[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE SYNTHESIS OF OXAZOLINE DERIVATIVES OF MONOSACCHARIDES AND THEIR RELATIONSHIP TO THE AMINO SUGARS[1]

WERNER H. BROMUND[2] AND ROBERT M. HERBST[3]

Received February 24, 1945

Several years ago, Zemplén, Gerecs, and Rados (1) described a compound formed by the interaction of D-glucose, potassium thiocyanate, and hydrochloric acid in concentrated aqueous solution which they considered to be μ-thiolglucoxazoline and to which they ascribed the structure I or Ia. The corresponding μ-hydroxyglucoxazoline (II) or (IIa) was obtained by oxidation of the thio analog with hydrogen peroxide in aqueous solution. Similar derivatives were prepared from D-fructose by Zemplén, Gerecs, and Illes (2). However, in neither case was conclusive evidence given for the mode of attachment of the heterocyclic nitrogen to the carbohydrate chain.

Assuming the structure assigned to the glucose derivatives to be correct, they seemed to offer a simple method for the introduction of nitrogen into the 2-position of the sugar molecule. With this in mind, we prepared analogous thiooxazoline derivatives from D-galactose (III), D-xylose (IV) and L-arabinose (V) by a method essentially similar to that of Zemplén and co-workers (1). Attempts to prepare the corresponding hydroxy derivatives unfortunately led only to non-crystallizable viscous syrups.

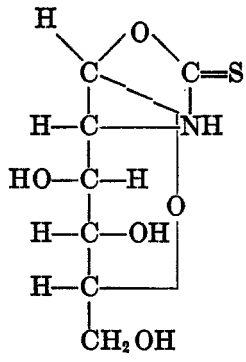
It was hoped that compounds of this type would provide a method of access to the group of 2-amino sugars simpler than that of Fischer and Leuchs (3) and the more recent procedures of Haworth and his collaborators involving the addition of ammonia to the anhydro sugars. However, all attempts to bring about hydrolytic rupture of the oxazoline ring of (I) and (II) led only to the recovery of the glucoxazoline under mild conditions or extensive destruction of the compounds under more drastic conditions. In one instance colorimetric estimation of glucosamine by the method of Elson and Morgan (4, 5, 6) indicated the presence of a trace of the amino sugar but attempts to isolate a solid derivative even by the procedure of Jolles and Morgan (7) were fruitless.

Our failure to isolate 2-aminoglucose by hydrolysis of the glucoxazoline derivatives can hardly be attributed to instability of the former, since it withstands rather drastic hydrolytic treatment during its preparation by hydrolysis of chitin. Although Zemplén (1) had reported the formation of phenylglucosazone from the glucoxazolines in amounts and under conditions comparable to its formation from glucosamine, our results suggested the desirability of attempting the stepwise synthesis of these compounds by a succession of unequivocal reactions. Several

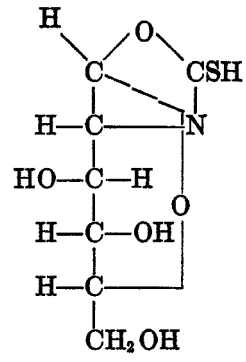
[1] Abstracted from a thesis presented by Werner H. Bromund to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Present address, Oberlin College, Oberlin, Ohio.

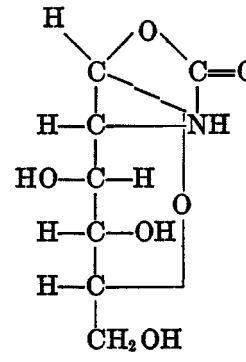
[3] Present address, E. Bilhuber, Inc., Orange, New Jersey.



