Bicyclic Nucleosides related to Pyrimidine Nucleosides. Part III.[1] 3-(β-D-Ribofuranosyl)isoguanine

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Ring closure of 4,5,6-triaminopyrimidin-2-one with thiourea was followed by conversion into 8-iodoisoguanine. Condensation of 8-iodoisoguanine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide afforded a good yield of 8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoguanine. The isomeric and anomeric structure of this nucleoside was established by successful conversion into 3-(β-D-ribofuranosyl)xanthine. Debenzoylation of 8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoguanine followed by dehalogenation of the unprotected nucleoside furnished the bicyclic cytidine nucleoside analogue 3-(β-D-ribofuranosyl)isoguanine.

THE isolation[2,3] and characterization[4] of 3-ribosyluric acid has generated a continuing interest in the synthesis of other 3-ribosylpurines[5] and related compounds.[6] Previous attempts to prepare 3-ribosylpurines have been complicated by the fact that whereas adenine is alkylated in neutral medium to afford primarily 3-substituted derivatives,[7-9] the ribosylation reaction is generally very unselective.

We have previously investigated[5] the introduction of a bulky group at the 8-position of purine as a steric blocking group in an effort to increase the selectivity of the ribosylation reaction and to reduce 9-ribosylation. A substituent such as the iodo-group provided such steric interaction which resulted in a strong preference for

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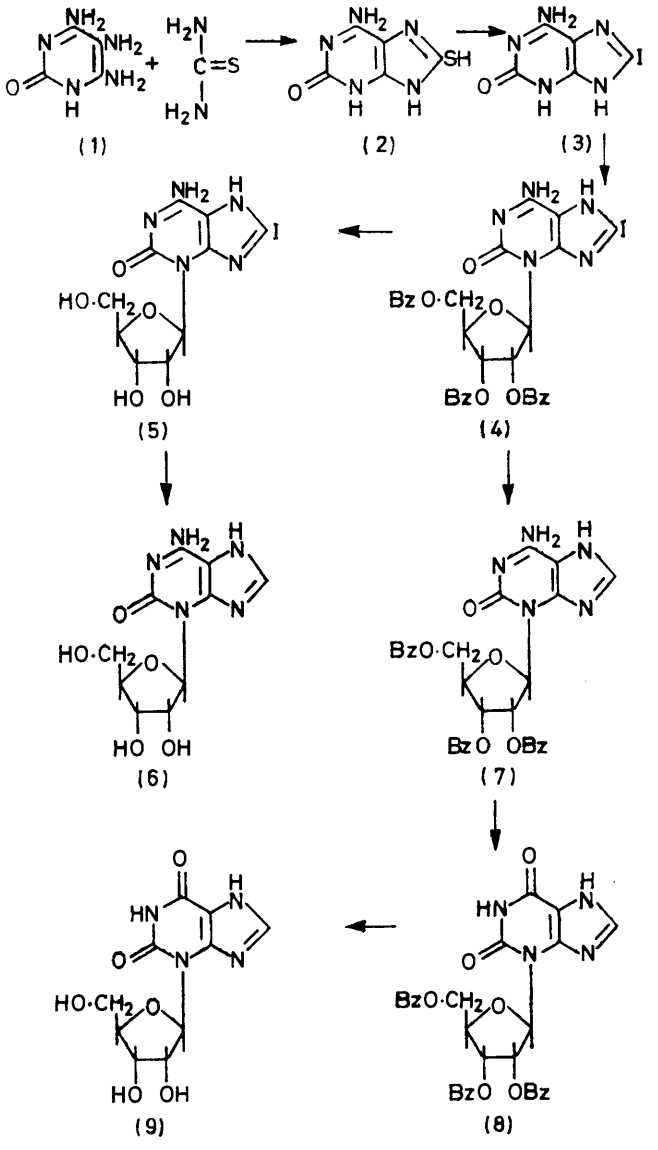
3-substitution. This method has now been applied to the synthesis of 3-ribosylisoguanine and found to afford a good yield of the desired product.[1]

