5-Thio-D-Xylopyranosylamines[1]

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5-Thio-D-xylopyranose reacts with arylamines to produce glycosylamines in a similar way to normal oxygen ring sugars. The glycosylamines also appear to undergo the normal Amadori rearrangement to produce 1-amino-1-deoxy-2-ketoses.

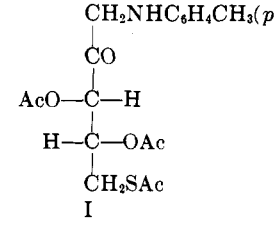
Several reports have appeared on the formation of 5-thio-D-pentoses[2-4] and -hexoses[5,6] and their derivatives. This work describes the preparation of glycosylamines of 5-thio-D-xylopyranose and their Amadori rearrangement.

5-Thio-D-xylopyranose reacts with aromatic amines in the presence of a small amount of acid such as acetic acid. Using this procedure, a number of crystalline glycosylamines are obtained in good yields. Alkylamines such as *n*-propyl- or *n*-butylamine or arylalkylamines such as benzylamine give dark-colored sirups which are not investigated further.

The ease of formation of the glycosylamines depends on the position of any substituent present in the aromatic amine,[7] the order being *para* > *meta* > *ortho*. *ortho*-Substituted amines require a reaction time of eight hours as compared to the usual two hours at 100° for *para*-substituted amines. With *o*-nitroaniline, no glycosylamine is obtained even after more extended heating. Various 5-thio-D-xylopyranosylamines are listed in Table I. These compounds are quite stable at 25°, but they decompose and darken at the elevated temperatures encountered during melting point determination.

An Amadori rearrangement of the glycosylamines occurs but to a minor extent when they are refluxed in either (1) isopropyl alcohol containing anhydrous oxalic acid, acetic acid, or concentrated hydrochloric acid, or (2) ethanol containing an active methylene compound such as diethyl malonate.[8] A solution of the glycosylamines in pyridine and ethanol with a small amount of acetic acid will produce, under reflux conditions, more extensive rearrangement and yield some free 5-thio-D-xylopyranose. Pyridine containing 10% acetic acid[9,10] at reflux temperature brings about an extensive Amadori rearrangement. Formation of Amadori products is followed by titration of the solution with 2,6-dichlorophenolindophenol.[9] The rearrangement is always accompanied by color formation. Micheel[11] found that *ortho–para*-directing substituents in the 2- and 4-position and *meta*-directing substituents in the 3-position, relative to the nitrogen atom in the glycosylamine, facilitated the rearrangement. This observation is verified here. Thus, the *N*-*p*-tolylglycosylamine rearranges much more readily than the *N*-phenyl compound. Reaction of 5-thio-D-xylopyranose with *m*-aminobenzoic acid does not produce the expected *N*-glycosylamine, but gives a dark tar, possibly from the Amadori rearrangement. The volumes of standard 2,6-dichlorophenolindophenol reagent required after definite reaction periods, per 0.1-ml. aliquots of alkaline reaction mixture containing equal glycosylamine concentration, are shown in Table II.

N-*p*-Tolyl-5-thio-D-xylosylamine under rearrangement conditions produces a compound with a slightly higher R_f value on thin layer chromatography than the starting material. After three hours of reaction other artifacts also appear. The reaction mixture has a strong reaction with alkaline triphenyltetrazolium chloride, methylene blue, and nitroprusside. The Amadori product could not be isolated by chromatography or by Kuhn's[10] procedure of forming the triazene. Acetylation of the reaction mixture gives two compounds on thin layer chromatography with quite different R_f values. The acetylated reaction mixture on separation on a silica gel column gives approximately a 65% yield of crystalline 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylopyranosylamine and a dark sirup. Decolorization and rechromatography on silica gel gives a light yellow sirup, which has a strong reaction with alkaline triphenyltetrazolium chloride, methylene blue, and 2,6-dichlorophenolindophenol, but gives a negative test with alkaline nitroprusside. Infrared spectra of the yellow sirup as a thin film shows the absence of hydroxyl groups and the presence of three carbonyl absorptions at 5.76, 5.91, and 6.02 μ which are ascribed to the presence of *O*-acetyl, *S*-acetyl, and a free keto group, respectively. Ultraviolet spectra reveal the presence of *S*-acetyl,[12] λ_{max}^{MeOH} 225 mμ (ϵ 9420). These observations and elemental analysis suggest the following open chain structure. It is observed[10] that Amadori products assume the pyranose structure if possible or occur in the open chain form.



