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Studies in Nucleosides: Part XVI—Synthesis of Azathioprine Analogues†

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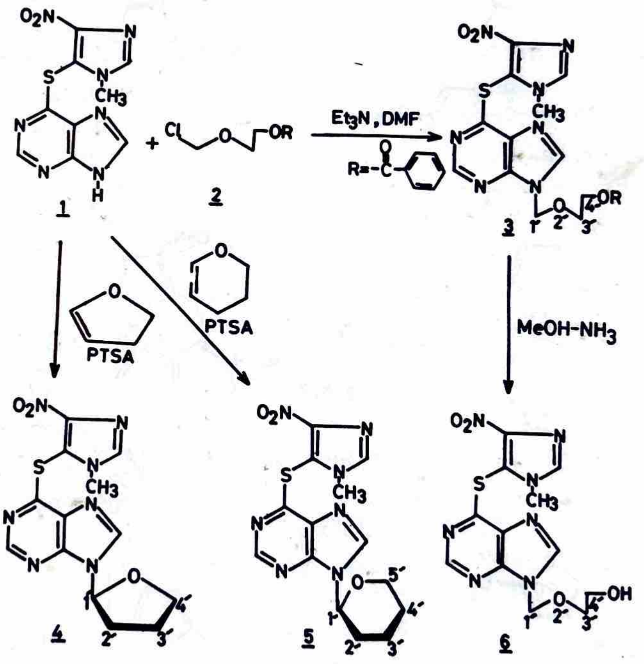
6-[(1-Methyl-4-nitroimidazo-5-yl)thio]-9-(1′-tetrahydrofuranyl)purine (**4**), 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(1′-tetrahydropyranyl)pyrine (**5**), 9-hydroxyethoxymethyl-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**), 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(*β*-D-ribofuranosyl)purine (**12**), 9-(*α*-D-arabinofuranosyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**16**) and 9-(*β*-D-2′-deoxyribofuranosyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**11**) have been synthesised. Condensation of **1** with dihydrofuran and dihydropyran gives **4** and **5** respectively in excellent yields. The reaction of **1** separately with benzoyloxyethoxymethylene chloride (**2**), 1-O-acetylribose derivative (**7**) and 1-chloro-2-deoxyribose derivative (**9**) and of the chloromercuric complex (**13**) with 1-bromoarabinose derivative (**14**) gives the blocked nucleosides (**3, 8, 10** and **15**) respectively. Deblocking of the nucleosides with methanolic ammonia finally affords **6, 12, 11** and **16** respectively.

Azathioprine (**1**), a drug in clinical use in the transplantation of organs and also effective against transplantable tumors and chronic granulocytic leukaemia[1], is a 6-mercaptopurine derivative. The glycosides, cyclic and alicyclic analogues of (**1**) appear to have not been synthesised. There are several reports where the riboside[2], deoxyriboside and arabinoside[3] have been found more effective than the parent base. Further the cyclic and alicyclic analogues of the bases probably act as pro-drugs[3]. Prompted by these reports, it was thought worthwhile to synthesize the riboside, deoxyriboside, arabinoside, cyclic and alicyclic analogues of **1**.

Condensation of **1**[4] with 2-benzoyloxyethoxymethylene chloride in the presence of triethylamine yielded **3** as the sole product. The deblocking of **3** with methanolic ammonia at ambient temperature gave 9-(hydroxyethoxy-methyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**). The acid-catalysed condensation of **1** with dihydrofuran and dihydropyran gave **4** and **5** respectively in excellent yields. (Scheme 1).

Treatment of **1** with 1-O-acetyl-2, 3, 5-tri-O-benzoyl-D-ribofuranose (**7**) in the presence of $BF_3.Et_2O$ gave the protected riboside (**8**) which on deblocking with methanolic ammonia yielded 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(β-D-ribofuranosyl)purine (**12**) (Scheme 2). Synthesis of **12** involving several steps has been reported[5]. The present approach to **12** is much simpler. The β-configuration of **12** was evident from the coupling constant of anomeric proton (H-1′, $J_{1',2'} = 5$ Hz).



