Purine Nucleosides. Part XXXII.† Synthesis and Reactivity of 6-Alkylseleno-9-(β-D-ribofuranosyl)purines ‡

By George H. Milne and Leroy B. Townsend,* Department of Biopharmaceutical Sciences and Department of Chemistry, University of Utah, Salt Lake City, Utah, 84112, U.S.A.

The alkylation of 6-selenoxo-9-(β-D-ribofuranosyl)purine with several alkyl halides under basic conditions has furnished the corresponding 6-alkylseleno-9-(β-D-ribofuranosyl)purines. A ready removal of the 6-methylseleno-group from the 6-methylseleno-derivative (3) with Raney nickel under mild conditions has furnished an almost quantitative yield of nebularine. Treatment of the 6-benzylseleno-derivative (4) with nucleophilic reagents has demonstrated the ease of displacement of the alkylseleno-group.

6-SELENOXO-9-(β-D-RIBOFURANOSYL)PURINE (1) (6-selenoinosine) has demonstrated essentially no antitumour activity, presumably owing to instability[1] at physiological pH. We have synthesized[2] the 2-amino-derivative of (1), which is much more stable under basic and approximate physiological pH conditions. We later found[3] that an additional increase in stability could be accomplished by conversion of the selenoxo-group into an alkylseleno-group. We also reported[3] that the 6-alkylseleno-group of a 2-amino-6-alkylseleno-9-(β-D-ribofuranosyl)purine could be easily displaced by nucleophiles. This prompted us to synthesize the corresponding selenopurine nucleosides without the 2-amino-group for a direct comparison of their relative reactivities towards nucleophilic displacement.

The sodium salt of 6-selenoxo-9-(β-D-ribofuranosyl)-purine[4] (1) was prepared *in situ* for use in the synthesis of several 6-(substituted seleno)-9-(β-D-ribofuranosyl)-purines. Treatment with benzyl bromide furnished a high yield of 6-benzylseleno-9-(β-D-ribofuranosyl)purine (4). That alkylation had occurred at the 6-selenoxo-group rather than at a ring nitrogen atom was established by the hypsochromic shift (from 345 to 302 nm) in the u.v. spectrum (methanol) and the conversion of the product (4) into 6-dimethylamino-9-(β-D-ribofuranosyl)-purine (7) (see later). The sodium salt of (1) also

† Part XXXI, C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, 1972, **37**, 2300.

‡ This research was supported by Chemotherapy, National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

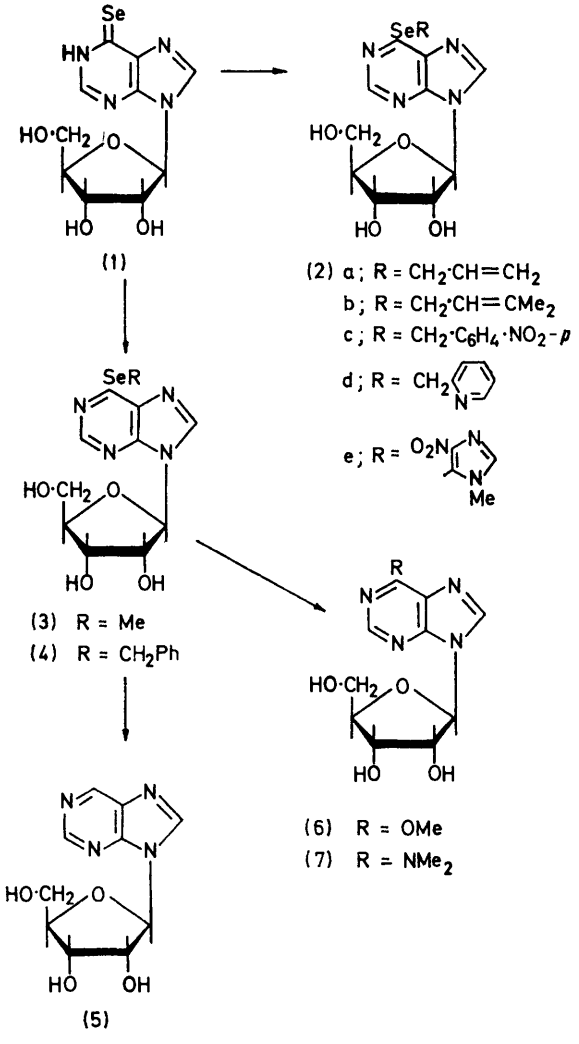
[1] H. G. Mautner, S.-H. Chu, J. J. Jaffe, and A. Sartorelli, *J. Medicin. Chem.*, 1963, **6**, 36.

