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SYNTHESIS OF 1-β-(3-PHENYLPYRAZOL-4-YL)-D-RIBOFURANOSIDE, A C-NUCLEOSIDE

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1-β- and 1-α-(3-Phenylpyrazol-4-yl)-D-ribofuranosides (7) and (8) have been prepared from 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (1) through ethynylation with mercuric phenylacetylide (2) and subsequent 1,3-dipolar addition of diazomethane, followed by removal of the protecting groups with ammonia.

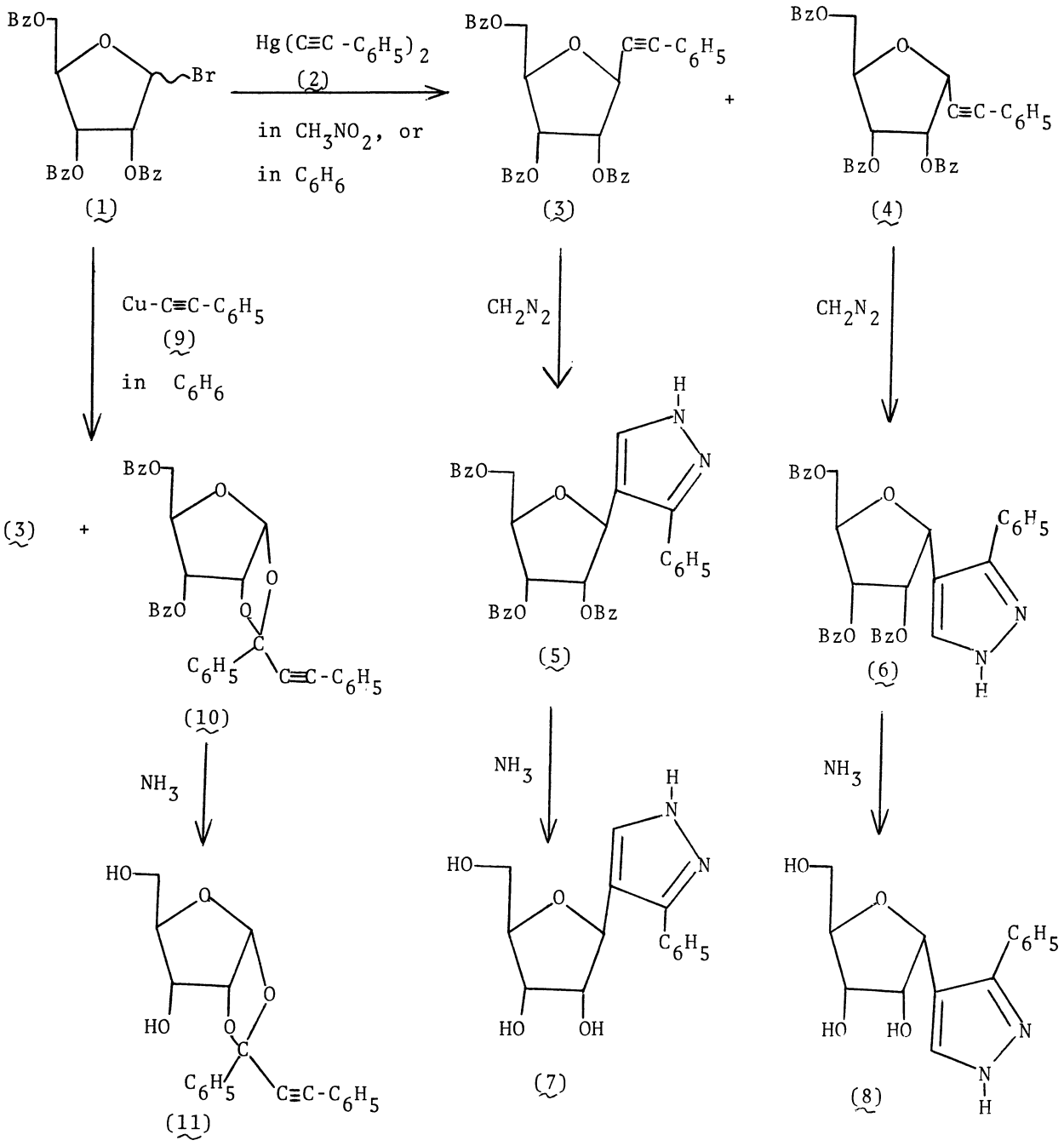
Recent publications on the structure and carcinogenic activity of formycin-A and -B, [1] pyrazomycin, [2] showdomycin,[3] and oxazinomycin [4] have stimulated synthetical investigations on the preparation of the naturally-occurring compounds as well as the analogous derivatives of C-nucleosides. [5,6,7] As part of our research on the synthesis and properties of pyrazole derivatives, we have been examining to establish general procedures to combine pyrazole-nuclei with furanose to obtain physiologically active materials. The present communication reports on a synthesis of pyrazolylribosides through two major steps: ethynylation of ribose by way of heavy metal process and transformation of the acetylenic linkage into pyrazole nucleus by addition of diazomethane.

