BIS(AROYLHYDRAZONES) OF 3-DEOXYALDOS-2-ULOSES*

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ABSTRACT

The reaction whereby aldose or ketose precursors are converted in acidified aqueous ethanol in the presence of *p*-toluidine into 3-deoxyaldos-2-uloses and the latter are trapped as the crystalline bis(benzoylhydrazones) is shown to be of wide generality. Sugar precursors having four-, five-, six-, and seven-carbon chains, and aroylhydrazines having the *p*-toluoyl, *p*-anisoyl, *p*-chlorobenzoyl, *p*-iodobenzoyl, or *p*-nitrobenzoyl groups, all reacted to give the desired bis(aroylhydrazones) of the respective 3-deoxyaldos-2-uloses as crystalline products in a single operation. The u.v. and n.m.r. spectra of representative examples of the 31 compounds described have been examined.

INTRODUCTION

We have shown[1] that aldoses and ketoses react with *p*-toluidine in aqueous, acidified ethanol in the presence of aroylhydrazines to give crystalline 3-deoxyaldos-2-ulose bis(benzoylhydrazones), the conversion of which into the respective 3-deoxyaldos-2-uloses affords a convenient synthetic route to this otherwise difficultly accessible group of compounds. The 3-deoxyaldos-2-uloses are important sugar derivatives from a number of standpoints. They are key intermediates in the non-enzymic browning sequence of reactions occurring between sugars and amino acids that leads to color formation and flavor deterioration in foodstuffs[2]. 3-Deoxy-D-*erythro*-hexos-2-ulose has been detected in post-mortem liver-tissue[3], and the possibility exists that this class of compounds may be useful in metabolic control by their effect on such enzyme systems as the glyoxalases[4] and α-ketoaldehyde dehydrogenase[5].

The present report describes extension and improvement of the method already described, to prepare, from C_4, C_5, C_6, and C_7 sugar precursors, a range of 3-deoxyaldos-2-ulose bis(aroylhydrazones) having various aroyl groups.

DISCUSSION

By treating D-*glycero*-D-*gulo*-heptose, D-glucose, D-galactose, L-sorbose, L-rhamnose, D- and L-arabinose, and D-erythrose with *p*-toluidine in refluxing aqueous

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TABLE I

3-DEOXYALDOS-2-ULOSE BIS(AROYLHYDRAZONES)

Formula	*Starting sugar*	*Reaction time (h)*	*Yield (%)*	$[\alpha]_D$ *(degrees)*	*m.p. (degrees)*	*Found (%)*			*Empirical formula*	*Calculated (%)*		
						C	*H*	*N*		*C*	*H*	*N*
3-Deoxy-D or L-aldos-2-ulose bis(*p*-toluoylhydrazones)												
1a	D-*glycero*-D-*gulo*-heptose	4	27	−129.0	212–4	59.6	6.1	11.7	$C_{23}H_{28}N_4O_6 \cdot 0.5H_2O$	59.4	6.2	12.0
7a	L-arabinose	2	30	+38.5	265–7	63.1	6.0	13.7	$C_{21}H_{24}N_4O_4$	63.6	6.1	14.1
8a	D-erythrose	2	16	±0.0	258–60	63.5	6.2	15.0	$C_{20}H_{22}N_4O_3 \cdot 0.5H_2O$	64.0	6.1	14.9
3-Deoxy-D or L-aldos-2-ulose bis(*p*-anisoylhydrazones)												
2b	D-glucose	7	26	+22.1	224–6	57.8	5.8	12.0	$C_{22}H_{26}N_4O_7$	57.6	5.7	12.2
3b	D-galactose	5	41	−87.5	232–4	57.3	6.0	12.0	$C_{22}H_{26}N_4O_7$	57.6	5.7	12.2
4b	L-sorbose	5	20	+87.4	232–4	57.2	6.0	11.7	$C_{22}H_{26}N_4O_7$	57.6	5.7	12.2
5b	L-rhamnose	5	30	−68.6	225–7	59.5	6.2	12.8	$C_{22}H_{26}N_4O_6$	59.7	5.9	12.7
6b	D-arabinose	2	54	−35.7	238–40			13.2	$C_{21}H_{24}N_4O_6$			13.1
6b	D-xylose	2	50	−35.0	239–40	58.6	5.6	13.0	$C_{21}H_{24}N_4O_6$	58.9	5.6	13.1
7b	L-arabinose	2	32	+36.0	238–40			13.0	$C_{21}H_{24}N_4O_6$			13.1