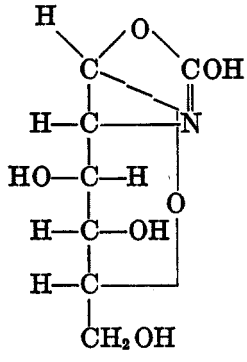
(I)



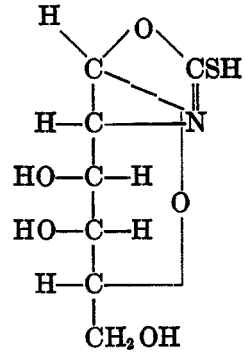
(Ia)



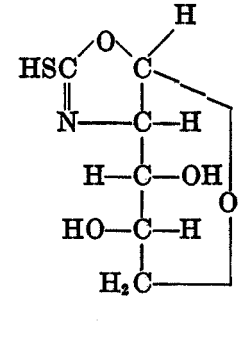
(II)



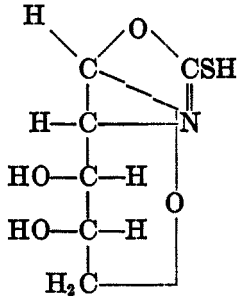
(IIa)



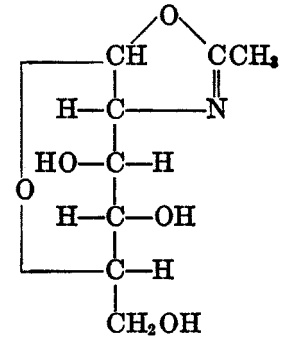
(III)



(IV)



(V)

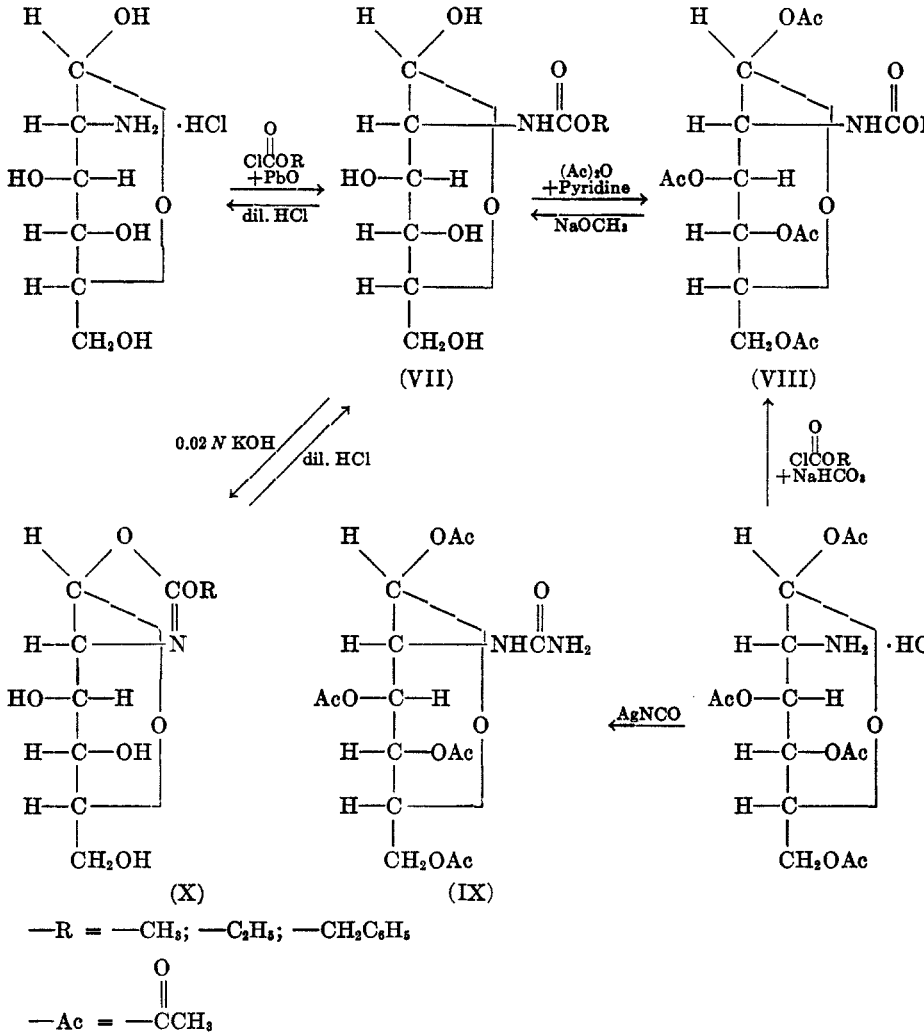


(VI)

