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Note

Facile synthesis of 3-deoxyaldos-2-ulose bis(thiosemicarbazones)*

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When aldoses are treated with arylamines, the *N*-substituted glycosylamines first formed undergo a series of rearrangements leading to Amadori compounds[1] (1-arylamino-1-deoxyketoses) and further[2] to the unstable 3-deoxyaldos-2-uloses. In earlier work, it was reported[3] that, if in addition to the aldose and the arylamine, an aroylhydrazine is also present in a hot aqueous–ethanolic medium containing acetic acid, then 3-deoxyaldos-2-ulose bis(aroylhydrazones) are formed. These hydrazones, having only slight solubility in the reaction medium, are precipitated and can be removed as solids upon cooling. Such compounds as benzoylhydrazine, which do not alter the desired chemical reaction and are capable of producing derivatives of the 3-deoxyaldos-2-uloses possessing low solubility in the reaction solvent and which have good crystallizing properties, function as "trapping agents". If compounds other than aroylhydrazines could be used as trapping agents, a variety of interesting derivatives might be produced. In this investigation, thiosemicarbazide, semicarbazide, aminoguanidine hydrogencarbonate, and *p*-toluenesulfonylhydrazine were tested as trapping agents. While the first reagent afforded crystalline 3-deoxyaldos-2-ulose bis(thiosemicarbazones), the others were found not to produce nicely precipitated products within 24 h of the general reaction procedure.

In the procedure here described, *p*-toluidine may be viewed as a catalyst promoting the rearrangement and elimination reactions, and the thiosemicarbazide as the trapping agent, allowing the elusive glycosuloses to be captured as crystalline, stable derivatives. Improved yields were obtained when the aromatic amine was allowed to interact with the aldose during an initial 30-min period of boiling under reflux before the addition of the trapping agent. Also, the maximal precipitation of product occurred when 2:1 ethanol–water was used as the solvent medium. Starting from D-*glycero*-D-*gulo*-heptose, prepared from a precursor 1,4-lactone *via* the pH-controlled sodium borohydride reduction devised by Wolfrom and Wood[4],

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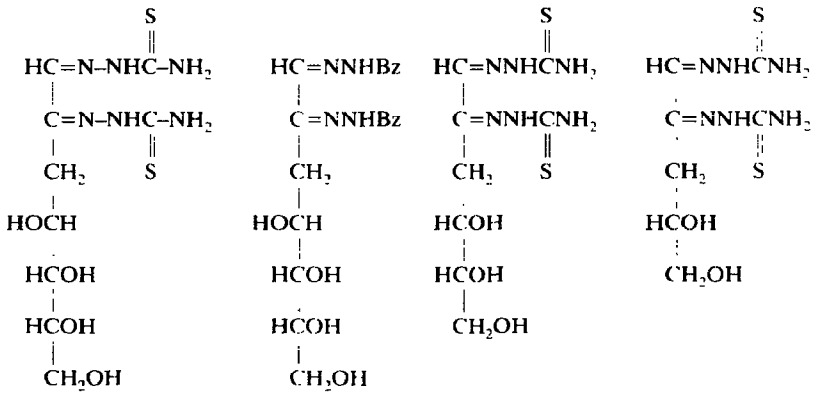

1 **2** **3** **4**

3-deoxy-D-*arabino*-hexos-2-ulose bis(thiosemicarbazone) (**1**) was obtained. The physical constants and spectra for **1** were identical to those of a sample of the bis(thiosemicarbazone) prepared from 3-deoxy-D-*arabino*-hexos-2-ulose that had been liberated from its known bis(benzoylhydrazone) **2**, following the procedure earlier described[3]. Although criticism[5,6] had been leveled at the reported[3] procedure for preparation of **2**, and related analogs from other sugars, we have consistently found it satisfactory. It is desirable to use a large excess of acetic acid over the amount of aromatic amine; this ensures generation of the 3-deoxyaldos-2-ulose derivative rather than a simple monohydrazone. The solvent system of 70% aqueous ethanol is satisfactory, although 70% aqueous 2-methoxyethanol is better, as it allows an increase in the concentration of reactants and shorter reaction times as the result of higher reaction temperatures under reflux.