Scheme 1

Condensation of chloromercuric complex (**13**) with 2, 3, 5-tribenzoyl-1-bromo-D-arabinose (**14**) gave the protected arabinoside (**15**) which was deblocked with methanolic ammonia in the usual way to give 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(α-D-arabinofuranosyl)purine (**16**) (Scheme 3). It is known that the arabinosides obtained by this procedure have α-configuration[6].

Condensation of **1** with 3, 5-di-(*p*-nitrobenzoyl)-2-deoxyribofuranosyl-1-chloride (**9**) in the presence of NaH gave, according to Robins' procedure[7], nucleoside (**10**) which on deblocking with methanolic ammonia gave 6-[(1-methyl-4-nitroimidazo-5-yl)thio]-9-(β-D-2′-deoxyribofuranosyl)purine (**11**).

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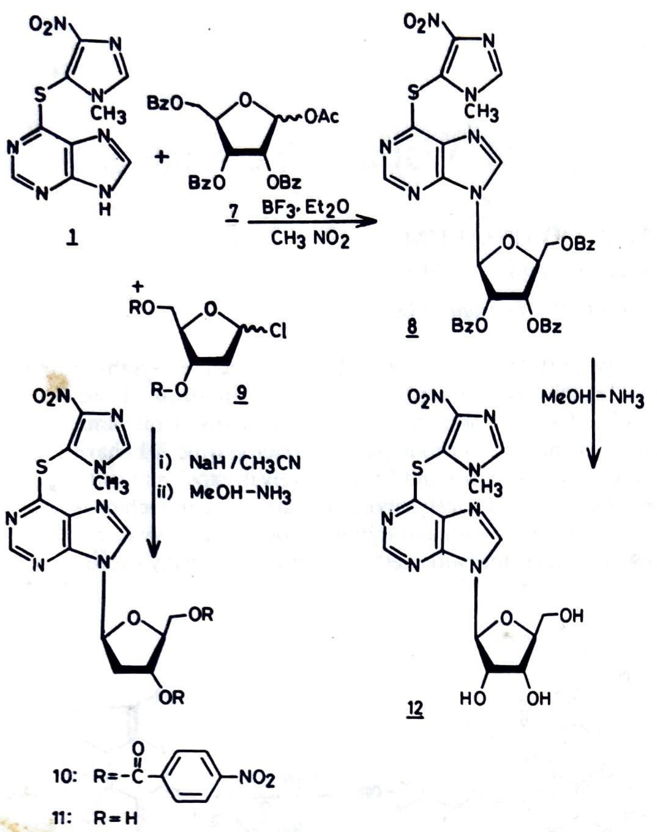
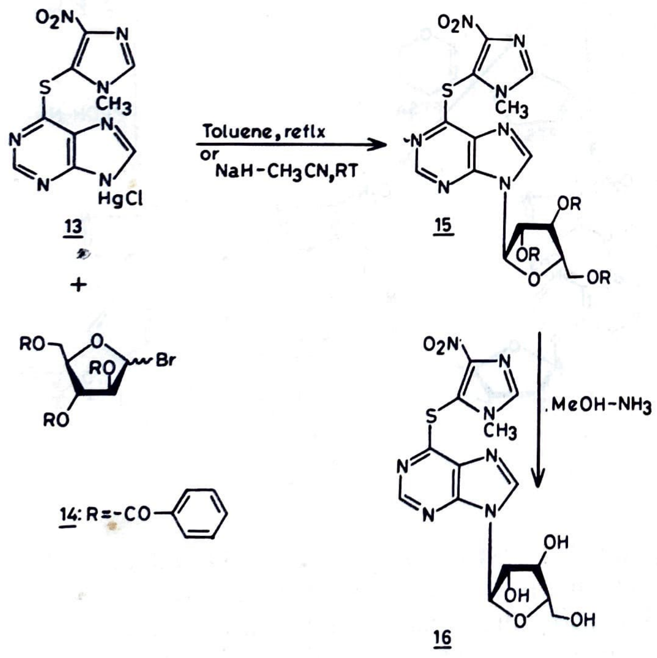
† CDRI Communication No. 3952.



