Synthesis of 4-Amino-6-glycosylpyrazolo[3,4-*d*]pyrimidines†

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Summary Benzyl glycosylthioformimidate reacts with 3-aminopyrazole-4-carbonitrile to yield 4-amino-6-glycosylpyrazolo[3,4-*d*]pyrimidine.

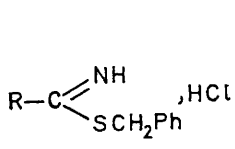
4-AMINOPYRAZOLO[3,4-*d*]PYRIMIDINE is active against Adenocarcinoma 755 and shows definite activity with **6**-mercaptopurine against other experimental tumours.[1] Moreover, its 6-alkyl derivatives have broad antibacterial activity.[2]

In connection with our work on *C*-nucleoside analogues, we wished to prepare a series of 4-amino-6-glycosypyrazolo-[3,4-*d*]pyrimidines as potential purine antagonists.

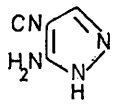
Known methods for the preparation of 6-substituted pyrazolo[3,4-*d*] pyrimidines are laborious with poor overall yield[3] or require drastic conditions[4] and therefore cannot be used in carbohydrate chemistry. A new approach, using much milder conditions has been developed from the key intermediate thioformimidates (**1**) which are quantitatively obtained from the corresponding cyano-1-glycosides[5] by a modified Pinner reaction. We have already described the condensation of the benzyl thioformimidate (**1a**) with α-aminonitriles forming amino-5-imidazoles[6]. A similar cyclisation with the pyrazole (**2**) (in refluxing of a pyridine–$CHCl_3$) gives in one step the fused pyrimidines (**3a**—**c**) (60%). The structure of these products was assigned on the basis of analyses, the absence of a nitrile function (i.r.), the u.v. spectra [λ_{max} (pH 1 265 (ε 9000), (pH 13) 268 (λ 8000), and 284 (5400) nm (shoulder)], and by analogy with a model reaction of the benzyl thioacetimidate (**1g**) with (**2**) which gives the previously reported pyrimidine (**3g**).[3,4]

The ribofuranosyl series gives only the β-anomer whilst the arabinosyl and 2-deoxy-D-erythropentofuranosyl series

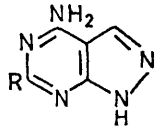
† For previous paper in the series: 'Synthesis of *C*-nucleosides, see: A. Kolb, C. Gouyette, T. Huynh Dinh, and J. Igolen, *Tetrahedron Letters*, 1973, 2971.



(1)

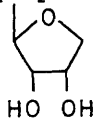


(2)

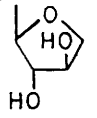


(3)

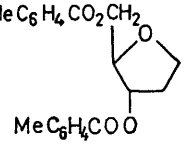
a; R = $PhCO_2CH_2$



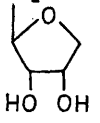
b; R = $PhCO_2CH_2$



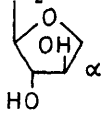
c; R = $MeC_6H_4CO_2CH_2$



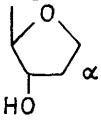
d; R = $HOCH_2$ β



e; R = $HOCH_2$ β



f; R = $HOCH_2$ β



g; R = Me

give the α- and β-anomers which can be separated by chromatography on silica gel {m.p. ($[\alpha]_D$): **(3a)**-β 136 °C (−5°); **(3b)**-α 243 °C (+44°); **(3c)**-α 200 °C (+43°); **(3c)**-β 219 °C (−26°)}. The protecting groups are readily removed by saturated methanolic ammonia at room temperature. Compounds **(3d—f)** are the first synthetic *C*-nucleosides described containing a C–C bond to a pyrimidine ring {m.p. ($[\alpha]_D$): **(3d)**-β 246 °C (−51°); **(3e)**-α 252 °C (+22°); **(3f)**-α 284 °C (+38°); **(3f)**-β 227 °C (+10°)}, and are structurally related to the antitumoral antibiotic formycin A.[7] Although no attempt has been made to optimise the yields obtained, the ease with which the reaction can be carried out makes this a valuable method for the preparation of fused pyrimidine heterocycles from aromatic *ortho*-aminonitriles.

All crystalline compounds gave analytical and spectral data (n.m.r., mass spectra) which were in accord with the proposed structures. Their biological evaluation will be reported elsewhere.

We thank the D.G.R.S.T. and the C.N.R.S. (A.T.P. 1972) for financial support.

(*Received*, 18*th June* 1973; *Com.* 870.)

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