Nucleosides LVII. A Simplified Method for the Synthesis of Pyrimidine Nucleosides (1,2)

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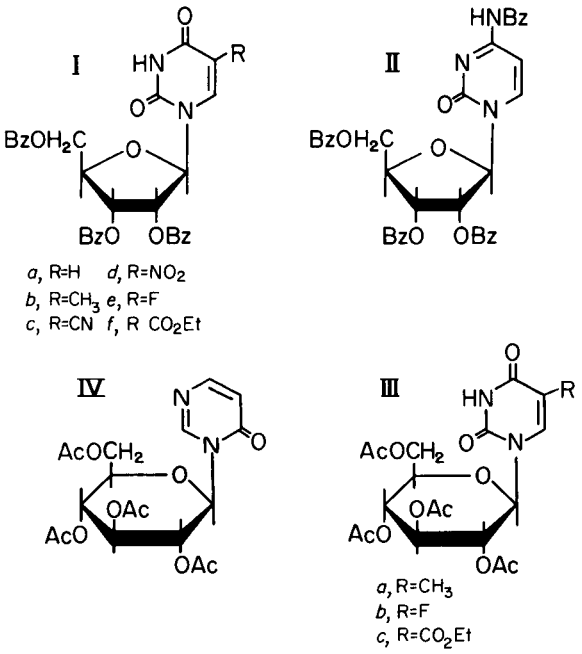
Although several methods are available for the synthesis of pyrimidine nucleosides, it is still of importance to devise simple procedures which will afford nucleoside derivatives in high yields. The commonly used mercuripyrimidine method (3) has now been significantly improved. Pyrimidine nucleosides may now be obtained easily in high yields by condensation of a pyrimidine directly with a poly-*O*-acylglycosyl halide in nitromethane in the presence of mercuric cyanide.

The mercuric cyanide-nitromethane modification was first introduced by Helferich *et al.* (4) to improve the yields of glycosides in the Koenigs-Knorr reaction. Later this reagent-solvent combination was adapted to the synthesis of certain purine and benzimidazole nucleosides (5) and to the synthesis of fully acylated 1-β-D-glucopyranosyl- (5) and 1-α-L-arabinofuranosyl-N^4-benzoylcytosine (6).

The mercuric cyanide-nitromethane modification has several inherent advantages. Prior isolation of mercuri derivatives of pyrimidines is not necessary. The reaction mixture becomes homogeneous during the reflux period. Also to be noted is the fact that high yields of blocked nucleoside products are obtained from pyrimidines bearing strongly electronegative substituents at C-5. Some of these products (*e.g.* Id) are not easily obtainable by alternative methods. Even uracil - which does not give a nucleoside product in a standard mercuri synthesis (3) - affords a 77% yield (Table 1) of blocked nucleoside (Ia) by use of mercuric cyanide-nitromethane reagent.

Table 1 lists the blocked nucleoside derivatives prepared by this method. The structures of the blocked nucleoside products were established either by direct comparison (m.p., mixed m.p., u.v. and nmr spectra) with authentic samples previously prepared in this laboratory or by deacylation to the free nucleosides all of which are reported in the literature. A standard procedure applicable to all these nucleoside preparations in Table 1 using the mercuric cyanide-nitromethane modification is described below in the synthesis of tri-*O*-benzoyluridine (Ia). For the syntheses of III and IV, tetra-*O*-acetyl-α-D-glucopyranosyl chloride was employed.



EXPERIMENTAL

1-(Tri-*O*-benzoyl-β-D-ribofuranosyl)uracil (Ia).

A suspension of uracil (1.2 g., 0.01 mole) and mercuric cyanide (5 g., 0.02 mole) in nitromethane (1000 ml.) was dried by azeotropic distillation of approximately 200 ml. of the solvent. To the stirred suspension was added dropwise 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride [prepared (3) from 10.5 g. (0.02 mole) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose] dissolved in nitromethane (20 ml.). The mixture was refluxed (***caution:*** use hood) for 6 hours and the solvent was slowly distilled off together with hydrogen cyanide which was liberated during the condensation reaction. During this reflux period the reaction mixture became homogeneous. The solvent was removed *in vacuo* and the residue was extracted with chloroform (300 ml.). The chloroform solution was washed with 30% aqueous potassium iodide and with water and the organic layer dried over sodium sulfate. After removal of solvent *in vacuo*, a syrup was obtained. Seed crystals of Ia were obtained as follows: A small amount of the syrup was dissolved in a benzene-ether mixture (1:1) and the solution was adsorbed on a silica gel column. The column was washed with a 1:1 mixture of benzene and ether to remove unreacted sugar derivatives after

TABLE I

Yields of Poly-*O*-acylated Pyrimidine Nucleosides Obtained by the Mercuric Cyanide-Nitromethane Procedure

Pyrimidine used	Nucleoside	Ref.	% Yield	M.P. (°C)	Formula (a)
Uracil	Ia	(7)	77	140-142 (b)	–
Thymine	Ib	(3)	85	164-165 (b)	–
5-Cyanouracil	Ic	(8)	70	205-207 (c)	$C_{31}H_{23}N_3O_9$
5-Nitrouracil	Id	(8b)	80	183-184 (d)	$C_{30}H_{23}N_3O_{11}$
5-Fluorouracil	Ie	(10)	88	210-211 (b)	–
5-Carbethoxyuracil	If		30	190-193 (e)	$C_{33}H_{28}N_2O_{11}$
N^4-Benzoylcytosine	II	(12)	77	207-208 (f)	$C_{37}H_{29}N_3O_9$
Thymine	IIIa	(3)	87	156-158 (b)	–
5-Fluorouracil	IIIb	(13)	65	156-157 (g)	$C_{18}H_{21}FN_2O_{11}$
5-Carbethoxyuracil	IIIc		85	208-209 (h)	$C_{21}H_{26}H_2O_{13}$
4-Oxopyrimidine	IV	(15)	52	212-213 (i)	$C_{18}H_{22}N_2O_{10}$

(a) Satisfactory elemental analyses were obtained for all compounds with formulae listed. (b) Undepressed by admixture with an authentic sample. (c) Ref. (8a) reports m.p. 185°; Ref. (8b) reports m.p. 208-211°. (d) Ref. (8b) reports m.p. 178-180°. The free nucleoside is known (9). (e) Uridine 5-carboxylic acid has been reported (11). (f) Ref. (12a), m.p. 203°; Ref. (12b), m.p. 208-209°. (g) Ref. (13), m.p. 146-150°. (h) 1-β-D-glucopyranosyl-5-carbethoxyuracil has been reported (14). (i) Reported (15) m.p. 209-210°.

which the product was eluted from the column with an ethyl acetate-ethanol (20:1) solution. The eluate was evaporated to dryness and the residue was crystallized from ethanol. The syrup obtained by concentration of the chloroform solution was dissolved in hot ethanol, and the solution was seeded with these crystals. Crystalline Ia thus obtained was recrystallized from ethanol, 2.3 g. (77%), m.p. 140-142°, undepressed by admixture with authentic material (7). The ultraviolet and nmr spectra of this material were identical with those of authentic Ia.

The nucleosides prepared from the various pyrimidine bases, mercuric cyanide and a sugar halide, using the same molar proportions and procedure as described for Ia, are listed in Table 1.

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