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SYNTHESIS OF TETRAZOLES FROM SOME PER-*O*-ACETYLALDONONITRILES*

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ABSTRACT

Synthesis of 5-(polyacetoxyalkyl)tetrazoles from some acetylated aldononitriles by reaction with ammonium azide is described. Deacetylation of these compounds afforded the corresponding 5-(polyhydroxyalkyl)tetrazoles.

INTRODUCTION

Synthesis of tetrazoles from acid nitriles under a variety of reaction conditions has been widely studied. The formation of 5-alkyl- and 5-aryl-tetrazoles having different substituents has been described in the literature[2], but no 5-(polyhydroxyalkyl)-substituted tetrazoles appear to have been prepared. Aldonic acid nitriles constitute suitable precursors for obtaining tetrazoles of this type; they would allow correlation of steric interactions and, in addition, would permit choice of the steric distribution of the side chain, so that, together with the heterocyclic moiety, the molecule might have the highest pharmacological activity.

During testing of a variety of reaction conditions, it had been found that aldonic acid acetates are much more sensitive to decomposition than the corresponding benzoates, and the optimal reaction conditions for both nitrile esters were found to consist in use of ammonium azide, in *N,N*-dimethylformamide as the solvent, at room temperature[1]. This reaction has now been extended to some per-*O*-acetylated aldononitriles, and the 5-(polyacetoxyalkyl)tetrazoles were obtained in fair yields. Their deacetylation with sodium methoxide in methanol gave the 5-(polyhydroxyalkyl)tetrazoles. The reaction is exemplified for tetra-*O*-acetyl-L-arabinononitrile, from which 5-(tetra-*O*-acetyl-L-*arabino*-tetritol-1-yl)tetrazole (**1**) was obtained in 41% yield; deacetylation of **1** gave 5-(L-*arabino*-tetritol-1-yl)tetrazole (**2**) in 100% yield.

By the same type of reaction, 5-(tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)tetrazole (**3**), 5-(tetra-*O*-acetyl-D-*xylo*-tetritol-1-yl)tetrazole (**5**), 5-tetra-*O*-acetyl-D-*ribo*-tetritol-1-yl)tetrazole (**8**), and 5-(penta-*O*-acetyl-D-*gluco*-pentitol-1-yl)tetrazole (**11**) were obtained.

*Synthesis of Tetrazoles from Acylated Aldononitriles. Part II. For Part I, see ref. 1.
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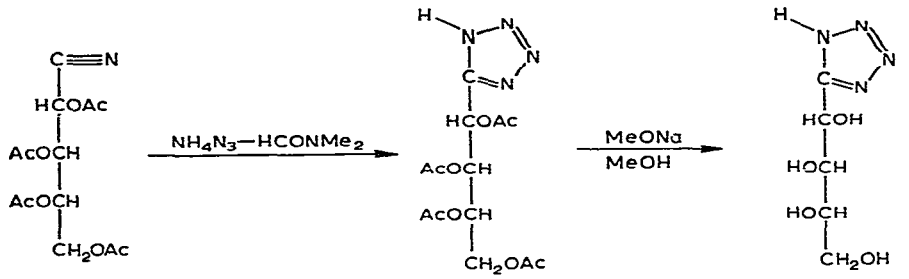

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The following (polyhydroxyalkyl)tetrazoles were prepared from the acetates by treatment with methanolic methoxide: 5-(D-*arabino*-tetritol-1-yl)tetrazole (**4**), 5-(D-*xylo*-tetritol-1-yl)tetrazole (**6**), 5-(D-*ribo*-tetritol-1-yl)tetrazole (**9**), and 5-(D-*gluco*-pentitol-1-yl)tetrazole (**12**).

5-(L-*manno*-1,2,3,4-Tetrahydroxypent-1-yl)tetrazole (**10**) and 5-(D-*manno*-pentitol-1-yl)tetrazole (**13**) were obtained in crystalline form by deacetylation of the corresponding reaction mixtures for the preparation of the 5-(polyacetoxypentyl)-tetrazoles, which were syrups that could not be satisfactorily purified. Acetylation of compound **13** gave 5-(penta-*O*-acetyl-D-*manno*-pentitol-1-yl)tetrazole (**14**) as a chromatographically pure syrup.

EXPERIMENTAL

General procedures. — Thin-layer chromatography (t.l.c.) was performed on plates coated with silica gel G (Merck, Germany), with 19:1 chloroform–methanol as the eluant, and iodine vapor for detection. Melting points are not corrected. The optical rotations were determined at 20°. Ammonium azide was purified by sublimation.