methods of synthesizing μ-oxazolones have been reported, as for instance the elimination of methanol from N-carbomethoxyethanolamine (8), the elimination of ammonia from β-hydroxyethylurea (11) and the treatment of N-phenylethanolamine with phosgene (12). None of these methods could be applied successfully to suitable derivatives of either 1-amino- or 2-amino-glucose.

In the course of these attempts a number of new derivatives of both 1-amino- and 2-amino-glucose were prepared. Thus N-carbomethoxyglucosamine-2

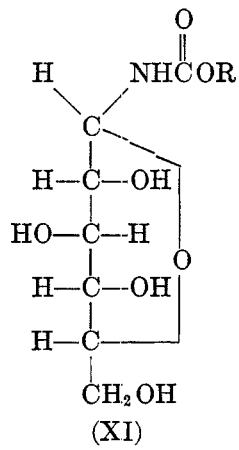
(VII) was prepared by the deacetylation of its tetraacetyl derivative and by the Forschbach method (9). The corresponding ethyl (9) and benzyl (10) esters have been previously described although their preparation from tetraacetylglucosamine-2 was not previously reported. 1,3,4,6-Tetraacetyl-N-carbobenzoxyglucosamine-2 (VIII) occurs in three modifications, two of which appear to be polymorphic modifications of the β-form while the third may be considered as the α-form.



A method for the preparation of a compound described as μ-methyl-Δ^2-glucoxazoline (VI) by White (13), when applied to the N-glucosyl carbamates (VII), led to products of similar intractable physical characteristics as those ascribed to (VI) by White. These compounds were characterized by relatively low specific rotations and low softening points. They gave intensely colored solu-

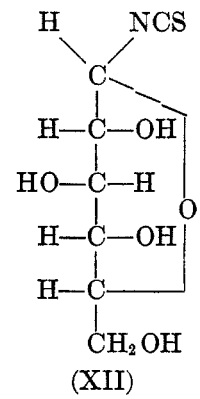
tions when treated directly with Ehrlich's reagent [compare White (13)], and upon hydrolysis with dilute hydrochloric acid at room temperature were converted in modest yield to the respective alkyl carbamates (VII). This behavior suggested that the products might be ethers of μ-hydroxyglucoxazoline and the structure (X) is suggested for them, although it has not been possible to achieve their conversion into compounds of the type (II) or the converse. The effect of mild hydrolytic conditions has been cited; more drastic conditions resulted in complete destruction of the structure. Even catalytic hydrogenation of the benzyl ether (X) by the technique of Freudenberg, Dürr, and von Hochstetter (14) gave results of dubious value. Only half the anticipated volume of hydrogen was absorbed and no solid product could be isolated. Although the resulting material still gave a color with Ehrlich's reagent and could be converted into glucosamine-2 with dilute hydrochloric acid at room temperature, the evidence hardly suffices to establish the reductive cleavage of the benzyl ether.

The possibility remained that the glucoxazolines (I) and (II) might be derived from 1-aminoglucose, whose structure has been established by numerous investigators (15, 16, 17, 18). The carbomethoxy and carbethoxy derivatives of 1-aminoglucose were obtained as amorphous, hygroscopic products, for which the structure (XI) is suggested, by the interaction of the amino sugar with methyl and ethyl chlorocarbonate. Attempts to prepare the corresponding benzyl ester were unsuccessful. These substances failed to exhibit mutarotation, developed no color with Ehrlich's reagent, and suffered extensive destruction when ring closure was attempted by White's (13) procedure. Attempts to close the



(XI)

—R = —CH_3, —C_2H_5



(XII)

ring by other methods (8, 12) were likewise unsuccessful.