I

Experimental

Preparation of 5-Thio-D-xylosylamines.—A 0.55-g. (0.0033 mole) sample of 5-thio-D-xylopyranose was added to 0.004 mole of

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TABLE I

5-THIO-D-XYLOPYRANOSYLAMINES

Amine	Yield, %	M.p. dec., °C.	$[\alpha]^{20}D$ (c 1.00, pyridine	Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
Aniline	83	206–207	−279	$C_{11}H_{15}NO_3S$	5.81	5.62	13.28	13.14
o-Toluidine	33	170–171	−316	$C_{12}H_{17}NO_3S$	5.49	5.43	12.54	12.59
m-Toluidine	66	185–186	−238	$C_{12}H_{17}NO_3S$	5.49	5.45	12.54	12.63
p-Toluidine	78	181–182	−265	$C_{12}H_{17}NO_3S$	5.49	5.33	12.54	12.46
o-Anisidine	61	194–195	−242	$C_{12}H_{17}NO_4S$	5.17	5.34	11.81	11.79
m-Anisidine	49	184–185	−222	$C_{12}H_{17}NO_4S$	5.17	5.29	11.81	11.72
p-Anisidine	80	172–173	−278	$C_{12}H_{17}NO_4S$	5.17	5.10	11.81	11.93
o-Bromoaniline	12	184–185	−250	$C_{11}H_{14}BrNO_3S$	4.38	4.17	10.00	10.04
m-Bromoaniline	60	196–197	−214	$C_{11}H_{14}BrNO_3S$	4.38	4.48	10.00	10.07
p-Bromoaniline	55	182–183	−196	$C_{11}H_{14}BrNO_3S$	4.38	4.35	10.00	9.92
α-Naphthylamine	68	200–201	−310	$C_{15}H_{17}NO_3S$	4.81	4.95	11.00	10.96
β-Naphthylamine	63	193–194	−202	$C_{15}H_{17}NO_3S$	4.81	4.64	11.00	10.93
m-Nitroaniline	29	203–204	−246	$C_{11}H_{14}N_2O_5S$	9.80	9.78	11.18	11.09
p-Nitroaniline	35	223–224	−116	$C_{11}H_{14}N_2O_5S$	9.80	9.72	11.18	11.17
o-Aminobenzoic Acid	82	199–200	−98	$C_{12}H_{15}NO_5S$	4.92	4.73	11.23	11.29
p-Aminobenzoic Acid	52	202–203	+58	$C_{12}H_{15}NO_5S$	4.92	4.97	11.23	11.17

TABLE II

GLYCOSYLAMINE REACTION TIME UNDER REFLUX[a]

	Hr. 1	2	3	4	5	6
N-Phenyl-5-thio-D-xylosylamine	5.0 ml.	10.0[b]	14.5	14.5	11.0	...
N-*p*-Tolyl-5-thio-D-xylosylamine	8.5	13.0	17.5[b]	24.0	23.0	19.0
N-*p*-Anisyl-5-thio-D-xylosylamine	11.5[b]	14.5	17.5	14.5	12.0	10.0

[a] The values in the table represent the volume (ml.) of 2,6-dichlorophenolindo–phenol reagent required after definite reaction periods (hr.) per 0.1-ml. aliquots of alkaline reaction mixture containing equal glycosylamine concentration. [b] At this point the reaction mixture turned dark.

