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SYNTHESIS OF 5-(D-RIBOFURANOSYL)-6-AZAURACIL

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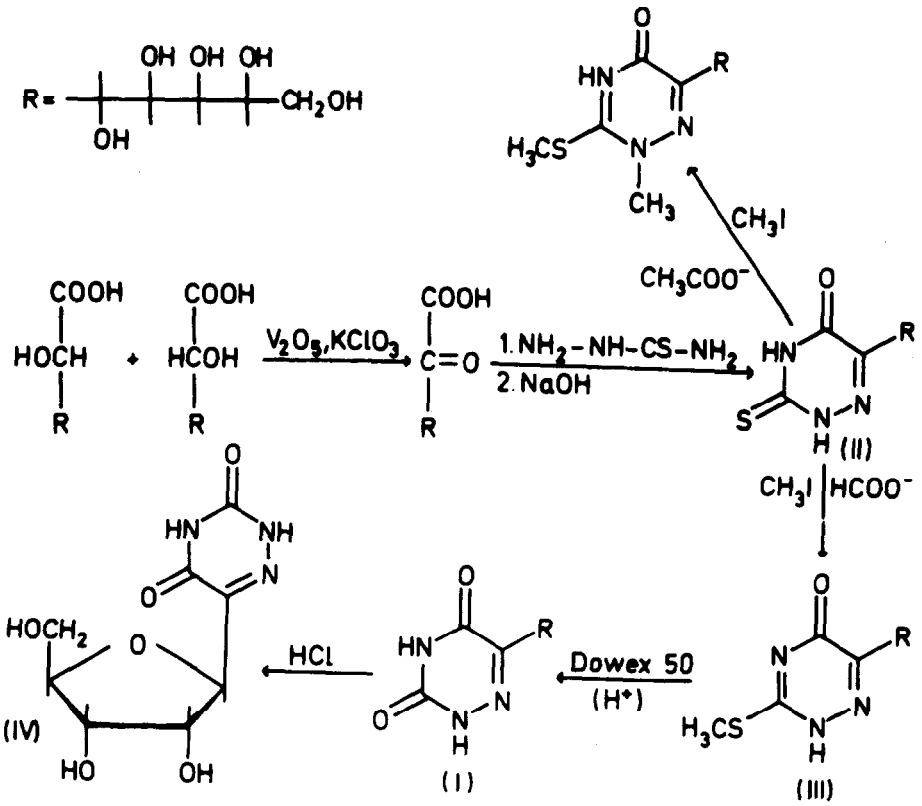
In connection with an investigation of the biological activity of 6-aza-analogues of natural pyrimidine nucleosides it appeared to be of interest to prepare 6-azapseudouridine.

In the synthesis we proceeded from 5-(D-altro-pentahydroxypentyl)-6-azauracil (I) as a key intermediate compound which was prepared by the same procedure as the one used previously for the synthesis of 5-hydroxymethyl-6-azauracil[1] and some 5-(tetrahydroxybutyl)-6-azauracils[2]. We started from D-altroheptulosonic acid prepared by oxidizing a mixture[3] of D-glycero-D-mannoheptonic acid and D-glycero-D-glucoheptonic acid with sodium chlorate and vanadium pentoxide in acid medium[4,5]. D-Altroheptulosonic acid was isolated from the reaction mixture as a sirup from Dowex 1 (acetate form). Treatment with thiosemicarbazide converted it to the thiosemicarbazone which was directly cyclized by treating with 1 N sodium hydroxide at 65° to yield 6-(D-altro-pentahydroxypentyl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (II). M.p. 209-210.5° (water); λ_{max} 266 mμ (water); α_D^{20} -127.5° (c 0.2 in water). Methyl iodide in aqueous solution converts compound II in the presence of Dowex 1

(formiate form) at 20° to 6-(D-altro-pentahydroxypentyl)-3-methylmercapto-2,5-dihydro-1,2,4-triazine-5-one (III) which, on account of its poor stability in aqueous solution was characterized only by its chromatographic behaviour. Compound III is readily hydrolyzed by applying Dowex 50 (H^+) to yield the desired product I.M.p. 204-205.5° (acetic acid-ethyl-acetate); λ_{max} 261 mu (water); α_D^{20} -69.3° (c 0.2 in water). The action of methyl iodide on compound II in aqueous solution in the presence of Dowex 1 (acetate form) afforded 6-(D-altropentahydroxypentyl)-2-methyl-3-methylmercapto-2,5-dihydro-1,2,4-triazine-5-one as the sole product. M.p. 172.5-174° (acetic acid-ethyl acetate); λ_{max} 236 mu(water); α_D^{20} -128.5° (c 0.2 in water).

Compound I, when heated in 10% hydrochloric acid for 9 hours, was converted into anhydro-derivative IV which on the basis of elemental analysis, course of oxidation with periodic acid and electrophoretic mobility in neutral borate buffer, is ascribed the structure of 5-(D-ribofuranosyl)-6-azauracil. M.p.182-183.5° (acetic acid-ethyl acetate); λ_{max} 260 mu; α_D^{20} -122.9° (c 0.2 in water). Assignment of configuration at the anomeric center of compound IV has not been attempted. From the analogy with the mechanism of acid-catalyzed cyclisation of phenylosotriazols to 3,6-anhydro-phenyltriazols[6,7] it may be assumed that the cyclization of compound I yields the anomer in which the 6-azauracil nucleus is situated in trans-position to the vicinal hydroxylic group.

Elemental analyses of all the compounds described are in good agreement with the calculated values.


R=
OH OH OH
CH2OH
OH
COOH
HOCH
R
COOH
HCOH
R
V2O5,KClO3
COOH
C=O
R
1. NH2-NH-CS-NH2
2. NaOH
CH3I
CH3COO⁻
CH3I
HCOO⁻
HCl
Dowex 50
(H⁺)
HOCH2
(IV)
HO
OH
(I)
(II)
(III)

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