[2] L. B. Townsend and G. H. Milne, *J. Heterocyclic Chem.*, 1970, **7**, 753.

[3] G. H. Milne and L. B. Townsend, *J. Heterocyclic Chem.*, 1971, **8**, 379.

[4] H. G. Mautner and J. J. Jaffe, *Cancer Res.*, 1960, **20**, 381.

reacted with various alkyl halides to furnish 6-allylseleno- (2a), 6-methylseleno-[5] (3), 6-(3-methylbut-2-enyl)seleno- (2b), 6-α-picolylseleno- (2d), 6-*p*-nitrobenzylseleno- (2c), and 6-(1-methyl-4-nitroimidazol-5-yl)seleno-9-(β-D-ribofuranosyl)purine (2e).



6-Benzylseleno-9-(β-D-ribofuranosyl)purine (4) and 2-amino-6-benzylseleno-9-(β-D-ribofuranosyl)purine [3] were each treated with sodium methoxide in absolute methanol at reflux temperature. The former was completely converted into 6-methoxy-9-(β-D-ribofuranosyl)purine [6] (6) after 1 h, as established by t.l.c. and the loss of u.v. absorption at 304 nm with concomitant appearance of absorption at 245 nm. The corresponding 2-amino-nucleoside required 24 h for complete reaction; this demonstrates the deactivating effect of the 2-amino-group towards nucleophilic displacement of a 6-alkylseleno-group. Similarly, when compound (4) was treated with dimethylamine in methanol at reflux temperature, the reaction was 95% complete in 4·5 h, and after 6 h conversion into 6-dimethylamino-9-(β-D-ribofuranosyl)purine [7] (7) was complete. We have reported [2] that 2-amino-6-benzylseleno-9-(β-D-ribofuranosyl)purine is unchanged under similar conditions after 24 h.

Treatment of the methylseleno-derivative (3) with Raney nickel in methanol at reflux temperature for 5 min effected complete removal of the methylseleno-group, as established by t.l.c. and the disappearance of the u.v. absorption at 302 nm with concomitant appearance of absorption at 260 nm. The product was identical with authentic nebularine.[8] This ready deselenation suggests that an alkylseleno-group is to be preferred to an alkylthio-group in such conversions.

EXPERIMENTAL

M.p.s were observed with a Thomas–Hoover capillary apparatus. U.v. spectra were obtained with a Beckman DK-2 spectrophotometer. Elemental analyses were performed by Heterocyclic Chemical Corporation, Harrisonville, Missouri. We used 0·25 mm thick Baker SilicAR 7GF plates and ethyl acetate–methanol (4 : 1 v/v) for t.l.c. separations unless otherwise specified.

Sodium Salt of 6-Selenoxo-9-(β-D-ribofuranosyl)purine (1).—6-Selenoxo-9-(β-D-ribofuranosyl)purine (1) (1 g) was suspended in well stirred methanol (25 ml) at room temperature and the minimum amount of methanolic sodium methoxide [from sodium hydroxide (1 g) in absolute methanol (25 ml)] was added to give a clear solution. This solution was then treated *immediately* with the appropriate alkyl halide for the preparation of 6-alkylseleno-9-(β-D-ribofuranosyl)purines.

6-(*3-Methylbut-2-enyl*)*seleno-9-(β-D-ribofuranosyl)purine* (2b).—To the foregoing sodium salt was added, with stirring, 1-bromo-3-methylbut-2-ene (450 mg). The solution was stirred at room temperature for 2 h and the pH was adjusted to 6 with glacial acetic acid. The clear solution was evaporated *in vacuo* to afford a solid foam, which was triturated with water (50 ml); the solid was filtered off and suspended in water. Sufficient methanol was added at reflux temperature to give a clear solution. The solution was kept at 5° for 18 h, and the solid was filtered off and dried under vacuum (Drierite) for 12 h to afford the *product* (2b) (625 mg), m.p. 50—52° (Found: C, 44·8; H, 5·05; N, 13·95. $C_{15}H_{20}N_4O_4Se$ requires C, 45·0; H, 5·0; N, 14·0%).