Synthesis of 5-(polyacetoxyalkyl)tetrazoles. — These compounds were prepared by dissolving the acetylated aldononitrile (5 g) in *N*,*N*-dimethylformamide (25–35 ml), and adding ammonium azide (1.2 g). The mixture was kept at room temperature, with occasional shaking, until the ammonium azide had completely dissolved. The reaction was monitored by t.l.c. until the nitrile had disappeared (~7 days). The solution was evaporated under diminished pressure (bath temp. 50°), and the residue was treated with water (30 ml). The 5-(polyacetoxyalkyl)tetrazoles were solids or syrups, which were purified as individually described.

Preparation of 5-(polyhydroxyalkyl)tetrazoles. — These compounds were obtained by dissolving the 5-(polyacetoxyalkyl)tetrazole (1 g) in methanol (100 ml), and adding 2% sodium methoxide solution to pH 8. The solution was kept for 24 h at room temperature, neutralized with Zeo Karb 225 (H^+) resin, the mixture filtered, the filtrate evaporated to dryness, and the product purified as individually described.

*5-(Tetra-*O*-acetyl-*L*-arabino-tetritol-1-yl)tetrazole* (**1**). — Tetra-*O*-acetyl-L-

arabinononitrile[3] was prepared by acetylation of L-arabinose oxime. The general procedure, applied to this nitrile, gave compound **1** as a white solid that crystallized from water as needles (41%) of m.p. 93–95°, $[\alpha]_D$ +2.5° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.45; H, 5.37; N, 15.38.

*5-(*L-arabino-*Tetritol-1-yl)tetrazole* (**2**). — The general procedure, applied to compound **1**, gave **2** as a white solid that crystallized from 4:1 methanol–water as rectangular prisms (100%) of m.p. 200–202°, $[\alpha]_D$ +22° (*c* 1, water).

Anal. Calc. for $C_5H_{10}N_4O_4$: C, 31.58; H, 5.30; N, 29.47. Found: C, 31.38; H, 5.50 N, 29.27.

*5-(Tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)tetrazole* (**3**). — Tetra-*O*-acetyl-D-arabinononitrile[4] was prepared by acetylation of D-arabinose oxime. From this nitrile, compound **3** was obtained as a white solid that crystallized from water as rectangular plates (45%) of m.p. 91–93°, $[\alpha]_D$ −3.1° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.85; H, 5.35; N, 15.50.

*5-(*D-arabino-*Tetritol-1-yl)tetrazole* (**4**). — From **3**, compound **4** was obtained as a white solid that crystallized from methanol as rectangular plates (100%) of m.p. 201–203°, $[\alpha]_D$ −24.5° (*c* 1, water).

Anal. Calc. for $C_5H_{10}N_4O_4$: C, 31.58; H, 5.30; N, 29.47. Found: C, 31.48; H, 5.22 N, 29.24.

*5-(Tetra-*O*-acetyl-*D*-xylo-tetritol-1-yl)tetrazole* (**5**). — Tetra-*O*-acetyl-D-xylononitrile was prepared as described by Hockett[5]. From this nitrile, compound **5** was obtained as a syrup. It was dissolved in water, decolorized several times with charcoal, and concentrated. Crystallization could not be induced and, after evaporation to dryness, a syrup was obtained (in 83.5% yield) that had $[\alpha]_D$ +42.8° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.40; H, 5.36 N, 15.60.

*5-(*D-xylo-*Tetritol-1-yl)tetrazole* (**6**). — Compound **5** gave **6** as a white solid that crystallized from absolute ethanol as needles (85%) of m.p. 139–140°, $[\alpha]_D$ +21.3° (*c* 1.2, water).

Anal. Calc. for $C_5H_{10}N_4O_4$: C, 31.58; H, 5.30; N, 29.47; Found: C, 32.06; H, 5.38; N, 29.92.

D-*Ribose oxime* (**7**). — Wohl's technique[3] for the preparation of oximes was applied to D-ribose, and, after 24 h at room temperature, compound **7** crystallized; recrystallized from 9:1 ethanol–water, it gave needles (88%) of m.p. 140–143°, $[\alpha]_D$ +52 (10 min) → +12.9° (120 h) (*c* 0.7, water).

Anal. Calc. for $C_5H_{10}NO_5$: C, 36.36; H, 6.71; N, 8.48. Found: C, 36.48; H, 6.39; N, 8.10.