The procedure here described for the preparation of bis(thiosemicarbazones) proved to be general. Starting from different aldoses (D-*glycero*-D-*gulo*-heptose, D-glucose, and D-arabinose), the corresponding derivatives of 3-deoxy-D-*arabino*-

TABLE I

^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **1**, **3**, AND **4**

Compound	*NH*	*H-1*	*OH*	*H-sugar chain*	*H-3,3'*
1	11.70, 10.70, 8.38 (× 2) 7.93, 7.78	7.68	5.24, 4.69, 4.50, 3.97	3.55–3.20 (H-4,5,6,7,7')	2.91
3	11.63, 10.65, 8.33 (× 2) 7.89, 7.70	7.63	5.55, 4.89	3.63,3.37 (H-4,5,6,6')	3.04, 2.65
4	11.69, 10.74, 8.37 (× 2) 7.94, 7.85	7.69	5.75, 4.91	3.73–2.50 (H-3,3',4,5,5')	

[a]At 200 MHz for solutions in Me_2SO-d_6 with Me_4Si as the internal reference.

TABLE II

^{13}C-N.M.R. DATA[a] FOR COMPOUNDS **1**, **3**, AND **4**

Compound	*C-5*	*C-1*	*C-2*	*C-sugar chain*	*C-3*
1	178.6, 178.1	142.4	148.9	73.1, 71.3, 68.5, 63.4	29.7
3	178.6, 178.2	142.0	149.3	74.3, 70.7, 62.8	28.6
4	178.6, 178.1	142.2	148.7	70.4, 64.8	29.1

[a]At 50 MHz for solutions in Me_2SO-d_6 with Me_4Si as the internal reference.

heptos-2-ulose (**1**), 3-deoxy-D-*erythro*-hexos-2-ulose (**3**), and 3-deoxy-D-*glycero*-pentos-2-ulose (**4**) were obtained in 45, 40, and 43% yields, respectively. The structures of **1**, **3**, and **4** were further confirmed from their ^{1}H- (Table I) and ^{13}C- (Table II) n.m.r.-spectral data. The protons bonded to nitrogen resonated at iowest field (δ 7.7–11.7), H-1 resonated as a singlet at δ 7.63–7.69, the sugar-chain protons gave complex multiplets, and signals at higher field (δ ~3.0) were attributed to the C-3 methylene group. The ^{13}C-n.m.r. spectra of compounds **1**, **3**, and **4** showed resonances for carbon bonded to sulfur at δ 178.1–178.6 and C-1 was firmly assigned because of its coupling with H-1. The signal for C-2 appeared slightly downfield of the C-1 resonances. The sugar-chain carbon atoms resonated between δ 62.8 and 74.3. A distinctive upfield peak (δ 28.6–29.7) clearly indicated a methylene carbon atom (C-3) in the sugar chain.

Thiosemicarbazide and substituted thiosemicarbazides have been employed as chelating reagents for metal cations[7,8]. As with various aldosulose bis(semicarbazones)[9], the bis(thiosemicarbazones) formed very stable complexes with copper salts. Analysis of the chelates showed a 1:1 ratio of Cu^{2+} to thiosemicarbazone. The structure of the complexes will be discussed elsewhere. Preliminary studies have shown that the copper chelate of **3** possesses *in vivo* antitumor activity in the murine L-1210 assay. Furthermore, it has been suggested[10] that such compounds as the 3-deoxyaldos-2-uloses themselves may be involved in preparations having carcinostatic activity. Furthermore, the derivative **1** constitutes a key intermediate in the preparation of 3-deoxy-D-*arabino*-heptos-2-ulosonic acid, whose 7-phosphate is one of the biological intermediates in the shikimic acid pathway[11,12].

EXPERIMENTAL

General methods. — Melting points were determined in open glass capillaries in a Thomas–Hoover apparatus, and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer 457 grating spectrophotometer. The

^{1}H- and ^{13}C-n.m.r. spectra were determined at 200 and 50 MHz, respectively, with a Bruker WP-200 spectrometer, operating in the F.t. mode, for solutions of the samples in dimethyl sulfoxide-d_6. X-Ray powder diffraction data give interplanar spacings (Å) for Cu$K\alpha$ radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; w, weak; v, very.

