Carbohydrate Research, 149 (1986) C5–C8
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

A new method for the synthesis of 3,6-anhydrohexose phenylosazones

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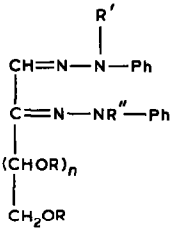
(Received January 24th, 1986; accepted for publication, February 25th, 1986)

Treatment of tetra-*O*-acetylhexosulose 1,2-bis(phenylhydrazones) (*e.g.*, **2a**) with sodium hydroxide in aqueous acetone yields dianhydrohexose phenylosazones[1,2], the correct structure of which (*e.g.*, **5**) was determined[3] by a ^{1}H-n.m.r. study of the monoacetates (*e.g.*, **6**). Under similar conditions, starting from the penta-acetate (**3**) of **2**, no dianhydrohexose phenylosazone was obtained but an unidentified amorphous product was formed[3]. Moreover, as *O*-acetyl-3,6-anhydrohexosazones (*e.g.*, **8** and **10**) failed[3] to give dianhydroosazones, the formation of a tetrahydrodiazine ring was postulated to precede[3] that of the 3,6-anhydro ring.

The mechanism of the formation of a 2-phenylazo-1-phenylhydrazono-2-alkene intermediate[1b,4–7] from the osazone **1** and the stereochemistry of the anhydro ring formation[8–10] in acidic media have been elucidated.



	R	R′	R″
1	H	H	H
2	Ac	H	H
3	Ac	Ac	H
4	Ac	Ac	Ac
a	D-*lyxo*	(*n* = 3)	
b	L-*xylo*	(*n* = 3)	

As the degree of acetylation of the osazones seems to determine the type of products formed in basic solutions, the alkaline transformations of acetylhexosulose 1,2-bis(phenylhydrazones) (**2**), 1-acetylphenylhydrazone 2-phenylhydrazones (**3**), and 1,2-bis(acetylphenylhydrazones)[11] (**4**) have been investigated.

Treatment of tetra-*O*-acetyl-D-*lyxo*-hexosulose 1-acetylphenylhydrazone 2-phenylhydrazone (**3a**) with sodium hydroxide in aqueous acetone afforded crystalline 3,6-anhydro-D-*lyxo*-hexosulose 1,2-bis(phenylhydrazone) (**7**) and not the unidentified amorphous material previously claimed[3]. Compound **7** was also obtained by the action of 2 mol of sodium methoxide in anhydrous methanol on tetra-*O*-acetyl-D-*lyxo*-hexosulose

0008-6215/86/$03.50

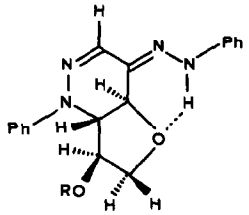
TABLE I

PREPARATION AND PHYSICAL DATA OF 1a, 7, AND 9

Product	*Starting material (mmol)*	*Solvent (mL)*	*Agent (mL)*	*Reaction time (h)*[a]	*Yield (%) [crude (pure)]*	*M.p. (deg.) (solvent of recrystn.)*	$[\alpha]_D^{23}$ *(deg.) (c, solvent)*	*Formula Anal.: found (calc.)*
1a	**4a**[11] (3)	$CHCl_3$ (5) MeOH (20)	conc. NH_4OH[b] (2)	24[c]	92 (51)	192–193[d] 180–182[e] ($MeOCH_2CH_2OH$)		$C_{18}H_{22}N_4O_4$[f]
7	**3a**[7,15] (24)	Me_2CO (625)	0.38M NaOh (816)	24	98 (54)	215–218[g,h] (MeCN)		$C_{18}H_{20}N_4O_3$ N, 16.47 (16.46)
	2a[16] (3)	$CHCl_3$[i] (5)	0.5M NaOMe/MeOH (6.5)	48	76 (40)	215–217[g,h] (MeCN)		
	3a[15] (12)	$CHCl_3$[i] (20)	0.5M NaOMe/MeOH (52)	20	95 (62)	222[g,h] (MeCN)	+61.3[j] (0.35, MeOH)	C, 63.27 (63.51) H, 5.95 (5.92) N, 16.44 (16.46)
	4a[11] (3)	$CHCl_3$[i] (5)	0.5M NaOMe/MeOH (13)	48	99 (57)	216–217[g,h] (MeCN)		[k]
9	**2b**[11] (3)	$CHCl_3$[i] (5)	0.5M NaOMe/MeOH (13)	28	94 (44)	215–217[l] (MeCN)	–62[m] (0.35, MeOH)	$C_{18}H_{20}N_4O_3$ C, 63.32 (63.51) H, 5.98 (5.92) N, 16.43 (16.46)