6-*p-Nitrobenzylseleno-9-(β-D-ribofuranosyl)purine* (2c).—The same procedure as for (2b), except that α-bromo-*p*-nitrotoluene (650 mg) was used and the solid was recrystallized from methanol–water, to give *compound* (2c) (800 mg), m.p. 178—180° with softening at *ca.* 150° (Found: C, 44·1; H, 3·8; N, 14·7. $C_{17}H_{17}N_5O_6Se$ requires C, 43·8; H, 3·65; N, 15·0%).

6-(*2-Pyridylmethylseleno*)-9-(β-D-*ribofuranosyl*)*purine* (2d).—The same procedure as for (2b), except that α-picolyl chloride hydrochloride (490 mg) and methanolic N-sodium methoxide were used and the product was recrystallized from absolute methanol, to give compound (2d) (650 mg), m.p. 203—205°. A sample recrystallized once from absolute methanol and then dried *in vacuo* for 18 h (Drierite)

[5] S.-H. Chu, *J. Medicin. Chem.*, 1971, **14**, 254.
[6] J. A. Johnson, jun., H. J. Thomas, and H. J. Schaeffer, *J. Amer. Chem. Soc.*, 1958, **80**, 699.
[7] L. B. Townsend, R. K. Robins, R. N. Leoppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, 1964, **86**, 5320.
[8] G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, 1953, **204**, 1019.

had m.p. 204—205·5° (Found: C, 45·0; H, 4·0; N, 16·95. $C_{16}H_{17}N_5O_4Se$ requires C, 45·5; H, 4·05; N, 16·6%).

6-*Benzylseleno*-9-(β-D-*ribofuranosyl*)*purine* (4).—The same procedure as for (2b), except that α-bromotoluene (513 mg) was used and the product was recrystallized from absolute methanol, to give *compound* (4) (1 g), m.p. 102—105°. A sample recrystallized once more from absolute methanol and dried in an Abderhalden apparatus over methanol at reflux temperature had m.p. 105—107° (Found: C, 49·05; H, 4·3; N, 13·1. $C_{17}H_{18}N_4O_4Se$ requires C, 49·45; H, 4·3; N, 13·3%).

6-*Methylseleno*-9-(β-D-*ribofuranosyl*)*purine* (3).—The same procedure as for (2b) was employed, except that methyl iodide (500 mg) was used and the solution was stirred at room temperature for 0·5 h. It was then evaporated to dryness *in vacuo* and the white solid was extracted (Soxhlet) with diethyl ether (125 ml) for 48 h. The solid was filtered off and the product was dried in an Abderhalden apparatus over Drierite with methanol at reflux temperature to yield compound (3) (650 mg), m.p. 158—160° (lit.[5] 154—155°) (Found: C, 36·4; H, 4·3; N, 15·25. Calc. for $C_{11}H_{14}N_4O_4Se,H_2O$: C, 36·4; H, 4·4; N, 15·4%).

6-*Allylseleno*-9-(β-D-*ribofuranosyl*)*purine* (2a).—The same procedure as for (2b) was employed, except that allyl bromide (350 mg) was used; the white foam produced was extracted (Soxhlet) with diethyl ether (125 ml) for 24 h. The ether was evaporated off and the residue recrystallized from ethyl acetate–cyclohexane. The product was dried in an Abderhalden apparatus over Drierite with methanol at reflux temperature for 12 h to yield compound (2a) (580 mg), slowly softens and melts >60° (Found: C, 42·2; H, 4·45; N, 14·8. $C_{13}H_{16}N_4O_4Se$ requires C, 42·05; H, 4·3; N, 15·1%).

