Synthesis of Nucleosides by Direct Replacement of the Anomeric Hydroxy-group

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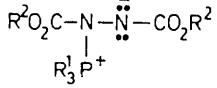
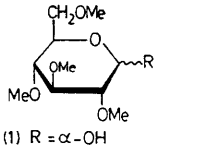
Summary A novel synthesis of purine nucleosides of aldoses and ketoses has been developed, by a method involving treatment of an appropriately protected sugar derivative having a free anomeric hydroxy-group with 6-chloropurine, diethyl azodicarboxylate, and methyldiphenylphosphine.

RESEARCH into the chemical syntheses and transformations of nucleosides is currently very active,[1] particularly in view of the utility of many nucleosides as biochemical tools and therapeutic agents.[2] Most of the chemical syntheses have involved condensations using polyacylated sugars or poly-*O*-acylglycosyl halides, although there have been a few

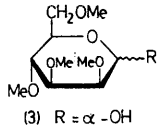


(A)

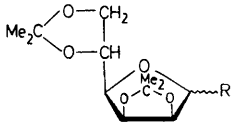
reports of condensations using unprotected sugars;[3] however, these latter reactions mostly give complex mixtures and low yields of nucleosides.[4,†] We report here a novel, convenient synthesis of purine nucleosides of aldoses and ketoses by treatment of an appropriately protected sugar derivative having a free anomeric hydroxy-group with 6-chloropurine, diethyl azodicarboxylate, and methyldiphenylphosphine.



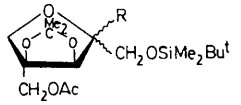
(1) R = α-OH
(2) R = β-(6-chloropurin-9-yl)



(3) R = α-OH
(4) R = β-(6-chloropurin-9-yl)
(5) R = α-(6-chloropurin-9-yl)



(6) R = α-OH
(7) R = β-(6-chloropurin-9-yl)
(8) R = α-(6-chloropurin-9-yl)



(9) R = OH
(10) R = 6-chloropurin-9-yl

The betaines (A)[5] formed from trivalent organophosphorus compounds and dialkyl azodicarboxylates have been found to be highly reactive and useful intermediates in organic synthesis[6] and in the carbohydrate field.[7] We have extended the method to the chemical synthesis of nucleosides.

† A. Holý and F. Šorm (*Coll. Czech. Chem. Comm.*, 1969, **34**, 3383) have described a synthesis of several nucleosides by the condensation of the sodium salts of bases with the free sugar derivative 2-*O*-*p*-tolylsulphonyl-5-*O*-trityl-L-arabinose (prepared in six steps from L-arabinose); however, these reactions may involve the intermediacy of 1,2-anhydro-5-*O*-trityl-L-ribofuranose.

To a solution of 6-chloropurine (1 mmol) in dry tetrahydrofuran (10 ml) were added $MePh_2P$ (1 mmol) and diethyl azodicarboxylate (1 mmol); the sugar derivative (1 mmol) was then added to the solution, and the mixture was kept at room temperature. The reactions were monitored by t.l.c.; when the reaction had ceased, further reagents (0·3 mol of each) were added. After *ca.* 12 h reaction, usually, starting material could not be detected. The reaction mixture was then concentrated to dryness, and the product was isolated by chromatography on silica gel.

The results with four representative substrates are given in the Table. All the product nucleosides gave elemental analyses and n.m.r. spectra consistent with the assigned structures; the u.v. absorption maximum at 263—265 nm is in agreement[3] with a 9-substituted purine. The distribution of anomers in the case of the reaction with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**3**) is noteworthy, since it has been reported[9] that the reaction of 2,3:5,6-di-*O*-isopropylidene-α-mannofuranosyl chloride with chloromercuri-6-benzamidopurine afforded a **39**:**14** mixture of α- and β-anomers, respectively, of 6-benzamido-9-(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)purine. The preparation of 6-chloro-9-[4-*C*-(acetoxymethyl)-3,4-*O*-isopropylidene-1-*O*-(t-butyldimethylsilyl)-DL-*erythro*-pentulofuranosyl]purine in 48% yield from the branched-chain ketose derivative (**4**)[10] is particularly significant, since it represents one of the rare examples of a nucleoside derivative of a ketose.

TABLE. Synthesis of nucleosides

Substrate	Product[a]	Yield (%)	$[\alpha]_D$/degrees[b]	M.p./°C	λ_{max} (EtOH)/nm	τ (1′-H)[c]	$J_{1',2'}$/Hz
(**1**)	(**2**)	66	− 3	122—123	263 (ε 9770)	4·40	9
(**3**)	(**4**)	34	+16	208—208·5	265 (ε 5670)	4·25	*ca.* 2
	(**5**)	37	+38	d	265 (ε 9620)	4·02	8
(**6**)	(**7**)	63	+22	158—159	264 (ε 8270)	3·85	3·5
	(**8**)	16	−17	99—101	265 (ε 7650)	3·95	<0·5
(**9**)	(**10**)	48	—	d	263 (ε 6280)	—	—

[a] All the product nucleosides gave elemental analyses consistent with the assigned structures. [b] Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter in $CHCl_3$ (*c ca.* 1·2). [c] N.m.r. spectra were determined in $CDCl_3$ at 60 MHz. [d] Syrupy product.

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