3-Deoxy-D-arabino-*heptos-2-ulose bis(thiosemicarbazone)* (**1**). — (*a*) *From* D-glycero-D-gulo-*heptose*. A solution of the sugar (1.8 g, 8.57 mmol), *p*-toluidine (0.94 g, 8.8 mmol), and acetic acid (2.1 mL) in ethanol (50 mL) and water (25 mL) was boiled under reflux for 30 min, whereupon thiosemicarbazide (1.64 g, 1.8 mmol) was added and boiling was continued for an additional 7 h. The dark solution was refrigerated overnight, affording yellow crystals (1.3 g, 45%). Recrystallization from water, and then from a large volume of methanol gave pale-yellow needles, m.p. 215–217°, $[\alpha]_D^{25}$ −284° (*c* 0.8, dimethyl sulfoxide); $\lambda_{max}^{H_2O}$ 332 nm (log ε 4.58); ν_{max}^{KBr} 3438, 3325, 3225, (NH, OH), 2948 (CH), and 1595 cm^{-1} (C=N).

Anal. Calc. for $C_9H_{18}N_6O_4S_2$: C, 31.9; H, 5.4; N, 24.8. Found: C, 32.1; H, 5.6; N, 25.0.

(*b*) *From 3-deoxy*-D-arabino-*heptos-2-ulose bis(benzoylhydrazone)* (**2**). — Compound **2** (4.9 g, 11.4 mmol) was converted into the corresponding free dicarbonyl sugar by the transhydrazonation procedure of Bayne[13]. The crude, syrupy product was dissolved in water (15 mL), and thiosemicarbazide (2.1 g, 23 mmol) and acetic acid (1 mL) were added. The mixture was heated on a steam bath for 2 h. Crystals were obtained after cooling, which were filtered off and rinsed successively with water, ethanol, and ether; yield 2.0 g (52%). Three recrystallizations from water afforded compound **1**, m.p. 214–215°, $[\alpha]_D^{31}$ −290° (*c* 1, dimethyl sulfoxide).

Anal. Calc. for $C_9H_{18}N_6O_4S_2$: C, 31.9; H, 5.4; N, 24.8; S, 18.9. Found: C, 31.8; H, 5.7; N, 25.1; S, 18.8.

3-Deoxy-D-arabino-*heptos-2-ulose bis(benzoylhydrazone)* (**2**). — A solution of D-*glycero*-D-*gulo*-heptose (4.2 g, 20 mmol), *p*-toluidine (2.25 g, 21 mmol), and acetic acid (2.5 mL) in 2-methoxyethanol (50 mL) and water (25 mL) was heated to reflux, benzoylhydrazine (5.7 g, 42 mmol) was added, and boiling under reflux was continued for an additional 2.5 h. The mixture was kept for 24 h at room temperature, filtered, and the solid product recrystallized from methanol, affording 2.3 g (27%) of compound **2**, m.p. 181° (lit.[3] m.p. 183°).

3-Deoxy-D-erythro-*hexos-2-ulose bis(thiosemicarbazone)* (**3**). — To a solution of D-glucose (25.2 g, 0.14 mol) in ethanol (400 mL) and water (200 mL), were added *p*-toluidine (15.0 g, 0.14 mol) and acetic acid (35 mL). The mixture was boiled under reflux for 30 min, thiosemicarbazide (25.5 g, 0.28 mol) was added, and boiling was continued for 7 h. The mixture was refrigerated overnight, affording a pale-brown precipitate (14.8 g). Evaporation of the mother liquors to ~400 mL gave a second crop of crystals (2.4 g); overall yield 17.2 g (40%). Two recrystallizations from 2:1 water–ethanol led to pale-yellow needles, m.p. 229°, $[\alpha]_D^{24}$ +512° (*c* 1.0, dimethyl sulfoxide); λ_{max}^{EtOH} 237 nm (log ε 4.08) and 350 nm (4.33); ν_{max}^{KBr} 3385,

3260 (NH, OH), 2980 (CH), and 1611 cm^{-1} (C=N); X-ray powder diffraction data: 7.98 m, 5.18 m (3), 4.70 m, 3.99 vw, 3.58 vs (1), and 3.42 s (2).