	3-Deoxy-D or L-aldos-2-ulose bis[(*p*-chlorobenzoyl)hydrazones]											
2c	D-glucose	5	60	+53.2	200–1	50.4	4.9	12.0	$C_{20}H_{20}Cl_2N_4O_5\cdot0.5H_2O$	50.3	4.4	11.8
3c	D-galactose	5	80	−44.2	226–8	51.5	4.4	12.1	$C_{20}H_{20}Cl_2N_4O_5$	51.4	4.3	12.0
4c	L-sorbose	4	20	+38.3	226–8	50.9	4.3	12.1	$C_{20}H_{20}Cl_2N_4O_5$	51.4	4.3	12.0
5c	L-rhamnose	4	55	−40.0	259–60	53.2	4.4	12.3	$C_{20}H_{20}Cl_2N_4O_4$	53.2	4.4	12.4
6c	D-arabinose	5	34	−20.0	259–60	52.6	4.3	12.7	$C_{19}H_{18}Cl_2N_4O_4$	52.2	4.1	12.8
7c	L-arabinose	5	31	+19.4	259–60	51.8	4.4	13.2	$C_{19}H_{18}Cl_2N_4O_4$	52.2	4.1	12.8
8c	D-erythrose	2	10	±0.0	255–7	50.9	4.5	13.5	$C_{18}H_{16}Cl_2N_4O_3\cdot H_2O$	50.8	4.2	13.2
	3-Deoxy-D or L-aldos-2-ulose bis[(*p*-iodobenzoyl)hydrazones]											
3d	D-galactose	5	33	−29.5	195–8			8.6	$C_{20}H_{20}I_2N_4O_5$			8.6
4d	L-sorbose	5	35	+30.3	196–8	36.1	3.4	7.9	$C_{20}H_{20}I_2N_4O_5\cdot H_2O$	35.8	3.3	8.4
5d	L-rhamnose	5	30	−85.2	255–7			8.7	$C_{20}H_{20}I_2N_4O_5$			8.8
6d	D-arabinose	5	32	−11.0	262–4			9.0	$C_{19}H_{18}I_2N_4O_4$			9.0
7d	L-arabinose	5	29	+10.2	262–4	37.0	2.9	8.8	$C_{19}H_{18}I_2N_4O_4$	36.8	2.9	9.0
	3-Deoxy-D or L-aldos-2-ulose bis[(*p*-nitrobenzoyl)hydrazones]											
2e	D-glucose	7	65	+18.0	228–9	49.2	4.5	17.1	$C_{20}H_{20}N_6O_9$	49.2	4.1	17.2
3e	D-galactose	5	62	−39.6	210–2	48.3	4.2	16.9	$C_{20}H_{20}N_6O_9\cdot0.5H_2O$	48.3	4.3	17.0
4e	L-sorbose	4	20	+40.4	210–2	48.4	4.4	16.8	$C_{20}H_{20}N_6O_9\cdot0.5H_2O$	48.3	4.3	17.0
5e	L-rhamnose	5	34	−18.0	262–4	51.0	4.4	17.8	$C_{20}H_{20}N_6O_8$	50.8	4.2	17.8
6e	L-arabinose	2	36	+17.4	265–7	48.8	3.8	18.1	$C_{19}H_{18}N_6O_8\cdot0.5H_2O$	48.9	4.1	18.0
8e	D-erythrose	2	20	±0.0	237–9	48.0	4.2	18.6	$C_{18}H_{16}N_6O_7\cdot H_2O$	48.4	4.0	18.8