Since Haring and Johnson (19) had shown that tetraacetylglucosyl 1-isothiocyanate would react with alcohols to form glucosylthiourethans, it was thought that the acetylated glucosyl isothiocyanate might undergo intramolecular urethan formation upon deacetylation. When deacetylated with sodium methoxide according to Zemplén (1, 20), tetraacetylglucosyl 1-isothiocyanate gave a colorless,

hygroscopic amorphous product which did not develop a color with Ehrlich's reagent, showed properties generally similar to those of the carbamates (XI) and for which the structure (XII) is suggested. Attempts to bring about ring closure led to extensive decomposition of the material with the evolution of hydrogen sulfide.

Deacetylation of tetraacetylglucosyl 1-isocyanate (21) with sodium methoxide led only to a non-crystallizable, yellow, hygroscopic syrup.

EXPERIMENTAL

Monosaccharide derivatives of μ-thioloxazoline (III) (IV) (V). The following procedure for the preparation of μ-thiol-D-galactoxazoline (III) was also applied to the preparation of μ-thiol-D-xyloxazoline (IV) and μ-thiol-L-arabinoxazoline (V), and is based on Zemplén's procedure for the preparation of μ-thiol-D-glucoxazoline (1).

Potassium thiocyanate (117 g., 1.20 moles) was dissolved in a warm solution of 108 g. (0.6 mole) of anhydrous D-galactose in 90 ml. of water to which, after cooling in an ice-bath, 108 ml. of 12 *N* hydrochloric acid (1.3 moles) was slowly added with continued cooling. After the solution had stood at room temperature for three days, a precipitate of potassium chloride and yellow amorphous material was filtered off. The clear filtrate was allowed to stand at room temperature for six weeks and then chilled thoroughly for four days. After a small amount of yellow amorphous solid was filtered off, the clear solution was evaporated to a paste under reduced pressure at 40–45°, and then to dryness in a vacuum desiccator over calcium chloride and sodium hydroxide. The thoroughly dried crystalline mass was pulverized, extracted with 750 ml. of boiling 95% ethanol and the extract decolorized by boiling with charcoal. The product which separated on chilling was recrystallized from 92% ethanol. All mother liquors were systematically exhausted. In the extraction and recrystallization of the μ-thioloxazoline derivatives of D-xylose[4] and L-arabinose, absolute ethanol was found to be a more useful solvent. Yields, physical constants, and analytical data for the galactose, xylose, and arabinose derivatives are given in Table I.

N-glucosyl alkylcarbamates (VII) (XI). A modification of the method devised by Forschbach (9) was used for the preparation of N-carbomethoxyglucosamine-2 (VII), N-carbethoxyglucosamine-2 (VII), N-carbomethoxyglucosamine-1 (XI), and N-carbethoxyglucosamine-1 (XI). The method is described in detail for N-carbomethoxyglucosamine-2.

To a solution of 25.0 g. (0.116 mole) of 2-aminoglucose hydrochloride in 150 ml. of water, 42 g. (0.19 mole) of yellow lead oxide was added. The mixture was cooled to 10° and 13.2 g. (0.140 mole) of methyl chlorocarbonate was added in several portions with continuous shaking and cooling. After one hour, 1.2 g. of methyl chlorocarbonate and 3.0 g. of lead oxide were added, and the thick suspension again shaken until the sharp odor of methyl chlorocarbonate had disappeared. After standing at room temperature for 24 hours, the mixture was filtered, and the solid washed with a small amount of water. The combined filtrate and washings were evaporated to one-third their total volume at 50° under reduced pressure. Lead chloride was precipitated by the addition of an equal volume of 95% ethanol and chilling. After removal of most of the ethanol by evaporation under reduced pressure, chloride ion was removed by treatment with silver sulfate, lead and silver were precipitated as sulfides, and sulfate ion was removed with barium carbonate. The resulting solution was concentrated by evaporation under reduced pressure and evaporated to dryness in a vacuum desiccator over calcium chloride. The residue was recrystallized by dissolution in a relatively large volume of absolute methanol, followed by partial evaporation of the solvent, and chilling of the concentrated solution.

