\( o \)-nitroaniline of high purity gave qualitatively the same chromatographic behavior as I under all conditions investigated.

A detailed presentation of the reconciliation of all known properties of benzo-furazan oxide with its structure, I, will be published shortly.

* The spectra were obtained both from Dr. Marjorie C. Caserio of the California Institute of Technology, Pasadena, and independently from Dr. LeRoy F. Johnson of Varian Associates, Palo Alto. This assistance is gratefully acknowledged.

8 Given as \( \lambda_{\max} \) 355 \( m_u \), \( \epsilon_{360} \) 6910 in ethanol by J. H. Boyer, U. Toggweiler, and G. A. Stoner, J. Am. Chem. Soc., 79, 1748 (1957).

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A CHEMICAL SYNTHESIS OF ISOMALTOSE*

BY M. L. WOLFROM, A. O. PITTET,† AND I. C. GILLAM†

DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY

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Among the naturally occurring oligo- and polysaccharides, a number of the most interesting compounds contain \( \alpha \)-linked \( \alpha \)-glucose units. The chemical synthesis of all but the simplest \( \alpha \)-\( \alpha \)-glucopyranosides has proved to be far more difficult than that of the \( \beta \)-anomers. The synthesis of a \( \beta \)-glucopyranoside link is readily achieved\(^1\) by use of the Koenigs and Knorr reaction\(^2\) in which a tetra-\( O \)-acyl-\( \alpha \)-\( \beta \)-glucopyranosyl halide reacts with a hydroxylic compound, generally in the presence of an acid acceptor. An application of the Koenigs-Knorr reaction to the synthesis of \( \alpha \)-glucosides has hitherto been of limited success. The known poly-\( O \)-acyl-\( \beta \)-glucopyranosyl halides are either unstable and tend to rearrange to the more stable \( \alpha \)-\( \alpha \) anomic form or they react with hydroxylic compounds by a mechanism involving participation of the trans 2-\( O \)-acyl group in the displacement at C-1 leading to products of \( \beta \)-configuration.\(^3\) The ability of the protecting group at C-2 to participate in this manner is believed to play an important role in the readiness with which the halides of the \( \beta \)-series anomerize. The two such compounds of this series which are relatively stable, namely, 3,4,6-tri-\( O \)-acyetyl-\( \beta \)-glucopyranosyl chloride and 3,4,6-tri-\( O \)-acyetyl-2-\( O \)\)-(trichloroacetyl)-\( \beta \)-glucopyranosyl chloride,\(^4\) are characterized by groups at C-2 which show only a slight tendency to participate.\(^5\) Thus, Hickinbottom\(^7\) was able to prepare, from these halides,
mixtures of the methyl α-glucopyranosides containing considerable proportions of the α-β-anomer. The uncertain course of the reactions of these two halides makes them of dubious value for synthesis of α-D-linked oligosaccharides; indeed, no such syntheses appear to have been reported.

Derivatives of a number of disaccharides containing α-D-glucopyranosyl residues have been synthesized by a variety of chemical methods. These include iso-
maltose, sucrose, maltose, α,α-trehalose, nigerose, kojibiose, and 2-O-α-
galactopyranosyl-D-glucose. In all cases but the first, the reported yields were low, and for some of the compounds the mechanism by which the α-D-gluco-
sidic bond is formed is not clear. We wish to report herein a novel approach to the synthesis of α-D-linked glucopyranosyl oligosaccharides. In this, use is made of a nitrate ester group which has been shown to be free of the undesirable property of participation in the displacement reaction at a neighboring carbon atom. Carbo-
hydrates containing a hydroxylic function can be nitrated under mild conditions to yield, in most cases, highly crystalline stable products; the nitrate groups may be removed by catalytic reduction when desired. An insertion of a nitrate ester group into the C-2 position of the known 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride afforded 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride. It was anticipated that the reaction of this compound with a hydroxylic derivative should lead to the formation of an α-D-glucopyranosyl bond.

Materials.—“Active” silver carbonate was prepared by a method developed in this Laboratory by Dr. L. H. Klemm. A solution of 16 gm of anhydrous sodium carbonate in 75 ml of water was added dropwise to a mechanically stirred solution of 80 gm of silver nitrate in 200 ml of water. Careful control of the rate of addition ensured that the silver oxide precipitate, which formed where the drops fell, was only transitory. A solution of 10 gm of anhydrous sodium bicarbonate in 125 ml of water was then added in two or three portions; the mixture foamed and the precipitate became yellow. The solid was recovered by filtration and washed at least 12 times by stirring with water and reflitering (the last filtrate should give a negative sodium flame test). The silver carbonate (63 gm) was dried over calcium chloride (not under reduced pressure) in the dark. Best results were obtained if the reactions were carried out in the dark at about 25°.