TABLE III

N-SUBSTITUTED 2,3,4-*O*-TRIACETYL-5-THIO-D-XYLOPYRANOSYLAMINE

N-Substitution group	M.p., °C.	$[\alpha]^{20}D$ (c 1.00, pyridine)	Formula	% N Calcd.	% N Found
Phenyl	220	−148	$C_{17}H_{21}NO_6S$	3.81	3.84
o-Tolyl	184	−184	$C_{18}H_{23}NO_6S$	3.67	3.81
m-Tolyl	207	−138	$C_{18}H_{23}NO_6S$	3.67	3.66
p-Tolyl	212	−132	$C_{18}H_{23}NO_6S$	3.67	3.70
o-Anisyl	165	−134	$C_{18}H_{23}NO_7S$	3.53	3.50
m-Anisyl	155	−116	$C_{18}H_{23}NO_7S$	3.53	3.64
p-Anisyl	173	−130	$C_{18}H_{23}NO_7S$	3.53	3.59
o-Bromphenyl	160	−146	$C_{17}H_{20}BrNO_6S$	3.14	3.12
m-Bromphenyl	208	−122	$C_{17}H_{20}BrNO_6S$	3.14	3.18
p-Bromphenyl	217	−102	$C_{17}H_{20}BrNO_6S$	3.14	3.22
α-Naphthyl	190	−242	$C_{21}H_{23}NO_6S$	3.36	3.31
β-Naphthyl	227	−162	$C_{21}H_{23}NO_6S$	3.36	3.46
m-Nitrophenyl[a]	256	+56	$C_{17}H_{20}N_2O_8S$	6.80	6.92
p-Nitrophenyl[a]	241	−108	$C_{17}H_{20}N_2O_8S$	6.80	6.85
o-Carboxyphenyl	195	−98	$C_{18}H_{21}NO_8S$	3.40	3.46
p-Carboxyphenyl	197	+144	$C_{18}H_{21}NO_8S$	3.40	3.49

[a] Crystallized from dilute pyridine.

the appropriate amine, 0.5 ml. of ethanol, 0.1 ml. of water, and 0.02 ml. of glacial acetic acid, and the mixture was heated at 100° for 2 hr. For amines containing *ortho* substituents the reaction time was increased to 8 hr. The glycosylamines separated during the heating period and were washed with ethanol and ether. The compounds were crystallized from isopropyl alcohol. Yield and analytical data are given in Table I. The compounds do not reduce 2,6-dichloroindophenol, methylene blue, 2,3,5-triphenyl-2*H*-tetrazolium chloride, or dinitrobenzene in 0.1 *N* sodium hydroxide solution at 15°.

The triacetates were prepared by treating 100 mg. of the appropriate glycosylamine with 1 ml. of pyridine and 1 ml. of acetic anhydride at 25° for 18 hr. The mixture was then poured into water and crystallized from methanol (see Table III).

Amadori Rearrangement.—A 250-mg. sample of the glycosylamine (*N*-phenyl-, *N*-*p*-tolyl-, *N*-*p*-anisyl-) was refluxed with 9.0 ml. of pyridine and 1.0 ml. of glacial acetic acid. At intervals, 0.10-ml. portions were withdrawn, made alkaline by addition of 1.2 ml. of 1 *N* sodium hydroxide solution, and titrated against 2,6-dichlorophenolindophenol by the procedure described by Rosen, *et al.*[9] The results are given in Table II.

In the case of *N*-*p*-tolyl-5-thio-*p*-xylosylamine, the reaction mixture was examined at intervals by thin layer chromatography on silica gel G with 15% methanol in benzene as developer and concentrated sulfuric acid or alkaline triphenyltetrazolium chloride as spray reagents. After 1 hr., the reaction mixture contained the starting material, R_f 0.18, and a substance with R_f 0.23. After 3.5–4 hr., the component with R_f 0.23 was in greatest concentration and other components, with R_f 0.53 and 0.60, appeared. The reaction mixture darkened appreciably. This reaction mixture was cooled and 1 ml. of acetic anhydride was added. After standing overnight, it was evaporated under reduced pressure at 50°, and the residue was distilled with water to remove pyridine. It was then distilled with benzene. Thin

layer chromatography on kieselgel G with 4% methanol in benzene as developer and concentrated sulfuric acid as a spray reagent revealed the presence of two components with R_f 0.14 and 0.46. The faster moving component was identified as 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylosylamine by comparison with authentic material. After a similar reaction sequence on 2.5 g. of *N*-*p*-tolyl-5-thio-D-xylosylamine the residue was taken up in 10 ml. of benzene containing 4% methanol, the mixture was cooled, and the undissolved 2,3,4-tri-*O*-acetyl-1-*N*-(*p*-tolyl)-5-thio-D-xylosylamine was removed by filtration. The filtrate was applied to a column of 200 g. of silica gel, the column was eluted with benzene containing 4% methanol, and the fractions were examined by a thin layer chromatography. The total amount of solid acetate recovered was 2.44 g. or 65%. A further 1.33 g. (35% yield) of a dark sirup was decolorized by stirring for 4 hr. with an equal weight of activated charcoal in 25 ml. of methanol. It was filtered through Celite, and the filter was washed twice with 10 ml. of methanol. Evaporation of the filtrate gave a yellow sirup which was rechromatographed on silica gel using 4% methanol in benzene. The fraction with R_f 0.14 was concentrated and dried over phosphorus pentoxide, $[\alpha]^{20}D$ $-1°$ (*c* 0.79, methanol).