Anal. Calc. for $C_8H_{10}N_6O_3S_2$: C, 31.2; H, 5.2; N, 27.2; S, 20.8. Found: C, 31.3; H, 5.1; N, 27.0; S, 20.7.

3-Deoxy-D-glycero-*pentos-2-ulose bis(thiosemicarbazone)* (**4**). — The preparation was essentially the same as for compound **3**, starting from D-arabinose (5 g, 33.3 mmol), *p*-toluidine (3.6 g, 33.3 mmol), and acetic acid (7 mL) in 2:1 ethanol–water, with subsequent addition of thiosemicarbazide (6.08 g, 66.6 mmol). Compound **4** was obtained as a brown powder (4.0 g, 43%); recrystallization (twice) from water, with a carbon treatment, gave fine, pale-yellow needles having m.p. 224°, $[\alpha]_D^{21}$ +246° (*c* 1, dimethyl sulfoxide); λ_{max}^{EtOH} 207 (log ε 4.00) and 345 nm (4.67); ν_{max}^{KBr} 3390, 3260, 3165 (NH and OH), 2985 (CH), and 1609 cm^{-1} (C=N); X-ray powder diffraction data: 6.84 s (2), 6.25 vw, 5.47 m, 4.81 w, 4.19 w, 3.73 m, 3.56 s (3), and 3.37 vs (1).

Anal. Calc. for $C_7H_{14}N_6O_2S_2$: C, 30.2; H, 5.1; N, 30.2; S, 23.1. Found: C, 30.2; H, 5.3; N, 30.3; S, 22.9.

3-Deoxy-D-erythro-*hexos-2-ulose bis(thiosemicarbazone) copper chelate.* — To a boiling solution of **3** (6.8 g, 22 mmol) in 2:1 methanol–water (400 mL), cupric acetate hydrate (4.4 g, 22 mmol) dissolved in hot water (30 mL) was added. Immediately the pale-yellow solution became a deep red-brown, and a precipitate began to form. The mixture was kept for 20 h at room temperature and then cooled at 0°, affording a brown solid (6.5 g, 80%); m.p. 208°; λ_{max}^{EtOH} 312 (log ε 4.34), and 487 nm (3.72); ν_{max}^{KBr} 3340, 3160 (NH, OH), 2920 (CH), 1650, 1615 (NH), 1587, 1537, 1440, 1218, 1611, and 1042 cm^{-1}; X-ray powder diffraction data: 10.99 vs (1), 8.62 (2), 6.71 w, 6.35 w, 5.54 m (3), 5.24 w, 5.71 m, 4.72 w, 4.47 w, and 4.33 w.

Anal. Calc. for $C_8H_{14}CuN_6O_3S_2$: C, 26.0; H, 3.8; N, 22.7. Found: C, 26.2; H, 4.1; N, 22.5.

3-Deoxy-D-glycero-*pentos-2-ulose bis(thiosemicarbazone) copper chelate.* — A solution of cupric acetate hydrate (0.36 g, 1.8 mmol) in water (5 mL) was added to a solution of compound **3** (0.5 g, 1.8 mmol) in water (5 mL), containing 2M aqueous sodium hydroxide (2 mL). The red-brown precipitate was filtered off and washed with water and ethanol; yield 0.52 g (85%). A small sample of this material was dissolved in hot acetonitrile; it precipitated upon cooling. The solid was analytically pure but amorphous by X-ray powder diffractometry; λ_{max}^{EtOH} 312 (log ε 4.35) and 493 nm (3.74); ν_{max}^{KBr} 3340, 3160 (NH, OH), 2920 (CH), and 1650 cm^{-1} (C=N).

Anal. Calc. for $C_7H_{12}CuN_6O_2S_2$: C, 24.7; H, 3.6; N, 24.7. Found: C, 24.7; H, 3.5; N, 24.4.

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