SCHEME 2



SCHEME 3

Experimental Procedure

For general directions see earlier papers in the series[8].

9-(Hydroxyethoxymethyl)-6-[(1-methyl-4-nitroimidazo-5-yl)thio]purine (**6**)

To a stirred mixture of **1** (0.3 g, 1 mmol), DMF (10 ml) and triethylamine (3 ml) was added dropwise a solution of benzoyloxyethoxymethylene chloride (**2**) (3g, 9.5 mmol) in DMF (5 ml) at 10-15° and the mixture further stirred at ambient temperature for 4 hr. Excess of solvent and reagent were removed under reduced pressure, the residue extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product which was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (90:10, v/v) gave **3**(0.4 g, 86%), m.p. 140°; IR(KBr):1680 (C=O); PMR($CDCl_3$ + DMSO-d_6): δ8.5 (*s*, 1H, H-8), 8.35 (*s*, 1H, H-2), 8.0-7.7 (*m*, 3H, H-2 of imidazole and Ar-*H*), 7.6-7.3 (*m*, 3H, Ar-*H*), 5.7 (*s*, 2H, H-1′), 4.5-4.3 (*m*, 2H, H-3′), 4.0-3.7 (*m*, 2H, H-4′) and 3.6 (*s*, 3H, N − CH_3) (Found: C, 49.9; H, 4.0. $C_{19}H_{17}N_7O_5S$ requires C, 50.2; H, 3.7%).

A mixture of **3** (6.6 g, 1.3 mmol) and methanol (10 ml) saturated with ammonia at 0° was kept at ambient temperature for 48 hr. Excess of methanolic ammonia was removed under reduced pressure and the residue chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (90:10, v/v) gave **6** (0.14 g, 31%), m.p. 180°; PMR($CDCl_3$ + DMSO-d_6): δ 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 8.0 (*s*, 1H, H-2 of imidazole), 5.8 (*s*, 2H, H-1′), 4.8 (*bs*, 1H, O*H*), 3.7 (*s*, 3H, N—CH_3), 4.0-3.4 (*m*, 4H, H-3′ and H-4′); (Found: C, 40.8; H, 4.0. $C_{12}H_{13}N_7O_4S$ requires C, 41.0; H, 3.7%).

6-[(1-Methyl-4-nitroimidazo-5-yl)thio]-9-(tetrahydrofuranyl)purine (**4**)

A mixture of **1** (1 g, 3.6 mmol), 2,3-dihydrofuran (1 g, 13.4 mmol) and *p*-toluenesulphonic acid (PTSA) (0.1 g) in ethyl acetate was stirred at 50° for 24 hr. The resulting mixture was washed with aq. K_2CO_3, water, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (92:8, v/v) gave **4** (1.07 g, 86%)), m.p. 151°; PMR($CDCl_3$ + DMSO-d_6): δ8.5 (*s*, 1H, H-8); 8.25 (*s*, 1H, H-2); 7.9 (*s*, 1H, H-2 of imidazole), 6.3 (*t*, 1H, H-1′, $J_{1',2'}$ = 5 Hz), 4.0 (*m*, 2H, H-4′), 3.7 (*s*, 3H, N − CH_3), 2.5-1.8 (*m*, 4H, H-2′ and H-3′) (Found: C, 44.6; H, 3.9. $C_{13}H_{13}N_7O_3S$ requires C, 45.0; H, 3.7%).