ethanol containing acetic acid, in the presence of the appropriate aroylhydrazine, there were obtained the crystalline 3-deoxyaldos-2-ulose bis(aroylhydrazones) having the general structures **1**–**8** and the respective aroyl groups: *p*-toluoyl (**a**), *p*-anisoyl (**b**), *p*-chlorobenzoyl (**c**), *p*-iodobenzoyl (**d**), and *p*-nitrobenzoyl (**e**). The compounds thus prepared are listed with their properties in Table I. In addition, in order to complete the bis(benzoylhydrazone) series, L-arabinose was converted into 3-deoxy-L-*glycero*-pentos-2-ulose bis(benzoylhydrazone) (**7f**), and D-fucose was converted into 3,6-dideoxy-D-*threo*-hexos-2-ulose bis(benzoylhydrazone) (**9f**).

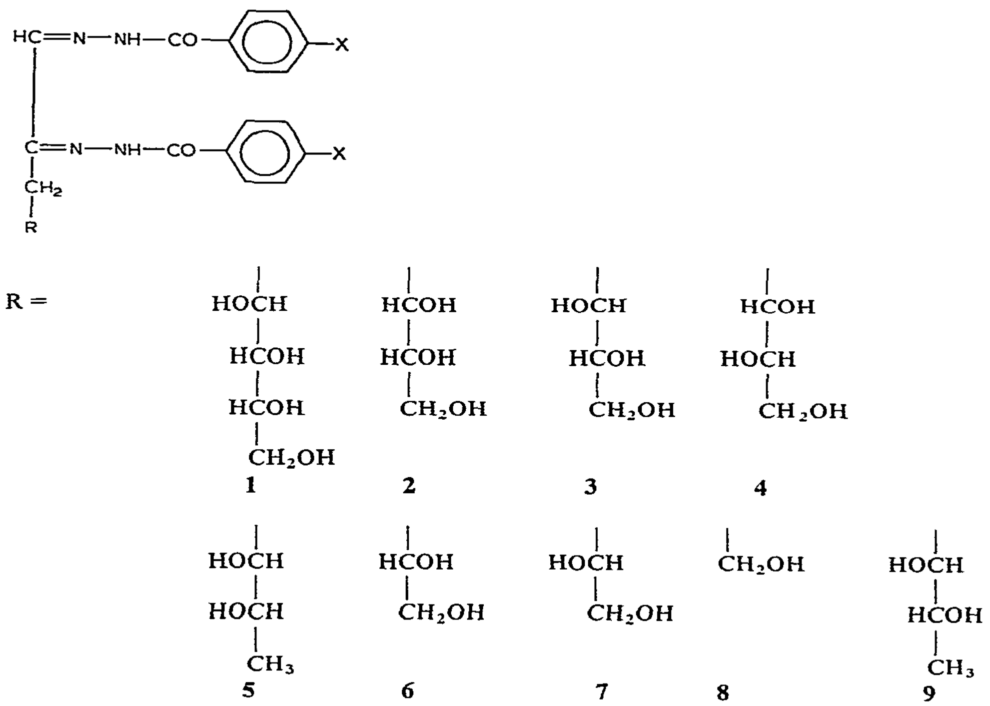
The *p*-substituted bis(benzoylhydrazones) listed in Table I, as well as the parent bis(benzoylhydrazones) already reported[1], possess excellent crystallizing properties, and are better suited for the characterization of 3-deoxyaldos-2-uloses than the*p*-chlorophenyl-, *p*-nitrophenyl-, and (2,4-dinitrophenyl)-osazones hitherto used[6,7] for the characterization of these compounds. The products usually separate as hydrates from the reaction mixture, and, following recrystallization, they are often obtained as solvates with water, methanol, or ethanol. Removal of all water of crystallization by dehydration is difficult, and some water occasionally remains in the analytical samples, even after drying for several hours (see Table I).