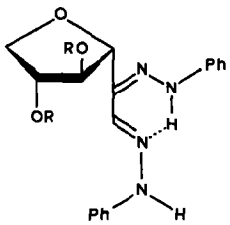
[a] At room temperature. [b] Added from a hypodermic syringe during 48 h. [c] After complete addition of the reagent. [d] Directly from the reaction mixture; lit.[13] m.p. 193–194° (from acetone–ether). [e] Lit.[14] m.p. 185–187° (from 2-methoxyethanol). [f] The R_F (0.45; t.l.c., 8:2 chloroform–acetone) and i.r. spectrum of **1a** are identical with those of an authentic[14] specimen. It was also identified by treatment with acetic anhydride–pyridine to give **2a**. [g] Lit. m.p. 213–214° (from methanol)[17], 214–216° [18], 215° [19,20], 215–216° [21], 216–217° (from methanol)[22], 220° (from acetonitrile)[23], 224–225° (from aqueous methanol)[24]. [h] The i.r. spectrum is identical with that of authentic[23] material. [i] Anhydrous. [j] Lit. $[\alpha]_D^{20}$ +53.5° (5 min) → +62.1° (24 h; *c* 0.38, methanol)[21], +70.5° (*c* 0.31, methanol)[23], +48.2° (methanol)[20], $[\alpha]_D^{22}$ +56° (*c* 0.5, methanol)[18], $[\alpha]_D^{24}$ + 71° (*c* 0.3, methanol)[22], $[\alpha]_D^{16}$ +71° (*c* 0.35, methanol)[19]. [k] Identified also by treatment with boiling acetic anhydride to give the triacetate identical (m.p. and t.l.c.) with an authentic[24,25] specimen. [l] Lit. m.p. 215–217° (from acetonitrile)[18]; the R_F value (t.l.c., 8:2 chloroform–acetone) and the i.r. spectrum are identical with those of authentic **7**[23] and **9**[18]. [m] Lit.[18] $[\alpha]_D^{22}$ –54° (*c* 0.52, methanol).

1,2-bis(phenylhydrazone) (**2a**), 1-acetylphenylhydrazone 2-phenylhydrazone (**3a**), and 1,2-bis(acetylphenylhydrazone) (**4a**). Under similar conditions, the formation of 3,6-anhydro-L-*lyxo*-hexosulose 1,2-bis(phenylhydrazone) (**9**, the enantiomer of **7**) starting from tetra-*O*-acetyl-L-*xylo*-hexosulose 1,2-bis(phenylhydrazone) (**2b**) demonstrated the validity of the stereochemical rule[8,9] for the formation of the 3,6-anhydro ring in acidic media from the unacetylated osazones.



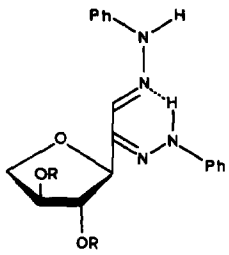
5 R = H

6 R = Ac



7 R = H

8 R = Ac



9 R = H

10 R = Ac

As >1 mol of sodium methoxide per mol of acetylated osazone was necessary to form the anhydro-osazone, the transient formation of a 2-phenylazo-2-alkene intermediate (similar to that suggested[1b,4–6] for the reactions of unacetylated osazones in acidic media) by loss of 1 mol of acetic acid must be supposed. This reaction, leading to the formation of an anhydro ring, is similar to that reported[12] for acetylated sugar formazans when treated with sodium methoxide. Accordingly, the treatment of **4a** (not capable of losing AcO-3 before being *N*-deacetylated at the 2-phenylhydrazono moiety) in chloroform–methanol with a trace of conc. ammonia, added at intervals of 1–2 hours, afforded, after deacetylation, D-*lyxo*-hexosulose 1,2-bis(phenylhydrazone) (**1a**) which could be reacetylated to give **2a**.

The reactions of **2**–**4** (n = 2 or 3) with O, N, and S nucleophiles are being studied.

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