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Preliminary communication

Synthesis of 8-β-D-ribofuranosylpyrazolo[1,5-*d*]-1,2,4-triazin-4(3*H*)-one, an inosine *C*-nucleoside analog

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Some *C*-nucleoside antibiotics, such as the formycins, pyrazomycin, and showdomycin, which possess carbon–carbon bonds between the sugar and the base[1,2], have shown interesting antineoplastic, antiparasitic, and antiviral properties. Recently, Fox *et al.*[3] described the synthesis of an inosine analog, namely, a ribofuranosylpyrazolo-[1,5-*a*]-1,3,5-triazinone nucleoside, that showed some interesting antitumor properties. We now describe the synthesis of another inosine analog, namely, 8-β-D-ribofuranosylpyrazolo[1,5-*d*]-1,2,4-triazin-4(3*H*)-one (**8**).

Because the pyrazolotriazinone ring of the parent base of the target compound **8** can be formed by the action of base on the (ethoxycarbonyl)hydrazone of pyrazole-3-carboxaldehyde[4], we reasoned that, if we could prepare the hitherto-unknown 4-β-D-ribofuranosylpyrazole-3-carboxaldehyde, we could cyclize it in the same way, and thus obtain the desired *C*-nucleoside.

The starting ethyl propiolate derivative (**1**) of D-ribose was prepared by the method of Fox *et al.*[5]. However, it was found advantageous to use some trialkylamine in order to solubilize the silver propiolate. This enabled us to complete the reaction overnight, instead of in the 10 days needed by Fox and co-workers. Reaction of the acetylenic ester **1** with diazomethane gave, after chromatographic separation to remove some undesired 1-methylpyrazole, the desired pyrazole ester (**2**). This was reduced with lithium aluminum hydride in oxolane to the crystalline pyrazolecarbinol (**3**) in 60% yield from ester **1**; m.p. of **3**, 164–165°; ^{1}H-n.m.r.: δ 1.28 and 1.53 (2 s, 6 H, CMe_2), 3.33 (m, 2 H, H-5′), 4.27 (m, 1 H, H-4′), 4.63 (m, 2 H, H-2′, 3′), 4.70 (s, 2 H, CH_2OH), 5.00 (broad s, 1 H, H-1′), and 7.2-7.7 (m, 16 H, trityl and H-5).

The primary alcohol **3** was readily oxidized with pyridinium dichromate in dichloromethane[6], but the yield of pyrazolealdehyde (**4**) isolated never exceeded 25%, even though all of the starting material had reacted (t.l.c.). The glassy product had a persistent, brown tint, and n.m.r. spectroscopy showed the presence of some paramagnetic material.

This route was later abandoned in favor of direct reduction of the acetylenic ester **1** to aldehyde **5**. It was at first presumed that this reduction, conducted with diisobutylaluminum hydride (DIBAL), would result in reduction of the triple bond, instead of reduction of the ester group[7]. However, when the α-D-ribosyl acetylenic ester (**9**) was