6-[(1-Methyl-4-nitroimidazo-5-yl)thio-9-(tetrahydropyranyl)purine (**5**)

This was essentially prepared by the procedure described above employing **1** (1 g, 3.6 mmol), 2, 3-dihydropyran (1 g, 11.9 mmol) and PTSA (0.1 g) work-up above gave **5** in 71% yield m.p. 163°; PMR ($CDCl_3$ + DMSO-d_6): 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 7.9 (*s*, 1H, H-2 of imidazole), 5.6 (*t*, 1H, H-1′, $J_{1',2'}$ = 4 Hz), 4.0-3.2 (*m*, 2H, H-5′), 3.4 (*s*, 3H, N-CH_3), 2.4-1.3 (*m*, 6H, H-2′, H-3′ and H-4′) (Found: C, 47.0; H, 4.0. $C_{14}H_{15}N_7O_3S$ requires C, 46.5; H, 4.2%).

6-[1-*Methyl-4-nitroimidazo-5-yl)thio*]-9-(β-D-ribofuranosyl)purine (12)

A mixture **1** (0.6 g, 2.1 mmol), 1-acetyl-2, 3, 5-tri-O-benzoylribofuranose (**7**) (1.2 g, 2.3 mmol) and anhyd. nitromethane (40 ml) was refluxed for 1 hr, cooled to 75°, BF_3-Et_2O (0.5 ml) added to it and again refluxed for 45 min. Excess of solvent and reagent were removed *in vacuo*, the residue extracted with ethyl acetate, washed with aq. $NaHCO_3$, dried (Na_2SO_4) and solvent removed. The oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (99:1, v/v) gave **8** (0.25 g, 30%), m.p. 153°; PMR ($CDCl_3$): δ 8.5 (*s*, 1H, H-8), 8.3 (*s*, 1H, H-2), 8.2-7.8 (*m*, 7H, H-2 of imidazole and Ar-*H*), 7.6-7.1 (*m*, 9H, Ar-*H*), 6.4 (*d*, 1H, H-1′, $J_{1',2'}$ = 4.5 Hz), 4.8 (*m*, 5H, H-2′, H-3′ and H-4′ and H-5′), 3.6 (*s*, 3H, N−CH_3).

Deblocking of **8** was carried out as described for **3**. The crude **12** thus obtained was purified by chromatography over SiO_2 column. Elution with $CHCl_3$:MeOH (88:12, v/v) gave **12** (50%), m.p. 169° (lit.[5], 167-71°); PMR($CDCl_3$ + DMSO-d_6): 8.5 (*s*, 2H, H-2 and H-8), 7.9 (*s*, 1H, H-2 of imidazole), 6.0 (*d*, 1H, H-1′, $J_{1',2'}$ = 5 Hz), 4.8-3.4 (*m*, 8H, H-2′, H-3′, H-4′, H-5′ and O*H*) 3.7 (*s*, 3H, N−CH_3).

9-(α-*D-Arabinofuranosyl*)-6-[(1-*methyl-4-nitroimidazo-5-yl)thio*]*purine* (16)

Method A: A suspension of chloromercuric complex (**13**) (1.2 g, 2.3 mmol) in xylene (60 ml) was refluxed azeotropically. To it was added a solution of 2, 3, 5-tri-O-benzoyl-D-arabinofuranosyl-l-bromide (**14**) (2 g, 3.8 mmol) in xylene (20 ml). The mixture was refluxed for 4 hr filtered hot and the filter cake washed with chloroform. The solvent from the filtrate was removed *in vacuo*, the residue dissolved in chloroform, washed with 30% aq. KI, dried (Na_2SO_4) and concentrated. The oily product was chromatographed over SiO_2. Elution with $CHCl_3$:MeOH (99:1, v/v) gave the protected arabinoside (**15**), m.p. 132°; PMR($CDCl_3$): 8.5 (*s*, 1H, H-8), 8.2 (*s*, 1H, H-2), 8.0-7.7 (*m*, 7H, H-2 of imidazole and Ar-*H*), 7.5-7.0 (*m*, 9H, Ar-*H*), 6.4 (*d*, 1H, H-1′, $J_{1',2'}$ = 2 Hz), 5.8 (*m*, 1H, H-2′), 5.3-4.5 (*m*, 4H, H-3′, H-4′ and H-5′), 3.6 (*s*, 3H, N—CH_3) (Found: C, 57.9; H, 3.5. $C_{35}H_{27}N_7O_9S$ requires C, 58.2. H, 3.8%).