The appropriate heterocycle for the application of this method, 8-iodoisoguanine, has reportedly[10] been synthesized from 6-amino-8-mercaptopurin-2-one (2). However, we could not trace the origin of (2) in the literature,



and were therefore obliged to begin our investigation with the synthesis of (2). This was accomplished by a fusion of 4,5,6-triaminopyrimidin-2-one[11] (1) with thiourea. Conversion of (2) into 8-iodoisoguanine according to the reported[10] method yielded a product which differed significantly in its physical properties from those reported.[10] However, elemental analysis indicated that our product was indeed the desired material (3), and this was confirmed by subsequent reactions.

8-Iodoisoguanine was silylated with hexamethyldisilazane, and the bistrimethylsilyl derivative was treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose to furnish a nucleoside which was presumed to be the desired

U.v. spectral data for isoguanine derivatives

	pH 1		pH 11		EtOH	
Compd.	$\lambda_{max.}$/nm	$\varepsilon_{max.}$ [a]	λ_{max}/nm	$\varepsilon_{max.}$	$\lambda_{max.}$/nm	$\varepsilon_{max.}$
(2)	329	28·0	315	22·1		
	262	14·0	(256) [b]	9·4		
(3)	295·5	16·3	292·5	17·4		
	(233)	10·3				
(4)					304	19·8
					(285)	13·0
(5)	297	20·8	296	21·0		
	(235)	11·7	(240)	10·6		
(6)	286	16·1	288	14·3		
			(239)	7·6		
(7)					282·5	16·1
					(276·5)	14·3
(9)	266·5	8·8	274	11·0		

[a] $\varepsilon \times 10^{-3}$. [b] Shoulders in parentheses.

8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoguanine (4). The benzoyl groups were removed by treatment with methanolic sodium methoxide, and hydrogenolysis of the product (5) over 5% palladium–charcoal yielded 3-(β-D-ribofuranosyl)isoguanine (6).

The u.v. spectral data of (6) were in close agreement with those reported[12] for 3-methylisoguanine [$\lambda_{max.}$ (pH 1) 285 nm] and entirely at variance with those for isoguanosine (9-ribosylisoguanine). Attempts to deaminate (6) with nitrous acid to obtain the known 3-(β-D-ribofuranosyl)xanthine (9)[13] were unsuccessful. Since this would have established unequivocally both the site of glycosylation and the anomeric configuration for all nucleosides in this investigation, an alternative route was undertaken which involved reductive dehalogenation of (4) with hydrogen over 5% palladium–charcoal in dimethylformamide to give (7), followed by deamination with nitrosyl chloride in dimethylformamide. This afforded 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)xanthine (8), which was then converted into 3-(β-D-ribofuranosyl)xanthine (9) by treatment with sodium methoxide in methanol. A comparison of u.v. spectral data and m.p. with those reported for the unequivocally synthesized nucleoside confirmed the identity of our starting material (2) and the site of glycosylation and anomeric configuration of all nucleosides in this investigation as N-3 and β, respectively. The result of previous studies on a variety of bicyclic nucleosides substituted in the pyrimidine portion imply that these nucleosides act as pyrimidine nucleoside analogues. A notable example is oxiallopurinol,[14] which is ribosylated enzymically to form 7-(β-D-ribofuranosyl)oxiallopurinol (analogous to 3-ribosylxanthine), which acts as an inhibitor of pyrimidine biosynthesis.[15] In addition, the failure of 3-ribo-

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syladenine to act as a pyrimidine analogue has been credited to the absence of a 2-oxo-group.[16] 3-Ribosylisoguanine (6) can be viewed as a 3-ribosyladenine with a C-2 oxo-group and should therefore prove to be of biological and chemotherapeutic interest.