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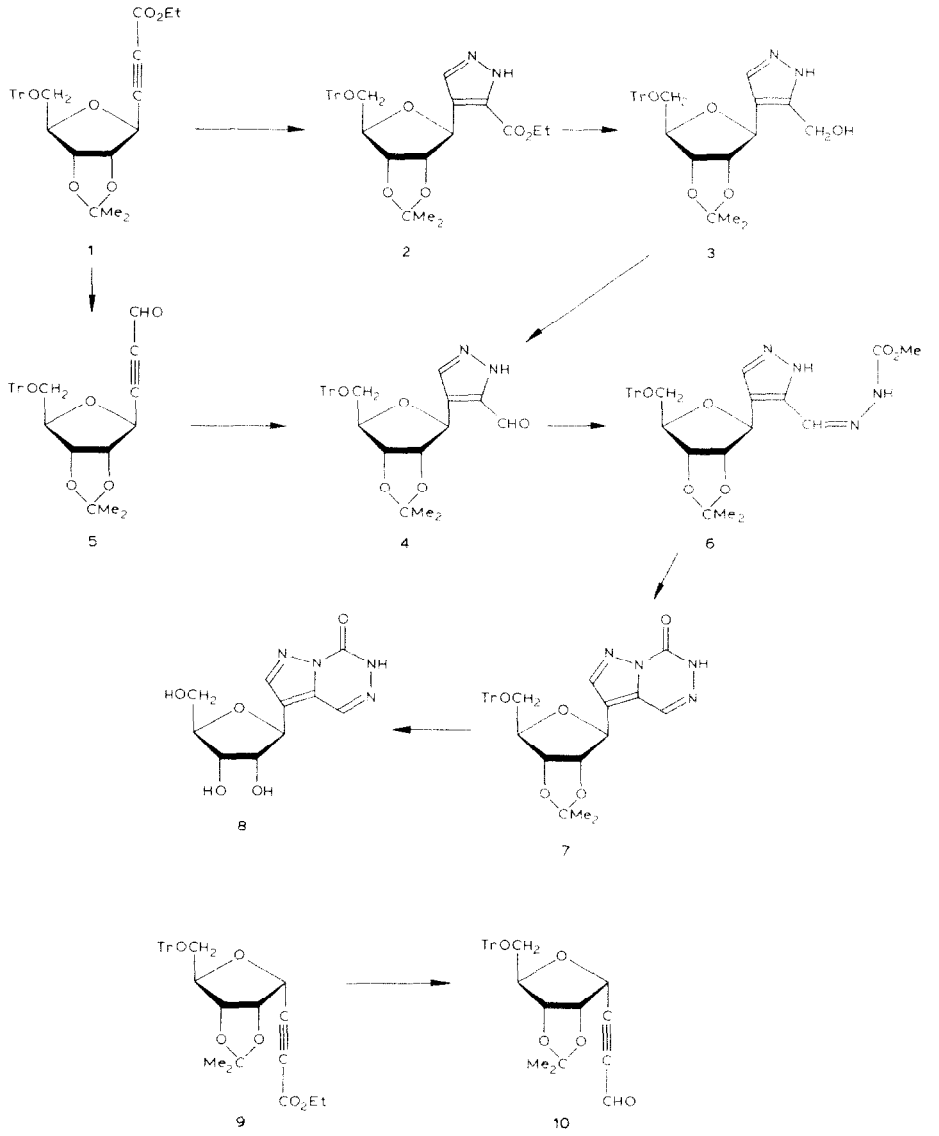

treated with DIBAL in dry toluene at −78°, crystalline, α-D-ribosyl acetylenic aldehyde (**10**) was isolated in 95% yield; m.p. 127-5–129°; ν_{max}^{KBr} 2750, 2240, and 1670 cm^{-1}; ^{1}H-n.m.r.: δ 9.17 (s, 1 H, aldehyde). The ethyl propiolate derivative (**1**) of D-ribose was then treated with one equivalent of diisobutylaluminum hydride in toluene at −78°, and after 30 min, all of the starting material had disappeared. Processing gave the acetylenic aldehyde **5** as a syrup in >90% yield; ν_{max}^{neat} 2740, 2260, and 1670 cm^{-1}; ^{1}H-n.m.r.: δ 1.32 and 1.48 (2 s, 6 H, CMe_2), 3.25 (d, 2 H, $J_{7,8}$ 5 Hz, H-8), 4.37 (m, 1 H, H-7), 4.77 (m, 3 H, H-4–6), 7.10–7.47 (15 H, trityl), and 8.90 (s, 1 H, H-1). A precursor of com-

pound **5**, lacking the trityl group, was prepared by Baggett *et al.*[8] in 5% yield by hydrolysis of the corresponding 1,1-diethoxypropyne derivative of D-ribose.

The acetylenic aldehyde **5** was immediately treated with diazomethane, to give the pyrazolealdehyde (**4**) as a solid foam in 50% yield (based on the ester); chromatographic separation was, however, needed, in order to remove some 1-methylpyrazole formed as a by-product; ^{1}H-n.m.r.: δ 7.80 (s, 1 H, pyrazole) and 10.0 (s, 1 H, aldehyde). The pyrazolealdehyde was then treated with an excess of methyl hydrazinocarboxylate, to afford the syrupy hydrazone **6** in quantitative yield; ^{1}H-n.m.r.: δ 3.65 (s, 3 H, OCH_3), 7.58 (s, 1 H, pyrazole), and 8.17 (s, 1 H, CH=N). Finally, the pyrazolotriazinone ring was closed by treating hydrazone **6** with cesium carbonate in refluxing ethanol, giving, first, an ethyl hydrazone formed by transesterification with the solvent. This intermediate was slowly converted into the blocked pyrazolotriazinone **7**; ^{1}H-n.m.r.: δ 8.10 (s, 1 H, pyrazole), 8.38 (s, 1 H, triazine), and 10.2 (bs, 1 H, NH). The nucleoside **7** was deblocked with 10% hydrogen chloride in methanol, and the product (**8**) crystallized from ethanol in 25% yield (based on aldehyde **4**); m.p. 199–201°; ^{1}H-n.m.r. (Me_2SO-d_6): δ 8.17 (s, 1 H, H-7), 8.57 (s, 1 H, H-1), and 12.75 (bs, 1 H, NH).

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