Elimination of the Exocyclic Secondary *p*-Tolylsulfonyloxy Group in a D-Glucofuranose Structure[1,2]

ROBERT E. GRAMERA, TRIMBAK R. INGLE, AND ROY L. WHISTLER

Department of Biochemistry, Purdue University, Lafayette, Indiana

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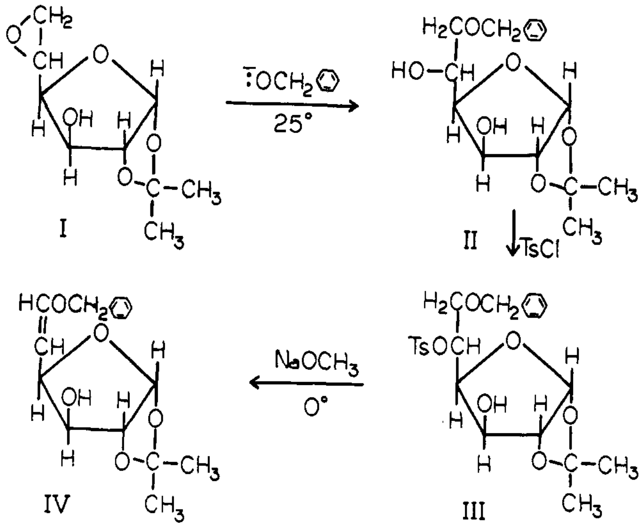
Although the stereochemical configuration of 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose would seem to permit formation of a 3,5-anhydro (oxetane) ring under experimental conditions usually adopted for anhydro ring formation, the olefin, 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose is nevertheless obtained in 95% yield by a desulfonyloxylation and β-elimination of the tosylated D-glucofuranose derivative. Reductive ozonolysis and n.m.r. indicate that the double bond in the olefin is between carbons 5 and 6. Mild catalytic hydrogenation of the vinylene sugar derivative affords crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.

Formation of an oxetane ring by base-catalyzed elimination of a suitably located tosyloxy group in the sugar molecule has been described previously in the literature.[3-5] A specific example wherein an exocyclic primary tosyloxy group in 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose is eliminated in the presence of sodium methoxide to give 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose was demonstrated by Levene and Raymond.[6]

In this work an attempt to introduce an oxetane ring into a D-glucofuranose derivative, by anionic elimination of the exocyclic secondary tosyloxy group, gives an unsaturated D-glucofuranose derivative in 95% yield rather than the expected anhydro sugar.

5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (I) prepared from 1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose serves as the starting compound for this synthesis. Compound I is treated with sodium benzyl alkoxide to give crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (II) in 80% yield. The benzyl group is stable in alkali and is removed conveniently by catalytic hydrogenolysis. Since the steric and electrical effects of the 6-*O*-benzyl group in II are closely analogous to the 6-*O*-benzoyl group as in 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose,[7] and selective tosylation of the more reactive C-5 hydroxyl group of the latter compound has been reported,[7,8] it is expected that monotosylation of II also would give a C-5 tosylated derivative. Crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III) is obtained in 50% yield by selective tosylation of III. Crystalline 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose obtained by catalytic hydrogenolysis of III is treated with sodium methoxide to give 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose. Isolation and identification of the known[9] anhydro derivative proves the structure of III. One product isolated after reductive desulfonyloxylation[10,11] of III with lithium aluminum hydride and subsequent hydrogenolysis with palladium on carbon is identified as 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.[12]

A crystalline product (IV) obtained from the reaction of III with sodium methoxide absorbs bromine from a bromine–carbon tetrachloride solution and decolorizes an aqueous potassium permanganate solution. Since the product obtained from a reductive ozonolysis of the crystalline olefinic sugar derivative is identified as 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[13] (V) on paper chromatography, and the latter is converted to 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose phenylhydrazone[13,14] (VI), the olefinic sugar is concluded to be 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IV). Acetylation of IV gives 3-*O*-acetyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose.