EXPERIMENTAL

M.p.s were determined with a Thomas-Hoover apparatus. ^{1}H N.m.r. spectra were determined with a Varian A 56/60 spectophotometer with 2,2-dimethyl-2-silapentane-5-sulphonate as internal standard and [$^2H_6$]dimethyl sulphoxide as solvent unless otherwise stated. Column chromatography was performed by using glass columns with sintered glass bottoms dry packed with Mallinckrodt SilicAR CC-7, (200—325 mesh). All solvent proportions are given by volume.

6-Amino-8-mercaptopurin-2-one (2).—4,5,6-Triaminopyrimidin-2-one sulphate (50·0 g) and thiourea (75·0 g) were mixed by grinding and heated in an oil-bath at 200° for 1 h. The resulting solid was reprecipitated from hot aqueous N-sodium hydroxide (1200 ml) by acidification to pH 5 with concentrated hydrochloric acid to yield *compound* (2) (39·7 g), m.p. >360° (Found: C, 28·5; H, 4·05; N, 33·2. $C_5H_5N_5OS,1·5H_2O$ requires C, 28·55; H, 3·85; N, 33·3%).

6-Amino-8-iodopurin-2-one (3)—To a suspension of the 8-mercaptopurine (2) (39·0 g) and sodium hydrogen carbonate (165 g) in water (920 ml) was added dropwise with stirring a solution of iodine (110 g) and potassium iodide (165 g) in water (400 ml). The mixture was stirred at room temperature for 24 h, then the solid was filtered off, washed with aqueous 10% potassium iodide (100 ml) and then water (100 ml), and recrystallized from aqueous N-sulphuric acid (1·5 l) containing potassium iodide (15 g) to yield *compound* (3) (24·3 g), m.p. 210—235° with evolution of iodine (Found: C, 18·3; H, 1·85; N, 21·35. $C_5H_4IN_5O,0·5H_2SO_4$ requires C, 18·4; H, 1·55; N, 21·5%).

6-Amino-8-iodo-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-purin-6-one (4).—6-Amino-8-iodopurin-2-one (3) (5·0 g) was added to hexamethyldisilazane (HMDS) (50 ml) containing ammonium sulphate and the mixture was heated in an oil bath at 120° for 36 h. The excess of HMDS was removed by vacuum distillation at 120°. The resulting syrup was dissolved in 1,2-dichloroethane (100 ml), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (7·0 g) and tin(IV) chloride (4·0 g, 1·8 ml) were added, and the solution was stirred at room temperature for 18 h. Pyridine (2·5 ml) was added and the precipitate was filtered off and washed with chloroform (100 ml). The combined filtrate and washings were extracted with saturated aqueous sodium hydrogen carbonate (4 × 50 ml) and water (2 × 50 ml), dried (Na_2SO_4), filtered, and evaporated. The resulting syrup was dissolved in chloroform (10 ml), applied to the top of a dry-packed column of SilicAR CC-7 (4·6 × 24 cm), and eluted with chloroform–acetone (19 : 1) (20 ml fractions). Fractions 15—40 were evaporated to dryness and the residue was recrystallized from chloroform–ethanol (4 : 1; 100 ml) to yield *compound* (4) (3·5 g), m.p. 262—263° (decomp.) (Found: C, 51·6; H, 3·5; N, 9·7. $C_{31}H_{24}IN_5O_8$ requires, C, 51·6; H, 3·35; N, 9·7%).

6-Amino-8-iodo-3-(β-D-ribofuranosyl)purin-2-one (5).—The tri-*O*-benzoyl nucleoside (4) (3·3 g) was suspended in anhydrous methanol (20 ml), sodium methoxide (0·4 g) was added, and the mixture was stirred for 15 h at room temperature. The solution was neutralized with Amberlite CG 50 resin (H^+ form), filtered, and evaporated to dryness. The residue was extracted with ether (4 × 50 ml) and the resulting solid recrystallized from water to yield *compound* (5) (1·43 g), m.p. 242° (decomp.); δ 6·22 (1H d, $J_{1',2'}$ 3·5 Hz, H-1′) (Found: C, 29·05; H, 3·25; N, 16·9. $C_{10}H_{12}IN_5O_5$ requires C, 29·35; H, 2·95; N, 17·1%).