Anal. Calcd. for $C_{18}H_{23}NO_6S$: C, 56.6; H, 6.04; N, 3.69. Found: C, 56.3; H, 6.15; N, 3.62.

Attempted deacetylation of this sirup with barium hydroxide, sodium methoxide, sodium hydroxide, or acid led to complex mixtures. Examination of these reaction mixtures by thin layer chromatography showed the absence of an Amadori product.

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Furano Compounds. II[1a]

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The greater ease of synthesis of simple or condensed furanopyrones carrying a β-methyl substituent in the furan ring over similar compounds lacking such a substituent is discussed. Further, the significance of the presence of a C-methyl group in a number of simple or condensed benzo-γ-pyrone derivatives of plant origin and that of a β-methyl substituent in the furan ring of a few naturally occurring benzofurans has been stressed. This is illustrated by a typical synthesis of 4′-methylfurano(3′,2′:4,3)xanthone and 4′,6-dimethylfurano-(3′,2′:4,3)xanthone.

In part I[1b] of this series, the occurrence of a furan nucleus in a number of related natural products, *viz.*, furanocoumarins, -chromones, -flavones, -isoflavones, and -xanthones, was discussed, and the synthesis of furano(3′,2′:4,3)xanthone, the xanthone analog of the well-known furanoflavone Karanjin, was recorded. This synthesis employs one of the typical methods for the preparation of benzofuran derivatives, *viz.*, a mixed Claisen-type condensation or internal aldol condensation using the appropriately substituted aldehyde or ketone and bromoacetic or bromomalonic ster. Thus, 4-formyl-3-hydroxyxanthone obtained rom 3-hydroxyxanthone was submitted to such a condensation employing bromomalonic ester which effected simultaneous esterification and internal aldol condensation (cyclization).

On the other hand, the corresponding ketones, *viz.*, 4-acetyl-3-hydroxyxanthones, which can also be submitted to a similar internal Claisen condensation leading to the formation of a furan skeleton, can be more easily prepared and in better yields from the hydroxyxanthones through a Friedel–Crafts–Fries reaction. However, while aldehydo esters give rise to furano compounds unsubstituted in the furan ring, the use of substituted ketones for such an internal Claisen condensation results in furano compounds carrying a methyl substituent in the β-position. It may be pointed out that the occurrence in nature of furano compounds carrying a methyl substituent is not uncommon. Thus menthofuran,[2] the chemical constituent of various peppermint oils, and Evodon,[3] a crystalline ketone from the essential oil of *Evodia hortensis*, are β-methylbenzofurans. It could also be expected that a methyl substituent in the β-position may affect the physiological properties of the furano compounds concerned. Further, the presence of a C-methyl group in the benzenoid ring of a number of related, naturally occurring, simple or condensed benzo-γ-pyrone derivatives[4] and its significance in the biogenetic evolution of such compounds made us attempt the synthesis of two typical examples of furanoxanthones, *viz.*, 4′-methylfurano(3′,2′:4,3)xanthone and 4′,6-dimethylfurano(3′,2′:4,3)xanthone, carrying a methyl substituent in the furan ring alone or with such substituents both in the furan ring and in the benzenoid nucleus. The first step in such synthesis, *viz.*, the preparation of the 4-acetyl derivatives from 3-hydroxyxanthone and 3-hydroxy-6-methylxanthone, is based on the valuable observations of Mustafa and Hishmat[5] and of Davies, Scheinmann, and Suschitzky.[6]

Thus, 3-hydroxyxanthone and 3-hydroxy-6-methylxanthone on treatment with acetyl chloride in the presence of aluminum chloride yield the appropriate 4-acetyl derivatives. These have been condensed with bromoacetic ester in presence of potassium carbonate to yield the 3-O-carbethoxy derivatives which on hydrolysis with aqueous potassium hydroxide give the corresponding carboxylic acids. The internal Claisen condensation (cyclization) of the acids has been effected by sodium acetate and acetic anhydride to yield 4′-methylfurano(3′,2′:4,3)xanthone (IIa) and 4′,-

(1) (a) This article forms part of the material for the Ph.D. thesis to be submitted by G. S. Puranik to the Karnatak University; (b) G. S. Puranik and S. Rajagopal, *Ber.*, **96**, 976 (1963).

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