N-carbomethoxyglucosamine-2 is a crystalline material, very soluble in water, slowly

[4] The D-xylose used had the equilibrium specific rotation +18.6° at 25° in 1.9% aqueous solution.

TABLE I

COMPOUND	NO.	YIELD, %	M.P. °C.	SPECIFIC ROTATION				FORMULA (FORMULA WT.)	ANALYSIS								
									Calculated: %				Found: %				
					Temp., °C.	g/100 ml solvent	Solvent		C	H	N	S	C	H	N (Dumas)	S	Residue
μ-Thiol-D-galactoxazoline	III	74.0	169–169.5 decomp.	−0.83°	26	0.7250	H_2O	$C_7H_{11}NO_5S$ (221.2)	38.00	5.01	6.33	14.49	37.91	4.85	6.52	14.30	
μ-Thiol-D-xyloxazoline	IV	79.2	131–132	+15.7°	25	0.7571	H_2O	$C_6H_9NO_4S$ (191.2)	37.68	4.74	7.33	16.77	37.55	4.88	7.39	16.51	
μ-Thiol-L-arabinoxazoline	V	51.5	136–137	+14.7°	25	0.7392	H_2O	$C_6H_9NO_4S$ (191.2)	37.68	4.74	7.33	16.77	37.59	4.80	7.25	16.55	
N-carbomethoxyglucosamine-2	VII	71.3	196–197 decomp.	−3.28° ↙ +34.4°	20	0.6096	H_2O	$C_8H_{15}NO_7$ (237.2)	40.50	6.38	5.91		40.55	6.43	5.74 5.88		
N-carbethoxyglucosamine-2	VII	73.3	176.5–178 decomp.	+46.2° ↙ +33.3°	28	0.5408	H_2O	$C_9H_{17}NO_7$ (251.2)	43.03	6.81	5.58		43.12	6.90	5.62		
N-carbomethoxyglucosamine-1	XI	88.5	75–81	−13.7°	25	1.452	H_2O	$C_8H_{15}NO_7$ (237.2)	40.50	6.38	5.91		40.62	6.02	5.68		0.63
N-carbethoxyglucosamine-1	XI	87.1	66–72	−24.5°	25	0.7421	H_2O	$C_9H_{17}NO_7$ (251.2)	43.03	6.81	5.58		43.21	6.59	5.35		0.51
Tetraacetyl-N-carbomethoxyglucosamine-2	VIII	58.5	148–149.5	+21.4°	20	1.215	$CHCl_3$	$C_{16}H_{23}NO_{11}$ (405.3)	47.39	5.72	3.46		47.28	5.79	3.57		

Tetraacetyl-N-carbethoxyglucosamine-2	VIII	28.8	144–145	+16.1°	25	0.6056	$CHCl_3$	$C_{17}H_{25}NO_{11}$ (419.4)	48.69	6.01	3.34		48.80	6.03	3.34 3.29		
Tetraacetyl-N-carbobenzyloxyglucosamine-2	VIII							$C_{22}H_{27}NO_{11}$ (481.4)	54.87	5.65	2.91						
Compound A		3.5	151.5–152	+19.7°	20	1.335	$CHCl_3$	"	"	"	"		54.60	5.75	2.97		
Compound B		52.8	110–111	+90.7°	20	1.390	$CHCl_3$	"	"	"	"		54.91	5.60	2.91		
Compound C		23.9	151.5–152	+19.1°	25	0.5976	$CHCl_3$	"	"	"	"		54.80	5.66	2.95 2.91		
μ-Methoxyglucoxazoline	X	71.6	71–75	−24.3°	25	0.7277	H_2O	$C_8H_{13}NO_6$ (219.2)	43.83	5.98	6.39		44.01	5.71	6.15		0.62
μ-Ethoxyglucoxazoline	X	75.2	75–80	−17.8°	25	0.7641	H_2O	$C_9H_{15}NO_6$ (233.2)	46.34	6.48	6.01		46.23	6.40	6.07		0.75
μ-Benzyloxyglucoxazoline	X	59.5	71–74	−25.1°	25	0.7083	H_2O	$C_{14}H_{17}NO_6$ (295.3)	56.94	5.81	4.74		57.17	5.65	4.43		0.65
Tetraacetylmonoglucosyl-(2)-urea	IX	64.1	190–191	+24.5°	20	1.305	$CHCl_3$	$C_{15}H_{22}N_2O_{10}$ (390.3)	46.15	5.68	7.18		46.09	5.70	7.14		
Glucosyl-1-isothiocyanate	XII	61.3	(dec.)	−12.8°	25	0.7509	H_2O	$C_7H_{11}NO_5S$ (221.2)	38.00	5.01	6.33	14.49	38.11	4.81	6.21	14.22	0.86

