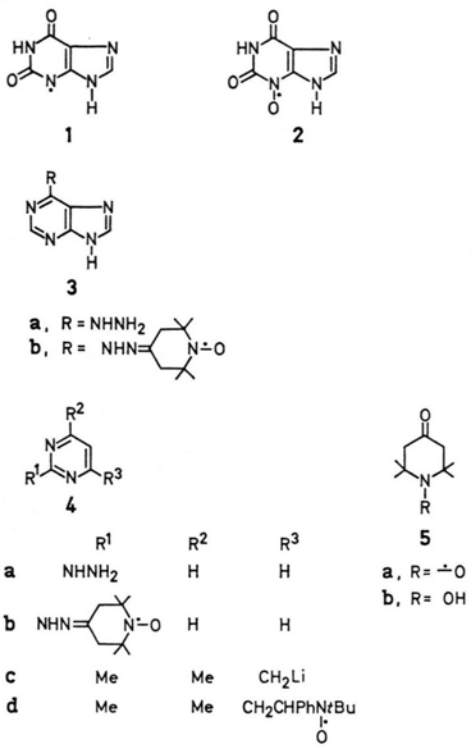

Experimental Section

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

To a saturated solution of 6-hydrazinopurine[5] (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[7] (0.5 g, 3 mmol). The mixture was shaken for 15 min, cooled and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated to give a solid that was chromatographed (silica gel with $CHCl_3$/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%. $C_{14}H_{20}N_7O$ requires: C, 55.61; H, 6.67; N, 32.43%. IR (KBr) 3200, 2965, 2922, 1622, 1326 cm^{-1}. UV $\lambda_{max.}^{EtOH}$ 298 (ε, 2.7×10^4), 224 (1.7×10^4). ESR. triplet, a_N = 1.425 mT (in benzene).

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

To a solution of 2-hydrazinopyrimidine[6] (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[7] (1.5 g, 9 mmol) and the mixture

shaken for 20 min. The product was extracted with ether and the ensuing solid was purified by preparative scale tlc ($CHCl_3 : Et_2O$ 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%. $C_{13}H_{20}N_5O$ requires C, 59.52; H, 7.68; N, 26.70%. IR (KBr) 3210, 2965, 2922, 1585, 1342, 1228 cm^{-1}. UV $\lambda_{max.}^{EtOH}$ 264 nm (ε 2.3×10^4). ESR triplet, $a_N = 1.50$ mT (in benzene).

We thank the Science Research Council for a research grant and Professor A. B. Foster for helpful comments. We also thank Dr. O. C. Yodor and Dr. T. A. Connors for biological assay data.

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