Treatment of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (1) with mercuric phenylacetylide (2) [8] in nitromethane or in benzene at 35°C for 5 days furnished, after separation by column chromatography on silica gel, 1-β- and 1-α-phenylethynyl-2,3,5-tri-O-benzoyl-D-ribofuranosides (3)*[36%, amorphous solid, $[\alpha]_D^{20}$ -60.50°(c=0.61 in $CHCl_3$); NMRδ($CDCl_3$): 4.52-4.80(3H,m:H_4,H_5,$H_{5'}$), 5.19(1H,d,$J_{1,2}$ =2.2Hz: H_1), 5.94(2H,m:H_2,H_3), 7.20-7.64(12H,m:aromatic), 7.89-8.20(8H,m:aromatic); IR νmax cm^{-1}($CHCl_3$): 2210(-C≡C-)] and (4)*[17%, m.p.89-91°; $[\alpha]_D^{22}$ +87.9°(c=0.67

in $CHCl_3$); NMR δ ($CDCl_3$): 4.63(2H,m:H_5,$H_{5'}$), 4.75(1H,m:H_4), 5.48(1H,m:H_2), 5.76(2H, m:H_1,H_3), 7.60-7.09(14H,m:aromatic), 7.77-8.12(6H,m:aromatic); IR νmax cm^{-1}($CHCl_3$): 2210(-C≡C-)], which reacted slowly with excess diazomethane in ether at room temperature[9] to give 1-β- and 1-α-(3-phenylpyrazol-4-yl)-2,3,5-tri-O-benzoyl-D-ribofuranosides (5)* [70%, m.p.70-72°; NMR δ($CDCl_3$): 4.66(2H,m:H_5,$H_{5'}$), 4.7›(1H,m:H_4), 5.40 (1H,d,$J_{1,2}$=6.8 Hz:H_1), 5.77(1H,t,$J_{2,3}$ =5.8 Hz:H_3), 5.89(1H,m:H_2), 7.23-8.22(21H,m: aromatic); IR νmax cm^{-1}($CHCl_3$): 3430 (N-H)] and (6)* [66%, m.p.68-70°; NMR δ ($CDCl_3$): 4.70(2H,m:H_5,$H_{5'}$),4.80(1H,m:H_4), 5.58(1H,d,$J_{1,2}$=3.2 Hz:H_1), 5.92(1H,t,$J_{2,3}$ =4.4 Hz:H_3), 6.05(1H,dd, $J_{1,2}$=3.2 Hz, $J_{2,3}$=4.4 Hz:H_2), 7.20-8.04(21H:aromatic); IR νmax cm^{-1}($CHCl_3$): 3430 (N-H)], respectively. Debenzoylation of (5) and (6) was carried out in methanol saturated with ammonia at room temperature to give 1-β- and 1-α-(3-phenylpyrazol-4-yl)-D-ribofuranosides (7) [83%, m.p.92-93°; UV λ max nm (logε)(EtOH): 242.5(3.77); Mass m/e [M^+]: Calcd. for $C_{14}H_{16}O_4N_2$ = 276.1109, Found: 276.1092] and (8) [70%, m.p.103-105°; UVλmax nm (logε)(EtOH): 242.5(3.92); Mass m/e [M^+] Found: 276.1102], respectively.

When cuprous phenylacetylide (9)[10] was applied in stead of the mercuric salt (2), there was obtained 3,5-di-O-benzoyl-1,2-O-(1-phenylethynylbenzylidene)-α-D-ribofuranose (10)* [32%, m.p.105-106°; $[\alpha]_D^{21}$ +34.23°(c=0.38 in $CHCl_3$); NMR δ ($CDCl_3$): 4.40-4.80(3H,m:H_3,H_5,$H_{5'}$), 5.51(1H,m:H_4), 5.32(1H,t,$J_{2,3}$=4.0 Hz:H_2), 6.23(1H,d,$J_{1,2}$ =4.0 Hz:H_1), 7.20-8.12(20H,m:aromatic); IRν max cm^{-1}($CHCl_3$): 2210 (-C≡C-), 1721 (C=O)] in addition to (3). The former benzoate (10) was debenzoylated with ammonia into ketal (11) [76%, m.p.143-145°; UV λ max nm(logε)(EtOH):241.5(4.34), 250(4.25); IRν max cm^{-1}(KBr): 3400(O-H), 2210(-C≡C-); Mass m/e: 338 [M^+], 307 [M-CH_2OH]$^+$].

In contrast to the mercuric cyanide process of the benzoate (1) which affords β-anomeric derivative exclusively,[5,11] the present process with mercuric acetylide produces the both anomers(3) and (4). The major product (3) of the reaction of (1) with the mercuric salt (2) was tentatively assigned as the β-anomer, because in the process with the cuprous salt (9) the only C_1-substituted product was identical with (3). Although the evaluation of the coupling constants of H_1 and H_2 does not offer any satisfactory proof for the determination of the C_1-configuration so far, more detailed discussion based upon the coupling constants of 2,3-isopropylidene derivatives [12] will be published elsewhere.


BzO
Br
BzO OBz
(1)
Hg(C≡C-C6H5)2
(2)
in CH3NO2, or
in C6H6
C≡C-C6H5
(3)
(4)
Cu-C≡C-C6H5
(9)
in C6H6
CH2N2
(5)
(6)
(10)
NH3
HO
HO OH
(7)
(8)
(11)
C6H5
N
H
Bz = -C-C6H5
O

SCHEME

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*) Elemental analyses of these compounds were in agreement with the calculated values within 0.3 %. The authors are grateful to the members of the Central Analysis Room of this school for the elemental analyses.

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