soluble in hot methanol and ethanol, and relatively insoluble in these alcohols when cold. It is insoluble in ether, acetone, benzene, chloroform, and ethyl acetate.

N-carbethoxyglucosamine-2 is very soluble in water, hot methanol, and hot ethanol. It is relatively insoluble in the cold alcohols, and insoluble in ether, acetone, benzene, chloroform, and ethyl acetate. When a hot, saturated alcohol solution of the substance is cooled, a firm gel invariably forms. On standing at 4° for several months, small crystal nuclei form to a limited extent in the gel.

Heating with normal hydrochloric acid at 97–98° for five hours causes only slight hydrolysis of the methyl and ethyl carbamates while the benzyl ester is almost completely converted to glucosamine-2 under these conditions.

N-carbomethoxy- and N-carbethoxy-glucosamine-1 were both prepared from 1-aminoglucose by a similar method. Both are colorless, hygroscopic non-crystalline solids which are very soluble in water, absolute methanol, and absolute ethanol. They are insoluble in ether, acetone, chloroform, and ethyl acetate.

The yields, physical constants, and analytical data for the four compounds are given in Table I.

Tetraacetyl derivatives of alkyl N-carboxylates related to 2-aminoglucose (VIII). Methyl, ethyl, and benzyl carboxy-1,3,4,6-tetraacetylglucosamine-2 were each prepared by two methods: (a) by treatment of the proper alkyl carboxyglucosamine-2 with anhydrous pyridine and acetic anhydride, and (b) by treatment of tetraacetylglucosamine-2 hydrochloride (22) with the proper alkyl chlorocarbonate. The procedures described for the preparation of N-carbomethoxy-1,3,4,6-tetraacetylglucosamine-2 are typical.

(a) *Acetylation of N-carbomethoxyglucosamine-2.* N-carbomethoxyglucosamine-2 (VII) (1.6 g.) was suspended in a mixture of 14 ml. of anhydrous pyridine and 8.5 ml. of acetic anhydride. The suspension was heated at 50° for eleven hours and then allowed to stand at room temperature for three days. The resulting solution was evaporated to dryness under reduced pressure at 50° and the crystalline residue washed with ice-water. The product was dissolved in ethyl acetate, decolorized with carbon and the hot solution treated with two volumes of (60–80° b.p.) anhydrous ligroin. The product crystallized on slow cooling and was recrystallized in the same manner.

(b) *Treatment of tetraacetylglucosamine-2 hydrochloride with methyl chlorocarbonate.* A solution of 3.84 g. of tetraacetylglucosamine-2 hydrochloride in 35 ml. of water was treated with 2.5 g. of sodium bicarbonate. After addition of 25 ml. of chloroform to dissolve the liberated base, 1.15 g. of methyl chlorocarbonate was added and the mixture shaken vigorously. The chloroform layer was separated, washed, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure at 50°. The residue was recrystallized as described in (a).

Acetylation of N-carbobenzyloxyglucosamine-2 by the method outlined in (a) led to the separation of three modifications of the compound. On partial extraction of the crude material with warm ether, modification A separated from the extract as a dense, granular material, while modification B crystallized from the mother liquor as needles. Modification C was obtained as needles from ether when the residual product was dissolved in this solvent. Modification A and C have identical physical constants and apparently are polymorphs. On treating tetraacetylglucosamine-2 with benzyl chlorocarbonate only modification C was obtained.