Chloroform (U. S. P.) was freed of alcohol by washing with water, drying over calcium chloride, and distilling from phosphorus pentoxide. It was kept in the dark in sealed tubes until required. Anhydrous ether was used in the condensation experiments. 1,2,3,4-Tetra-O-acetyl-β-D-glucose was prepared by the method of Thompson, Wolfrom, and Inatome.

3,4,6-Tri-O-acetyl-β-D-o-nitro-β-D-glucopyranosyl chloride: To a mixture of absolute nitric acid, acetic acid, and acetic anhydride (60, 15, and 25 ml, respectively, mixed at 0°), stirred at −40°, was added 9.6 gm of finely powdered 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride. The reaction mixture was allowed to warm to 0° over a period of 20 min and was then poured onto 2 kg of cracked ice. When the acetic anhydride had hydrolyzed, the white solid was filtered, washed with cold aqueous sodium hydrogen carbonate, then with ice water, and finally dried over phos-
phorus pentoxide. Crystallization from ethyl acetate-heptane afforded the pure nitrate; yield 9.63 gm (87%), mp 123.5°, [α]D +10° (c 1.0, chloroform); [α]D +15.2° (c 4.0, acetone), constant over 49 hr; [α]D +12.5° (c 0.28, ether) constant over 17 hr.

Anaylytis: Calculated for C39H32ClNO8: C, 38.10; H, 4.36; N, 3.79; Cl, 9.57. Found: C, 38.21; H, 4.27; N, 3.88; Cl, 9.74.

Methyl 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranoside: A suspension of 3 gm of Drierite (CaSO4 as soluble anhydrite; W. A. Hammond Drierite Co., Xenia, Ohio) and 0.5 gm of silver carbonate in 30 ml of absolute methanol was stirred in the absence of light (foil) for 15 min. To this was added 100 mg of silver perchlorate and 1.00 gm of 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride. The reaction mixture was stirred in the dark at room temperature for 3 hr and filtered. The sirupy residue obtained on solvent removal was dissolved in 75 ml of benzene, filtered, and again evaporated. The product was dissolved in 100 ml of ethanol, 50 mg of 10% palladium-on-
charcoal was added, and the mixture was subjected to 45 p.s.i. of hydrogen for 4.5 hr. The sirupy residue obtained on filtration and solvent removal was acetylated with 0.5 gm of sodium acetate and 10 ml of acetic anhydride at 110° for 75 min. The acetylated mixture was cooled and ice-water (250 ml) added. The mixture was stirred to hydrolyze the acetic anhydride and extracted with chloroform. The chloroform layer was washed successively with aqueous sodium hydrogen carbonate and water, dried, and evaporated to a sirup which yielded crystals; yield 846 mg (86%), mp 97–102°. This material was recrystallized from heptane; yield 765 mg (78%), mp 100–101°, undepressed on admixture with authentic methyl tetra-O-acetyl-α-D-glucopyranoside, [α]D +130° (c 1.08, chloroform).

When the above reaction was carried out in the absence of silver perchlorate, the yield of product was reduced to 35%.

β-Isomaltose octaacetate: To 100 ml of anhydrous ether was added 3 gm of Drierite, 2 gm of silver carbonate, 100 mg of silver perchlorate, and 2.70 gm (7.5 mM) of 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose. To this mixture, stirred in the absence of light, was added 1.00 gm (2.71 mM) of 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride. The reaction mixture was stirred for 5 hr at room temperature, after which no chloride ion was detectable. The suspension was filtered through carbon and washed with 100 ml of ether. The combined filtrate and washings were evaporated to a sirup, which was dissolved in 200 ml of abs. ethanol, filtered, and hydrogenated at 50 min at 33 p.s.i. with 10% palladium-on-charcoal catalyst (100 mg). Filtration and evaporation gave a sirup, which was acetylated at 130° for 30 min with sodium acetate and acetic anhydride. The cooled reaction mixture was poured into an excess of ice and water and the mixture was extracted with chloroform. The chloroform extract was washed with aqueous sodium hydrogen carbonate and water, and a sirup was dissolved in benzene (24 ml). This solution was chromatographed, in two equal parts, on two 25 × 5 cm (diam.) columns of Magnesol-Celite® (5:1 by wt). Development with 1% tert-butyl alcohol in benzene (1,600 ml), extrusion, and streaking with alkaline permanganate solution resulted in the appearance of two zones. The combined and sectioned zones were extracted with acetone. The extracts were evaporated and the residues were re-evaporated from ethanol solution whereupon they crystallized. β-D-Glucopyranose pentaacetate was obtained on evaporation of the column eluate; yield 2.1 gm, mp and mixed mp 127–129°. The faster-moving band of the column furnished crystalline β-isomaltose octaacetate: yield 1.1 gm (60%), mp 133–143°. Recrystallization afforded pure material; yield 1.01 gm (55%), mp and mixed mp 144–145°, [α]D +95° (c 1, chloroform). The slower-moving band afforded β-gentiobiose octaacetate; yield 112 mg (6%), mp 173–184°. Pure material was obtained on recrystallization from ethanol; yield 91 mg (5%), mp and mixed mp 180–191°.