Comparison of the Reactivities of the 6-*Benzylselenopurine riboside* (4) *and* 2-*Amino*-6-*benzylseleno*-9-(β-D-*ribofuranosyl*)*purine towards Nucleophilic Displacement*.—Compound (4) and 2-amino-6-benzylseleno-9-(β-D-ribofuranosyl)purine were each (250 mg) dissolved in methanol (25 ml) containing sodium methoxide (250 mg) and heated under reflux for 1 h. The reactions were monitored by u.v. spectroscopy and t.l.c. [ethyl acetate–methanol (10 : 1 v/v)]. After 1 h, complete conversion of compound (4) into 6-methoxy-9-(β-D-ribofuranosyl)purine (6) had occurred. The reaction with the 2-amino-derivative contained only a small amount of 2-amino-6-methoxy-9-(β-D-ribofuranosyl)purine after 1 h; 24 h was required for complete conversion under these conditions.

6-*Dimethylamino*-9-(β-D-*ribofuranosyl*)*purine* (7).—6-Benzylseleno-9-(β-D-ribofuranosyl)purine (4) (250 mg), dissolved in methanol (25 ml) containing dimethylamine (5 ml) was stirred and heated under reflux for 6 h; the reaction was monitored by u.v. spectroscopy and t.l.c. [ethyl acetate–methanol (10 : 1 v/v)]. After 4·5 h *ca.* 95% conversion into 6-dimethylamino-9-(β-D-ribofuranosyl)purine had occurred, and after 6 h only one compound was present (t.l.c.). The solution was evaporated to dryness *in vacuo* and triturated with ethyl acetate (25 ml), and the mixture was again evaporated to dryness. The resulting solid crystallized from acetone to yield compound (7) (150 mg, 86%), identical with authentic [7] material {$\lambda_{max.}$ (MeOH) 274 nm [lit.,[7] $\lambda_{max.}$ (pH 7) 275 nm], m.p. and mixed m.p. 179—181° (lit.,[7] 183—184°); t.l.c. in four solvent systems}.

9-(β-D-*Ribofuranosyl*)*purine* (5) (*Nebularine*).—6-Methylseleno-9-(β-D-ribofuranosyl)purine (3) (250 mg) was dissolved in hot methanol (50 ml) and Raney nickel * (*ca.* 1 g wet wt.) was added with stirring. After 5 min, the u.v. spectrum revealed no absorption at 302 nm but a new absorption at 260 nm. The Raney nickel was removed and washed with hot methanol (50 ml). The filtrate was evaporated to dryness *in vacuo* to yield nebularine (175 mg, 96%) m.p. 177—180° (lit.,[8] 180—181°) identical (mixed m.p., u.v. spectra, and t.l.c. in four solvent systems) with authentic [8] material.

6-(1-*Methyl*-4-*nitroimidazol*-5-*yl*)*seleno*-9-(β-D-*ribofuranosyl*)*purine* (2e).—6-Selenoxo-9-(β-D-ribofuranosyl)purine (1) (1·5 g) was added to dry methanol (absolute; 30 ml) and to this solution was added dry methanol (5 ml) containing sodium methoxide (275 mg). The solution was stirred and 5-chloro-1-methyl-4-nitroimidazole (725 mg) was added. Stirring was continued at room temperature for 1 h, then the pH was adjusted to 6 with glacial acetic acid. The solution was evaporated to a solid foam (*in vacuo*); the residue was suspended in water (50 ml) and then heated to boiling with just enough methanol being added to effect dissolution at the b.p. of the mixture. The solution was kept at 5° for 18 h, and the solid was filtered off, washed with cold water, dried, and recrystallized from methanol–water to furnish a yellow crystalline *solid* (1·3 g), m.p. >100° (foams). This was dried over Drierite in an Abderhalden apparatus over methanol at reflux temperature for 18 h under high vacuum to furnish material of m.p. 100—102° (foams) (Found: C, 36·0; H, 3·55; N, 20·9. $C_{14}H_{15}N_7O_6Se,0·5H_2O$ requires C, 36·15; H, 3·45; N, 21·05%) ($0·5H_2O$ verified by n.m.r. spectrum).

[2/1414 *Received*, 19*th June*, 1972]

* W. R. Grace and Co.