The yields, physical constants, and analytical data for the compounds described above are given in Table I.

Derivatives of μ-hydroxyglucoxazoline (X). μ-Methoxyglucoxazoline, μ-ethoxyglucoxazoline, and μ-benzyloxyglucoxazoline were prepared by a modification of a method described by White (13). A solution of 7.0 g. of N-carbomethoxyglucosamine-2 (VII) in 1481 ml. of 0.02 *N* potassium hydroxide solution was heated to 75° for 35 minutes. The solution developed a deep red color and smelled slightly of ammonia. After cooling rapidly to 10° and adjusting to *p*H 7 with 0.1 *N* hydrochloric acid, the solution was warmed to 40°, decolorized with carbon and evaporated under reduced pressure to a volume of 150 ml.

The solution was again adjusted to *p*H 7 with 0.1 *N* hydrochloric acid, decolorized with carbon at 40° and evaporated under the above conditions to a volume of 40 ml. After again repeating the above treatment the solution was evaporated to a thick yellow sludge under reduced pressure at 45°. The residue was thoroughly dried in a vacuum desiccator over concentrated sulfuric acid and solid sodium hydroxide and then shaken with 40 ml. of absolute methanol for 48 hours at room temperature. The supernatant liquid was decolorized with carbon and evaporated under reduced pressure at 40° until a frothy solid residue remained. The residue after drying in a vacuum desiccator over concentrated sulfuric acid, was extracted with 35 ml. of ice-cold absolute methanol. The methanol solution was filtered, evaporated to dryness, and dried again as described above. Another treatment with 30 ml. of ice-cold methanol dissolved all but a very small amount of material. On prolonged standing at 4° the supernatant solution deposited a considerable amount of brown syrupy material. Evaporation of the supernatant liquid after decantation and treatment with charcoal gave a frothy solid which dissolved very readily in 40 ml. of ice-cold absolute methanol. Dropwise addition of 50 ml. of absolute acetone precipitated a flocculent solid. Slow addition of 100 ml. of absolute ether to this mixture caused further precipitation. Standing at 4° under the methanol-ether-acetone solution changed the precipitate to a dense, light yellow powder. After decantation of the supernatant solution the solid was washed with 50 ml. of absolute ether and dried in a vacuum desiccator over sulfuric acid.

The three glucoxazoline derivatives had the same general characteristics as reported by White (13) for μ-methylglucoxazoline (VI), including the formation of a red solution on treatment with a strongly acid solution of *p*-dimethylaminobenzaldehyde in ethanol.

The yields, physical constants, and analytical data for the three compounds are given in Table I.

Tetraacetylmonoglucosyl-2-urea (IX). A solution of 3.84 g. of tetraacetylglucosamine-2 hydrochloride (22) in 40 ml. of water was treated with 1.9 g. of silver cyanate. The suspension was stirred at a temperature of 45–50° until the supernatant liquid gave a negative test for chloride ion. After removal of the silver salts by filtration, the solution was saturated with hydrogen sulfide to remove silver ion. The water-white filtrate was evaporated to dryness under reduced pressure at 45° and the crystalline residue dried in a vacuum desiccator over sulfuric acid and sodium hydroxide. The product was recrystallized from ethanol.

The yield, physical constants, and analytical data for this compound are given in Table I.

Glucosyl 1-isothiocyanate (XII). A solution of 5.0 g. of tetraacetyl-D-glucosyl 1-isothiocyanate in 14 ml. of anhydrous chloroform was chilled in an ice-salt mixture and treated carefully with an ice-cold solution of 1.3 g. of sodium in absolute methanol. After ten minutes, ice-cold water was added, and the syrup that separated dissolved by stirring the mixture. After neutralization with 1:1 acetic acid, the aqueous layer was separated, washed with chloroform, and treated with charcoal. The aqueous solution was evaporated to a sludge under reduced pressure at 40°, transferred to a crystallizing dish and evaporated to dryness in a vacuum desiccator.