6-Amino-3-(β-D-ribofuranosyl)purin-2-one[*3-(β-D-Ribofuranosyl)isoguanine*] (6).—The 8-iodonucleoside (5) (1·0 g) was suspended in water (25 ml) containing triethylamine (0·75 ml) and 5% palladium–carbon (0·5 g). The suspension was stirred under 1 atm of hydrogen for 1 h (total uptake 69 ml) and filtered through Celite, and the palladium–carbon was washed with boiling water (100 ml) containing concentrated ammonium hydroxide (10 ml). The filtrate and washings were combined and acidified to pH 6 with N-hydrochloric acid and the resulting solid was dissolved in boiling water (50 ml) containing the minimum amount of ammonium hydroxide required for dissolution. The product was reprecipitated with N-hydrochloric acid to yield *compound* (6) (0·5 g), slow decomp. >285°; δ 7·34 (1H, s, 8-H) and 6·42 (1H, d, $J_{1',2'}$ 7 Hz, H-1′) (Found: C, 42·4; H, 4·75; N, 24·6. $C_{10}H_{13}N_5O_5$ requires C, 42·4; H, 4·6; N, 24·75%).

6-Amino-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)purin-2-one (7).—The tri-*O*-benzoyl 8-iodonucleoside (4) (1·0 g) was dissolved in dimethylformamide (10 ml) containing triethylamine (0·4 ml). Palladium–carbon (5%; 0·35 g) was added and the suspension was stirred under 1 atm of hydrogen for 40 min (total uptake 40·5 ml). The palladium–carbon was filtered off through celite and washed with hot dimethylformamide (5 ml). The filtrate was evaporated to dryness and the residue was dissolved in boiling chloroform (300 ml); the solution was filtered and concentrated to 150 ml. Ethanol (150 ml) was added and the solution was again concentrated, to 200 ml, to yield *compound* (7) (0·57 g), m.p. 270–271° (Found: C, 60·55; H, 4·5; N, 11·4. $C_{31}H_{25}N_5O_8,H_2O$ requires C, 60·7; H, 4·4; N, 11·45%).

3-(β-D-Ribofuranosyl)purine-2,6-dione (9).—A solution of the tri-*O*-benzoyl nucleoside (7) (0·15 g) in dimethylformamide (3 ml) containing pyridine (0·1 ml) was cooled in an ice-bath and a solution of nitrosyl chloride (0·08 g) in dimethylformamide (2 ml) was added dropwise during 10 min with stirring. The solution was stirred at 0° for 20 min, then slowly poured into saturated aqueous sodium hydrogen carbonate (50 ml) with vigorous stirring to give a solid. This solid was filtered off, washed with water (10 ml), and dissolved in chloroform (30 ml). The solution was dried (Na_2SO_4), filtered, and evaporated. The resulting syrup was dissolved in chloroform–acetone–methanol (80 : 17 : 3), applied to a dry-packed column of SilicAR CC-7 (1 × 20 cm), and eluted with the same solvent mixture. Fractions 7—9 (5 ml fractions) contained pure 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine-2,6-dione (8) (75 mg), which was used directly.

Compound (8) (50 mg) was suspended in anhydrous methanol (10 ml) and sodium methoxide (10 mg) was added. The solution was stirred for 24 h, after which t.l.c. (chloroform–acetone–methanol, 70 : 15 : 15) revealed the absence of starting material. The solution was neutralized with Amberlite CG–50 resin (H^+ form), and the resin was filtered off and washed with boiling methanol. The

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filtrate and washings were combined and evaporated to dryness. The residue was extracted with ether (4 × 10 ml) to leave a solid (29 mg) which was recrystallized from propan-2-ol to give compound (9) (20 mg), m.p. 204—205° (lit.,[14] 203—205°).

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