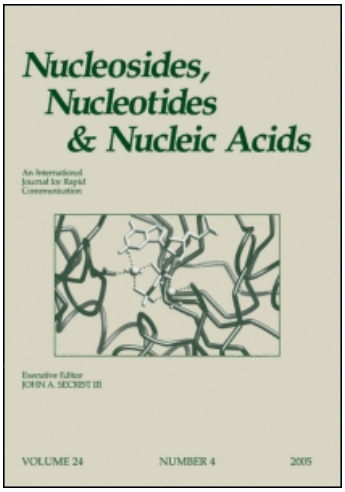

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NOVEL SYNTHESIS OF A 2,5'-O-CYCLOIMIDAZOLE NUCLEOSIDE

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Abstract: A novel conversion of ethyl 5-amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxylate (2) to the corresponding 2,5'-cyclo derivative (4) occurs with alkaline hypobromite or N-chlorosuccinimide and alkali.

As part of a project designed to prepare inhibitors of enzymes involved in the de novo biosynthesis of purine nucleotides we earlier recorded[1] two syntheses and a preliminary enzyme inhibition study[2] of ethyl 5-amino-2-bromo-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazole-4-carboxylate (1). The best preparation of (1) (65% yield) involved the reaction of ethyl 5-amino-1(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxylate (2) with N-bromacetamide in dry THF at -65°C. A second preparation involving the reaction of (2) with bromine in aqueous disodium hydrogen phosphate and dioxan at 0-5°C gave a lower (20%) yield. In a separate unrecorded experiment we carried out the latter reaction at room temperature and with a higher concentration of the phosphate, and the crude product, assumed (on the basis of TLC) to be largely (1) was condensed with silver fluoride[3] in hot DMF in the hope of producing the 2-fluoroimidazole (3). Evaporation of the clarified solution however gave a crystalline halogen-free compound which gave a positive Bratton-Marshall test[4] and had a UV absorption spectrum characteristic of an aminoimidazole nucleoside. We assign the 2,5'-O-cycloimidazole nucleoside structure (4) to the compound and this is confirmed by elemental analysis and the mass spectrum (M^+325, aglycone peak m/z 154).

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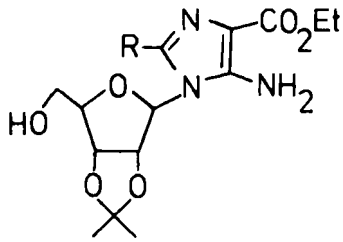
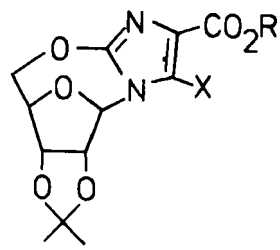




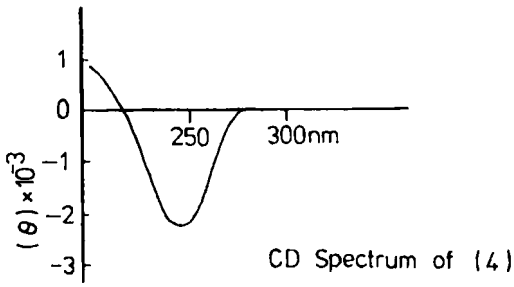
(1) R = Br
(2) R = H
(3) R = F
(6) R = Cl

(4) R = Et, X = NH_2
(5) R = Me, X = H

The CD spectrum (FIG 1) showed a marked negative Cotton effect similar to that of (2) and the 2,5'-O-cycloimidazole nucleoside[5] (5). In addition the ^{1}H NMR spectrum of the compound had no peak near δ 7.5 ppm corresponding to absence of H-2 but showed a singlet at δ 5.74 (H-1') and geminal coupling of the 5'-protons.

When the product produced in the last mentioned bromination reaction was re-examined by TLC in a variety of solvents it was found to be a mixture of (1) and (4) which have very similar R_F values in most systems. Apparently treatment of the mixture with silver fluoride under the forcing conditions used served merely to decompose (1) leaving a relatively pure sample of (4). This was confirmed by treatment of a pure specimen of (1) with silver fluoride under the same conditions when compound (4) was not produced. Similarly when (1) was heated with bases there was no evidence for formation of any cyclonucleoside.

A possible mechanism for the production of (4) would involve prior formation from (2) of the hypobromite (7) followed by a nucleophilic intramolecular attack at C-2 of the imidazole ring. (FIG. 2). Since alkyl hypobromite formation is favoured at high pH then it would be reasonable to expect cyclonucleoside formation to be favoured also at high pH. This was confirmed by reaction of (2) with N-chlorosuccinimide and a slight excess of M-potassium hydroxide in THF. Column



CD Spectrum of (4)

FIG 1

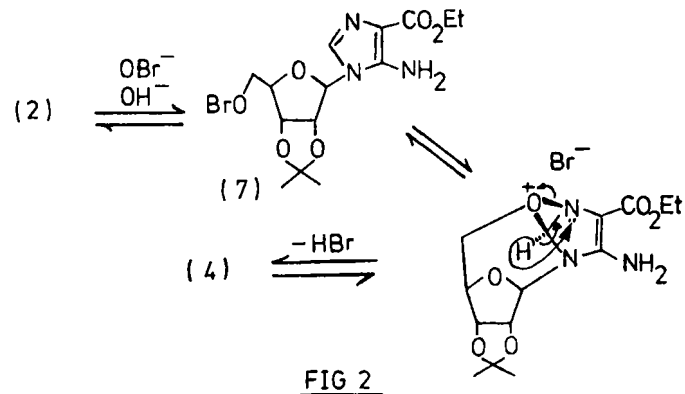


FIG 2

chromatography of the reactants on silica gel gave the crystalline cyclonucleoside (4) (32% yield), identical (m.p., mixed m.p., IR, ^{1}H-NMR) to the compound prepared earlier. The starting material (2) was also recovered (58% yield) together with a small amount (2%) of ethyl 5-amino-2-chloro-(2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazole-4-carboxylate (6).