*5-(Tetra-*O*-acetyl-*D*-ribo-tetritol-1-yl)tetrazole* (**8**). — Tetra-*O*-acetyl-D-ribononitrile was prepared by acetylation of the oxime **7**; it had the same constants as those described in the literature[6]. From this nitrile, compound **8** was obtained as a syrup. It was dissolved in water, and the solution decolorized several times with charcoal,

and concentrated. Crystallization could not be induced and, after evaporation to dryness, a syrup was obtained (in 94% yield) that had $[\alpha]_D$ +19.8° (*c* 1.3, ethanol).

Anal. Calc. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.30; H, 5.38; N, 15.92.

5-(D-ribo-*Tetritol-1-yl*)*tetrazole* (**9**). — From **8**, compound **9** was obtained as a white solid that crystallized from absolute ethanol as needles (85%) of m.p. 146–148°, $[\alpha]_D$ +17.7° (*c* 1, water).

Anal. Calc. for $C_5H_{10}N_4O_4$: C, 31.58; H, 5.30; N, 29.47. Found: C, 31.77; H, 5.57; N, 29.72.

5-(L-manno-*1,2,3,4-Tetrahydroxypent-1-yl*)*tetrazole* (**10**). — Tetra-*O*-acetyl-L-rhamnononitrile[7] was prepared by acetylation of L-rhamnose oxime. From this nitrile, by the general technique, was obtained a syrup from which 5-(L-*manno*-1,2,3,4-tetraacetoxypent-1-yl)tetrazole could not be obtained in a chromatographically pure form. The crude tetraacetate was deacetylated by the general procedure, and a white solid was obtained that was crystallized from methanol, to give compound **10** as needles (60%) of m.p. 204–205°, $[\alpha]_D$ +32.2° (*c* 1, water).

Anal. Calc. for $C_6H_{12}N_4O_4$: C, 32.59; H, 5.92; N, 27.44. Found: C, 32.80; H, 5.60; N, 27.48.

5-(*Penta*-O-*acetyl*-D-gluco-*pentitol-1-yl*)*tetrazole* (**11**). — Penta-*O*-acetyl-D-gluconononitrile[3] was prepared by acetylation of D-glucose oxime. From this nitrile, compound **11** was obtained as a white solid that crystallized from water as rectangular prisms (45%) of m.p. 151–154°, $[\alpha]_D$ +67.6° (*c* 0.8, chloroform).

Anal. Calc. for $C_{16}H_{22}N_4O_{10}$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.87; H, 5.08; N, 13.15.

5-(D-gluco-*Pentitol-1-yl*)*tetrazole* (**12**). — From **11**, compound **12** was obtained as a white solid that crystallized from 4:1 methanol–water as needles (94%) of m.p. 195–197°, $[\alpha]_D$ +19.2° (*c* 0.9, water).

Anal. Calc. for $C_6H_{12}N_4O_5$: C, 32.73; H, 5.49; N, 25.45. Found: C, 32.45; H, 5.78; N, 25.35.

5-(D-manno-*Pentitol-1-yl*)*tetrazole* (**13**). — Penta-*O*-acetyl-D-mannononitrile[8] was prepared by acetylation of D-mannose oxime. From this nitrile was obtained a syrup from which compound **14** could not be obtained pure. Deacetylation of the reaction mixture gave **13** as a white solid that, after recrystallization from 4:1 methanol–water, gave needles (80%) of m.p. 200–202°, $[\alpha]_D$ −29.6° (*c* 0.9, water).

Anal. Calc. for $C_6H_{12}N_4O_5$: C, 32.73; H, 5.49; N, 25.45. Found: C, 33.00; H, 5.80; N, 25.35.

5-(*Penta*-O-*acetyl*-D-manno-*pentitol-1-yl*)*tetrazole* (**14**) — Compound **13** (0.1 g) was acetylated with 4.5 ml of 1:1 acetic anhydride–pyridine at room temperature. After 24 h, the solution was evaporated in a desiccator, and the resulting syrup dissolved in water and the solution decolorized with charcoal The compound was chromatographically pure, but crystallization could not be induced After evaporation, 0 16 g (82%) of **14** was obtained as a syrup, $[\alpha]_D$ +12.2° (*c* 0.7, chloroform)

Anal Calc for $C_{16}H_{22}N_4O_{10}$: C, 44 65; H, 5.15; N, 13.02 Found: C, 44.35; H, 5.53; N, 13.21.

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