Method B: A mixture of **1** (0.95 g, 5 mmol), NaH (50% oil, 0.25 g, 6.2 mmol) and anhyd. CH_3CN (35 ml) was stirred at ambient temperature under N_2 atmosphere for 30 min. To it was added (**14**), the mixture stirred for 15 hr and the separated solid removed by filtration. The solvent from the filtrate was removed *in vacuo* and the oily residue was chromatographed over SiO_2 column. Elution with $CHCl_3$:MeOH (99:1 v/v) gave **15** (0.73 g, 55%), m.p. 135°.

Deblocking of **15** as described for **3** gave crude **16** which was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH (85:15, v/v) gave **16** (37%), m.p. 155°; PMR($CDCl_3$ + DMSO-d_6): 8.5 (*s*, 2H, H-2 and H-8), 8.0 (*s*, 1H, H-2 of imidazole), 6.0 (*d*, 1H, H-1′, $J_{1',2'}$ = 3 Hz), 4.7-3.3 (*m*, 8H, H-2′, H-3′, H-4′, H-5′ and O*H*) 3.6 (*s*, 3H, N—CH_3) (Found: C, 41.1; H, 3.7. $C_{14}H_{15}N_7O_6S$ requires C, 41.07; H, 3.7%).

9-(β-D-2′-*Deoxyribofuranosyl*)-6-[(1-*methyl-4-nitroimidazo-5-yl)thio*]*purine* (11)

A mixture of **1** (0.95 g, 3.4 mmol), NaH (50% oil, 0.25 g) and anhyd. CH_3CN was stirred at ambient temperature under nitrogen atmosphere for 30 min. To it was added 1-chloro-2-deoxy-3, 5-di-O-(*p*-nitrobenzoyl)ribofuranose (**9**) (1.6 g, 3.4 mmol). The mixture was stirred for 15 hr and worked up in the usual manner. The crude product was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH (98:2, v/v) gave the protected nucleoside (**10**) (1.2 g, 55%), m.p. 160°; PMR($CDCl_3$): 8.6 (2*s*, 2H, H-2 and H-8), 8.3 (*m*, 4H, 4 Ar-*H*), 8.0 (*m*, 5H, H-2 of imidazole, Ar-*H*), 6.2 (*dd*, 1H, H-1′, $J_{1',2'}$ = 11, 1.5 Hz), 5.7 (*m*, 2H, H-3′ and H-4′), 4.2 (*m*, 2H, H-5′), 3.7 (*s*, 3H, N—CH_3), 2.45 (*m*, 2H, H-2′) (Found: C, 48.3; H, 3.1. $C_{28}H_{21}N_9O_{11}S$ requires C, 48.6; H, 3.1%).

Deblocking of **10** as usual afforded crude **11** which was chromatographed over a column of SiO_2. Elution with $CHCl_3$:MeOH:CH_3COCH_3 (88;10;2, v/v) gave **11** (0.43 g, 50%), m.p. 215° (d); PMR($CDCl_3$ + DMSO-d_6): 8.6 (*s*, 1H, H-8), 8.5 (*s*, 1H, H-2) 8.1 (*s*, 1H, H-2 of imidazole), 6.0-5.6 (*dd*, 1H, H-1′, $J_{1',2'}$ = 11.2 Hz), 4.9-4.5 (*m*, 2H, H-3′, H-4′), 4.0-3.5 (*m*, 4H, H-5′, O*H*), 3.7 (*s*, 3H, N—CH_3), 2.4-1.8 (*m*, 2H, H-2′) (Found: C, 42.5; H, 3.9. $C_{14}H_{15}N_7O_5S$ requires C, 42.7; H, 3.8%).

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