A further procedural improvement in the preparative method, leading to higher yields and to products uncontaminated by the corresponding glyculose bis(aroylhydrazones) that sometimes separate out in admixture with the 3-deoxy analogs, involves initial reaction of the sugar precursor with *p*-toluidine before addition of the aroylhydrazine (see Experimental section).

In addition to the foregoing compounds, the bis[(2,4-dinitrophenyl)hydrazones] of 3-deoxy-L-*threo*-hexos-2-ulose and 3,6-dideoxy-L-*erythro*-hexos-2-ulose were prepared by treating the corresponding bis(benzoylhydrazones) with benzaldehyde, to give the free 3-deoxyaldos-2-uloses, and then bringing the latter into reaction with (2,4-dinitrophenyl)hydrazine.

The u.v. spectra of the *p*-substituted bis(benzoylhydrazones) of 3-deoxyaldos-2-uloses resemble those of the bis(benzoylhydrazones) previously prepared[1] and show three characteristic bands (see Table II). A moderate absorption at shortest wavelength (224–227 nm) is little influenced by substitution on the phenyl ring. A second, moderate to strong band is observed between 237 and 262 nm, and its absorption maximum is markedly influenced by substitution; it is absent from the spectrum of the bis(anisoylhydrazone) examined. A third band, of strong intensity, is observed between 320 and 334 nm, and it, likewise, shows the effect of a strong bathochromic shift upon substitution at the *para* position of the phenyl ring.

To confirm the structures assigned to the products, representative examples were examined by n.m.r. spectroscopy in pyridine-d_5 (see Table III). At lowest field, near $\tau -2.7$ the separate signals of the two imino protons of the bis(hydrazone) group were observed; the proximity of these signals indicates that both NH protons are strongly chelated[8]. The H-1 signal in the spectrum of each example appeared in the region of the aryl-proton and solvent resonances. A 2-proton multiplet near τ 5.9 could be attributed to the terminal CH_2 group of the chain, and a higher-field,



X = **a** Me, **b** OMe, **c** Cl, **d** I, **e** NO_2, **f** H

TABLE II

ULTRAVIOLET SPECTRA OF SUBSTITUTED BIS(BENZOYLHYDRAZONES) OF 3-DEOXYALDOS-2-ULOSES

Compound	λ_{max} (*nm*)[a]	λ_{min} (*nm*)
3-Deoxytetros-2-ulose bis(benzoylhydrazone)[1] (**8f**)	237m 320s	260
3-Deoxy-D-*threo*-hexos-2-ulose bis(*p*-toluoylhydrazone) (**3a**)	225m 251m 325s	234 270
3-Deoxy-D-*threo*-hexos-2-ulose bis(*p*-anisoylhydrazone) (**3b**)	226m 270m[b] 328s	242
3-Deoxy-D-*erythro*-hexos-2-ulose bis[(*p*-chlorobenzoyl)hydrazone] (**2c**)	225m 248m 323s	232 274
3-Deoxy-D-*threo*-hexos-2-ulose bis[(*p*-iodobenzoyl)hydrazone] (**3d**)	224m 262m 324s	236 280
3-Deoxy-D-*threo*-hexos-2-ulose bis[(*p*-nitrobenzoyl)hydrazone] (**3e**)	226m 260s 334s	230 289

[a] m, moderate; s, strong. [b] Shoulder.