Much lower yields of the octaacetates of β-isomaltose (9%) and gentiobiose (5%) were obtained on omission of the silver perchlorate, as was reported previously.*

Conversion of 3,4,β-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride to 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride with titanium tetrachloride: To a solution of 1 gm of 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride in 20 ml of chloroform was added 3 ml of titanium tetrachloride; an immediate precipitation of a yellow solid occurred. An additional 3 ml of titanium tetrachloride in 20 ml of chloroform was added to the reaction mixture and the whole was heated under reflux for 1 hr. The reaction was terminated by pouring the suspension into 70 ml of ice and water. The mixture was stirred to hydrolyze the excess titanium tetrachloride and was then extracted with chloroform. The chloroform extract was washed successively with water, aqueous sodium hydrogen carbonate solution, and again with water. After solvent removal from the dried chloroform solution, the colorless sirup obtained was crystallized from ethyl acetate–petroleum ether (bp 40–60°); yield 525 mg (62%), mp 86.5–88.5°, [α]D +181° (c 1, chloroform). Recrystallization from the same solvent mixture yielded needles; mp 89–91°, undepressed on admixture with authentic 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride.† The material contained chlorine but gave a negative test for nitrate.

Discussion.—Nitration of 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride was readily achieved by dissolution in a cold mixture of nitric acid, acetic anhydride, and acetic acid. The crystalline product, isolated in good yield, was 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride (I); its optical rotation indicated that
the chloride had not anomerized during the period of reaction. A solution of this substance in acetone or ether exhibited no mutarotation over observation periods of 20 to 50 hours.

An attempt to effect the anomerization of compound I to the presumably more stable α-D-form was made by treating it with titanium tetrachloride in chloroform solution. The product of the reaction was 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride. Thus, anomerization was effected, but the nitrate ester group was cleaved without deacetylation.

Methanolysis of 3,4,6-tri-O-acetyl-2-O-nitro-β-D-glucopyranosyl chloride at room temperature in the presence of silver carbonate yielded, after hydrolysis and acetylation of the product, methyl tetra-O-acetyl-α-D-glucopyranoside (35%) as the only isolable product. A more vigorous reaction occurred when a catalytic quantity of silver perchlorate was added to the reaction mixture, and an improved yield (78%) of methyl tetra-O-acetyl-α-D-glucopyranoside was obtained. Bredereck and associates22 have reported the use of silver perchlorate alone in the synthesis of gentiobiose by the condensation of tetra-O-acetyl-α-D-glucopyranosyl bromide with tetra-O-acetyl-6-O-trityl-β-D-glucopyranosyl in nitromethane solution.

In a typical Koenigs-Knorr reaction,1,2 the rate-limiting step, apparently, is the heterogeneous interaction of the glycosyl halide with the insoluble silver carbonate. In our modification, an excess of silver carbonate was maintained and the perchloric acid, formed on reaction with compound I with the soluble silver perchlorate, acted on the silver carbonate to regenerate the silver perchlorate in solution (2). The driving force of this reaction is probably the concerted exchange, with inversion, of the β-D-chloro atom with the alkoxide through the formation of insoluble silver chloride (1).

\[
\begin{align*}
\text{I} & \quad \text{O}^\text{Cl} \quad + \quad \text{AgClO}_4 \quad + \quad \text{CH}_3\text{OH} \rightarrow \quad \text{O}^\text{HCH}_3 \quad + \quad \text{AgCl} \quad + \quad \text{HClO}_4 \\
& \quad \text{ONO}_2 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 

[\text{2HClO}_4 \quad + \quad \text{Ag}_2\text{CO}_3 \quad \rightarrow \quad 2\text{AgClO}_4 \quad + \quad \text{H}_2\text{O} \quad + \quad \text{CO}_2]
\end{align*}
\]

The modification of the Koenigs-Knorr reaction described above was then applied to the synthesis of isomaltose, 6-0-α-D-glucopyranosyl-d-glucose. Ether was selected as a suitable inert solvent, and compound I was reacted with an excess of 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose under these conditions. The syrupy reaction product was denitrated18 with hydrogen and palladium, and the acetylated product was separated chromatographically22 by silicate column chromatography. β-Isomaltose octaacetate was obtained in 55 per cent yield together with a 5 per cent yield of β-gentiobiose octaacetate. This is an excellent yield of the former substance for this type of reaction. The deacetylation of those octaacetates to the unsubstituted disaccharides is well established.