The dried, pulverized solid was extracted with three 20-ml. portions of absolute ethanol. The sodium acetate which had dissolved in the ethanol was precipitated by the addition of dry ether and the supernatant liquid was evaporated to dryness under reduced pressure at 35°. Several repetitions of this treatment led to the formation of a material which was rapidly and completely soluble in cold ethanol. The yield, physical constants, and analytical data for the white, hygroscopic, non-crystalline solid so obtained are given in Table I.

SUMMARY

1. A number of derivatives of 2-aminoglucose and 1-aminoglucose have been prepared in an attempt to synthesize oxazolone derivatives of glucose by applica-

tion of a sequence of unequivocal reactions. It was hoped that the preparation of these compounds would furnish a basis for the structure assigned to μ-thiolglucoxazoline and μ-hydroxyglucoxazoline by Zemplen and his collaborators.

2. It has been demonstrated by the preparation of analogous sulfur-containing derivatives of D-galactose, D-xylose, and L-arabinose, that the reaction described by Zemplén is applicable to monosaccharides other than glucose and fructose.

3. Several non-crystalline hygroscopic derivatives formed by ring closure from the alkyl N-glucosyl-2 carbamates have been prepared and are believed to be μ-methoxy-, μ-ethoxy-, and μ-benzyloxy-glucoxazoline, since the characteristics of these compounds agree generally with those of the analogous methyl-Δ^2-glucoxazoline. The characteristics of these compounds differ widely from those of Zemplén's compounds.

4. Glucosyl isothiocyanate and several alkyl N-glucosyl-1 carbamates have been prepared as non-crystalline hygroscopic powders.

NEW YORK, N. Y.

REFERENCES

(1) ZEMPLÉN, GERECS, AND RADOS, *Ber.*, **69**, 748 (1936).
(2) ZEMPLÉN, GERECS, AND ILLES, *Ber.*, **71**, 590 (1938).
(3) FISCHER AND LEUCHS, *Ber.*, **36**, 24 (1903).
(4) ELSON AND MORGAN, *Biochem. J.*, **27**, 1824 (1933).
(5) MORGAN AND ELSON, *Biochem. J.*, **28**, 998 (1934).
(6) MORGAN, *Biochem. J.*, **30**, 909 (1936).
(7) JOLLES AND MORGAN, *Biochem. J.*, **34**, 1183 (1940).
(8) FRANCHIMONT AND LUBLIN, *Rec. trav. chim.*, **21**, 46 (1902).
(9) FORSCHBACH, *Beitr. Chem. Physiol. u. Path.*, **8**, 313 (1906).
(10) CHARGAFF AND BOVARNICK, *J. Biol. Chem.*, **118**, 421 (1937).
(11) KNORR AND RÖSSLER, *Ber.*, **36**, 1278 (1903).
(12) OTTO, *J. prakt. Chem.*, (2), **44**, 17 (1891).
(13) WHITE, *J. Chem. Soc.*, 428 (1940).
(14) FREUDENBERG, DÜRR, AND VON HOCHSTETTER, *Ber.*, **61**, 1735, 1742 (1928).
(15) LOBRY DE BRUYN, *Rec. trav. chim.*, **12**, 286 (1893); **14**, 98, 134 (1895); **15**, 81 (1896); **18**, 72 (1899); *Ber.*, **28**, 3083 (1895).
(16) FISCHER AND LEUCHS, *Ber.*, **35**, 3787 (1902).
(17) IRVINE, *Biochem. Z.*, **22**, 363 (1909).
(18) SCHMUCK, *Ber.*, **56**, 1817 (1923).
(19) HARING AND JOHNSON, *J. Am. Chem. Soc.*, **55**, 395 (1933).
(20) ZEMPLÉN, *Ber.*, **59**, 1254 (1926).
(21) JOHSON AND BERGMANN, *J. Am. Chem. Soc.*, **54**, 3360 (1932).
(22) BERGMANN AND ZERVAS, *Ber.*, **64**, 975 (1931).