TABLE III

N.M.R. SPECTRAL DATA FOR SOME BIS(AROYLHYDRAZONES) OF 3-DEOXYALDOS-2-ULOSES IN PYRIDINE-d_5

Compound	*Chemical-shift data (τ values)*			
	NH[a]	*H-3*	*Aryl*[b]	*Other*[c] *(Assignment)*
3-Deoxy-tetros-2-ulose bis(benzoylhydrazone)[1] (8f)	−2.80, −2.65	6.60–6.78	2.42–2.82	5.80–5.99 (4-CH_2)
3-Deoxy-D-*glycero*-pentos-2-ulose bis(*p*-anisoylhydrazone) (6b)	−2.85, −2.67	6.40–6.57	2.40–3.05	5.87–6.00 (5-CH_2), 5.38 (H-4), 6.37 (OMe)
3-Deoxy-L-*glycero*-pentos-2-ulose bis(*p*-toluoylhydrazone)	−2.95, −2.70	6.40–6.58	2.40–2.90	5.93–6.03 (5-CH_2), ~5.38 (H-4), 7.80 (Ar-CH_3)
3-Deoxy-L-*glycero*-pentos-2-ulose bis(benzoylhydrazone) (7f)	−2.91, −2.73	6.40–6.60	2.40–2.85	5.92–6.04 (5-CH_2), 5.38 (H-4)
3-Deoxy-D-*arabino*-heptos-2-ulose bis(benzoylhydrazone)[1] (1f)	−2.90, −2.75	6.20–6.40	2.40–2.82	5.40–5.86 (H-4,5,6,7,7′)
3,6-Dideoxy-D-*threo*-hexos-2-ulose bis(benzoylhydrazone) (9f)	−2.90, −2.75	6.35–6.54	2.38–2.75	5.55–5.98 (H-4,5), 8.40[d] (6-CH_3)

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[a] Disappears on deuteration. [b] Solvent resonances also observed in this and in lower-field region; unambiguous assignment of H-1 resonance not attempted. [c] HOD peak observed near τ 4.9. [d] Doublet, *J* 7 Hz.

2-proton multiplet near τ 6.5 was assigned to the methylene group at C-3; other assignments were made that were concordant with the structures, and these are listed in Table III.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. U.v. spectra were recorded with a Bausch & Lomb Model 505 u.v. spectrophotometer. Optical rotations were measured in 1-dm tubes with a Perkin–Elmer Model 141 polarimeter. Infrared spectra were recorded with a Perkin–Elmer Model 137 i.r. spectrophotometer. N.m.r. spectra were recorded, for solutions in pyridine-d_5, at 60 MHz with a Varian A-60 n.m.r. spectrometer. Chemical shifts are given on the τ scale, with tetramethylsilane ($\tau = 10.00$) as the internal standard. Elemental analyses were performed by W. N. Rond.

Original method for preparation of 3-deoxyaldos-2-ulose bis(aroylhydrazones). — A solution of the sugar (2 or 4 g, 1 molar equiv.), the aroylhydrazine (2.1 molar equivs.), and *p*-toluidine (0.5 or 1.0 g) in ethanol (50 or 100 ml) containing water (5 or 10 ml) and acetic acid (0.5 or 1.0 ml) was refluxed for 2–7 h, and the cooled solution was left to evaporate slowly in an open dish at room temperature. The product that separated after 24 h was filtered off, washed successively with ethanol and ether, and recrystallized from ethanol [from methanol for the *p*-anisoylhydrazones, and from ethanol–ethyl acetate for the (*p*-nitrobenzoyl)hydrazones]. For the *p*-toluoylhydrazones, (*p*-iodobenzoyl)hydrazones, and (*p*-nitrobenzoyl)hydrazones, the smaller quantities specified were used; for the *p*-anisoylhydrazones and (*p*-chlorobenzoyl)hydrazones, the larger quantities were used.

Table I lists all of the derivatives prepared by this general procedure; it lists the starting sugar used and the time of reaction, and gives yields and characterizing data.

*3-Deoxy-*L-glycero*-pentos-2-ulose bis(benzoylhydrazone)* (7f). — A solution of L-arabinose (2.5 g), benzoylhydrazine (3.2 g), and *p*-toluidine (1 g) in ethanol (50 ml) containing water (10 ml) and acetic acid (1 ml) was refluxed for 5 h, and then allowed to evaporate slowly at room temperature in a crystallization dish. The product that separated after 24 h (yield 1.7 g, 28%) was filtered off, washed successively with ethanol and ether, and recrystallized from ethanol as needles, m.p. 230–232° (dec.), $[\alpha]_D^{25}$ $+18.6°$ (*c* 1, pyridine); ν_{max}^{KBr} 1660 (CONH) and 3350 cm^{-1} (OH).