The origin of the octaacetate of β-gentiobiose, 6-0-β-D-glucopyranosyl-d-glucose, is not established. The stability of I in the solvent employed would appear to rule out anomerization of this glycosyl halide. It is probable that its origin lies in a preliminary solvent-assisted dissociation of the glycosyl halide into an ion pair type24 of reaction (3). Indeed, it is asserted25, 26 that glycosyl halides react nor-
mally by such a mechanism. The reaction may well occur on the surface of the silver carbonate, and it has been noted that the adsorption of a halogen compound on the polar surface of an insoluble salt facilitates the dissociation of the carbon-halogen bond.

\[
\begin{align*}
\text{ONO}_2^- + \text{Cl}^- & \rightarrow \text{ONO}_2^2^- + \text{OR}^2^- \\
\text{Cl}^- & \rightarrow \text{OR}^2^- \\
\text{ONO}_2^- & \rightarrow \text{ONO}_2^2^-
\end{align*}
\]

(3)

**Summary.**—The synthesis of 3,4,6-tri-O-acetyl-2-O-nitro-\(\beta\)-D-glucopyranosyl chloride, a substance with a non-participating group at C-2, furnishes a new approach to the synthesis of the \(\alpha\)-D-glucopyranosyl linkage. The halide is rather unreactive but it is shown that the addition of catalytic amounts of silver perchlorate to the Koenigs-Knorr reaction greatly facilitates the formation of the \(\alpha\)-D-glucopyranosyl bond. Methanalysis of the halide with subsequent denitration and reacetylation furnishes methyl \(\alpha\)-D-glucopyranoside (tetraacetate) in 78 per cent yield. Reaction with 1,2,3,4-tetra-O-acetyl-\(\alpha\)-D-glucopyranose furnishes isomaltose (\(\beta\)-octaacetate) in 55 per cent yield together with a small amount (5 per cent) of gentiobiose (\(\beta\)-octaacetate).


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2 Koenigs, W., and E. Knorr, *Ber.*, 34, 957 (1901).
A MATHEMATICAL AID IN OPTIMIZING ENGINEERING DESIGNS, II

BY A. E. FEIN

WESTINGHOUSE RESEARCH LABORATORIES, PITTSBURGH

Communicated by Clarence Zener, March 28, 1961

The following analysis pertains to a method of finding stationary points of a special type of engineering design function of several variables as described in the previous paper by C. Zener. In this analysis, it will be shown that the method described by Zener is rigorously valid under a set of necessary and sufficient conditions, and those conditions will be described. Further, Zener's analysis stops upon determining the optimum value of their function without specifying the values of the dependent variable at which the extrema occur. Here, the determination of these values will be carried out.

The type of function considered is

$$C(x_1, \ldots, x_{n-1}) = \sum_{j=1}^{n} T_j,$$

where

$$T_j = A_j \prod_{k=1}^{n-1} x_k^{\beta_{jk}},$$

where $A_j$ and $\beta_{kj}$ are numbers independent of $(x_1, \ldots, x_{n-1})$. That is, the function $C$, whose extrema are to be found, is a function of $n - 1$ variables and is expressed as the sum of $n$ terms each of which is a product of powers of the $n - 1$ variables.

The first step in Zener's approach is to construct a set $(\alpha_1, \ldots, \alpha_n)$ such that

$$K = \prod_{j=1}^{n} T_j^{\alpha_j}$$

is independent of $(x_1, \ldots, x_{n-1})$. We shall now derive a means of determining these exponents $\alpha_j$. From (2),

$$K = \prod_{j=1}^{n} A_j^{\alpha_j} \prod_{k=1}^{n-1} x_k^{\beta_{kj} \alpha_j} = A \prod_{k=1}^{n-1} x_k^{\gamma_k},$$

where

$$A = \prod_{j=1}^{n} A_j^{\alpha_j}$$

and

$$\gamma_k = \sum_{j=1}^{n} \beta_{kj} \alpha_j = 0 \quad (k = 1, \ldots, n - 1),$$