Extension of the reaction to other imidazole nucleosides will be reported elsewhere.

Experimental

Ethyl 5-amino-2,5'-cyclo-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazole-4-carboxylate (4).

(a) Ethyl 5-amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazole-4-carboxylate (1.1 g, 3.3 mmol) was dissolved in a mixture of 'peroxide free' dioxane (45 ml) and 10% aqueous disodium phosphate (45 ml). Bromine (0.53 g, 3.3 mmol) in dioxane (3 ml) was added dropwise with shaking and the mixture was set aside for ca. 6 h. TLC examination (silica gel, $CHCl_3$:MeOH:9:1) showed a Bratton-Marshall active spot (R_F 0.60) and starting material (R_F 0.54). The solution

was extracted with chloroform (3 x 30 ml), the extract dried (anh. Na_2SO_4) and evaporated to a gum (0.9 g). A solution of the residue in chloroform (5 ml) was applied to a silica gel column (3 x 60 cm). The product (R_F 0.60) was eluted by methanol:chloroform (1:100) and the starting material (R_F 0.57) by methanol:chloroform (3:100). The fractions were separately evaporated. The recovered crystalline imidazole nucleoside (2) (300 mg 27%) had m.p. and mixed m.p. 152-4°C. The product (R_F 0.60) was obtained as a white brittle foam (250 mg). Finely divided silver fluoride (3 g) was added to a solution of the foam in DMF (15 ml). The mixture was stirred and refluxed with the exclusion of moisture for 1.5 h. The silver salts were removed by filtration and the filtrate evaporated to a dark brown gum. TLC examination (silica gel; $CHCl_3$:MeOH:9:1) of the gum showed one Bratton-Marshall active spot (R_F 0.60). A solution of the gum in chloroform (1 ml) was applied to a silica gel cclumn which was eluted with CH_3OH:$CHCl_3$ (3:100). The fraction containing the product was evaporated to a gum which crystallised slowly from methanol to give the cyclonucleoside as needles (80 mg, 9%) m.p. 221°C. It had $[\alpha]_D^{-20}$ - 23° (C, 1.0% in DMSO), UV (in methanol) λ_{max} 272 nm (ε13,980). The mass spectrum showed M^+325 and an aglycone peak at m/z 154. The ^{1}H NMR spectrum (100 MHz $CDCl_3$) had δ (ppm from Me_4Si), 1.36 (s, 3H, exo-CMe), 1.36 (t, 3H, $CO_2CH_2CH_3$, J 7 Hz), 1.56 (s, 3H, endo-CMe), 4.03, (d, 1H, 5'-H, J 12 Hz), 4.32 (q, 2H, CO_2CH_2, J 7 Hz), 4.3 (d, 1H, 5'-H), 4.66 (bs, 1H, 4'-H), 4.86 (d, 1H, 3'-H, J 6 Hz), 5.08 (d, 1H, 2'-H, J 6 Hz), 5.74 (s, 1H, 1'-H). The product did not contain bromine or fluorine.

Anal. Calcd. for $C_{14}H_{19}N_3O_6$: C, 51.7; H, 5.85; N, 12.9. Found: C, 51.8; H, 5.95; N, 12.8.

(b) A solution of (2) (0.5 g) in peroxide-free THF (15 ml) was shaken with N-chlorosuccinimide (0.41 g) and M-potassium hydroxide (2.3 ml) then set aside over three days at room temperature. The mixture was evaporated in vacuo and the residual gum chromatographed on a silica gel column using toluene:ethyl acetate (3:7) as the eluting solvent to yield the cyclonuclecside (0.16 g, 32%), (2) (0.29 g, 58%) and a small amount (12 mg, 2%) of ethyl 5-amino-2-chloro-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxylate (6) as a glass, the mass spectrum of which showed M^+361 (363). The ^{1}H-NMR spectrum (100MHz,

$CDCl_3$) had δ (ppm from $MeSi_4$), 1.30 (t, 3H, $CO_2CO_2C\underline{H}_3$), 1.36 (s, 3H, exo-CMe), 1.55 (s, 3H, endo-CMe) 3.69 (m, 2H, 5'-H), 4.25 (q and m, 3H, $CO_2C\underline{H}_2$ and 4'-H), 4.72 (m, 1H, 2'-H), 5.14 (m, 1H, 3'-H), 5.72 (br., 1H, 1'-H), 7.60 (bs., 1H, OH exch. with D_2O).

REFERENCES

1. G. Mackenzie and G. Shaw, J. Chem. Research (S), 184 (1977); (M) 2145, (1977).
2. G. Mackenzie, G. Shaw and S.E. Thomas, J.C.S. Chem. Commun., 453 (1977)
3. A.E. Beaman and R.K. Robins, J. Amer. Chem. Soc., 85, 242 (1963).
4. C. Bratton, D. Babbitt, A.R. Hendrickson and E.K. Marshall, J. Biol. Chem., 128, 537, (1939).
5. H. Tanaka, J. Takachachi, H. Togashi and T. Ueda, Chem. Pharm. Bull., 26, 3322 (1978).

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