Anal. Calc. for $C_{19}H_{20}N_4O_4$: C, 62.0; H, 5.4; N, 15.2. Found: C, 62.1; H, 5.6; N, 15.1.

*3,6-Dideoxy-*D-threo*-hexos-2-ulose bis(benzoylhydrazone)* (9f). — A solution of D-fucose (1 g), benzoylhydrazine (2.5 g), and *p*-toluidine (0.5 g) in ethanol (75 ml) containing water (5 ml) and acetic acid (1 ml) was boiled under reflux for 24 h. The product that separated after 24 h was filtered off, washed successively with methanol and ether, and dried; yield 0.48 g (20.8%). It was recrystallized from ethanol–water as needles, m.p. 233–234° (dec.), $[\alpha]_D^{24}$ $-58.4°$ (*c* 0.5, pyridine); ν_{max}^{KBr} 1675 (CONH) and 3250 cm^{-1} (OH).

Anal. Calc. for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.75; N, 14.65. Found: C, 63.04; H, 6.01; N, 14.61.

Improved general procedure for preparation of 3-deoxyaldos-2-ulose bis(aroylhydrazones). — The following procedure was developed after the foregoing work was completed; it is regarded as superior from the standpoint of yield and purity of the product, especially for the bis(benzoylhydrazones). A solution of the sugar (1–2 g, 1 molar equiv.) and *p*-toluidine (0.5–1.0 g) in a mixture of ethanol (50–100 ml), water (5–10 ml), and acetic acid (1–2 ml) was boiled under reflux for 30 min. The appropriate aroylhydrazine (3 molar equivs.) was then added, and boiling under reflux was continued for 6–12 h. The resultant solution was transferred to a crystallization dish, and set aside for 24 h to crystallize. To separate the product (yield 20–35%) from the syrupy residue, the mixture was triturated with methanol and the product was filtered off, washed successively with methanol and ether, and then dried. Recrystallization was effected from ethanol or ethanol–water.

*3-Deoxy-*L-threo-*hexos-2-ulose bis[(2,4-dinitrophenyl)hydrazone].* — A solution of 3-deoxy-L-*threo*-hexos-2-ulose bis(benzoylhydrazone)[1] (2 g) in ethanol (60 ml), water (100 ml), acetic acid (2.4 ml), and freshly distilled benzaldehyde (3.2 ml) was refluxed for 6 h. After 3 h, benzaldehyde benzoylhydrazone started to separate out. Ethanol was removed by evaporating off 60 ml of the solution, with simultaneous, gradual addition of 100 ml of water. After 24 h, the precipitated benzaldehyde benzoylhydrazone was filtered off, and the filtrate was concentrated and then extracted with six 25-ml portions of ether. The extracts were combined, clarified with charcoal, and evaporated to a thick syrup that was dissolved in water (10 ml) and shaken with Amberlite IR-120 (H^+) and Amberlite IR-4B (OH^-). Removal of the resin and evaporation of the solution to dryness gave a syrup; yield 0.4 g (50%), $[\alpha]_D^{25}$ $-10.6°$ (*c* 6, water), that was converted into the crystalline bis[(2,4-dinitrophenyl)hydrazone]; m.p. 260–263° (dec.).

Anal. Calc. for $C_{18}H_{18}N_8O_{11}$: N, 21.5. Found: N, 21.4.

*3,6-Dideoxy-*L-erythro-*hexos-2-ulose bis[(2,4-dinitrophenyl)hydrazone].* — A solution of 3,6-dideoxy-L-*erythro*-hexos-2-ulose bis(benzoylhydrazone)[1] (**5f**, 2 g) was treated with benzaldehyde in the usual way[9]. The product (yield 0.35 g, 41%) was converted into the crystalline bis[(2,4-dinitrophenyl)hydrazone], m.p. 269–270° (dec.).

Anal. Calc. for $C_{18}H_{18}N_8O_{10}$: N, 22.1. Found: N, 22.4.

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