Two different melting points of IV are observed. One crystalline form shows a constant melting point of 113° on recrystallization. However, when the crystals are melted and cooled, the melting point increases to 119.5° and remains at this value on subsequent remelts. The lower melting crystalline form exhibits birefringence and is obtained as long needles. The higher melting form is amorphous in appearance

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[2] Presented before the Division of Carbohydrate Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(3) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **63**, 2241 (1941).

(4) E. E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 1585 (1938).

(5) R. M. Hann, N. K. Richtmyer, H. W. Diehl, and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 561 (1950).

(6) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 331 (1933).

(7) H. Ohle and E. Dickhauser, *Ber.*, **58**, 2593 (1925).

(8) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961).

(9) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

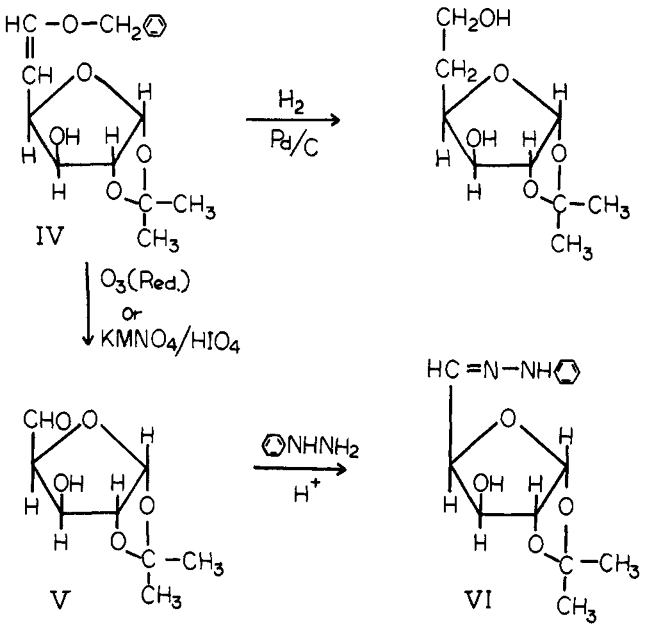
(10) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2149 (1952).

(11) H. L. Goering and C. Serres, Jr., *ibid.*, **74**, 5908 (1952).

(12) T. E. Whiteley (Ohio State University, Columbus), University Microfilms, Ann Arbor, Mich., L. C. Card No. Mic. 60-6419, p. 122 ff.; *Dissertation Abstr.*, **21**, 2121 (1961).

(13) K. Iwadare, *Bull. Chem. Soc. Japan*, **16**, 40 (1941).

(14) S. Akiya and T. Osawa, *J. Pharm. Soc. Japan*, **76**, 1280 (1956).



but has a crystalline X-ray pattern. Both forms have the same absorption spectra in infrared.

The n.m.r. spectrum of II obtained in deuterated chloroform shows a specific proton coupling at τ 3.1 to 3.8 due to the hydrogens on the C-6 position. A proton coupling of this nature which is not observed in the spectrum of IV reveals that there is one hydrogen on C-6 and, therefore, suggests that a double bond is located between C-5 and C-6.

Examination of the infrared spectrum of IV reveals specific absorptions at 1310 and 975 cm.$^{-1}$, indicative of a *trans* arrangement of hydrogens.

Crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose is obtained in about 90% yield by a simultaneous catalytic hydrogenation and hydrogenolysis of IV with palladium on carbon.

This observed phenomena wherein an exocyclic secondary tosyloxy group is eliminated with an accompanying β-proton elimination in a D-glucofuranose structure is interesting, since the vinylene sugar obtained contains an activated double bond due to the electron-withdrawing effect of the adjacent benzyl ether group. Vinylene sugar derivatives of this type are not known and, therefore, synthetic possibilities of similar compounds are now under investigation in our laboratory to determine their potential usefulness as either dienophiles for the synthesis of Diels-Alder type addition compounds and as activated monomers for polymerization.

Experimental

Analytical Methods.—Chromatographic identifications of sugar derivatives were made at 25° on Whatman No. 1 filter paper and developed in irrigants A, 1-butanol-ethanol-water (40:11:19 v./v.), or B, ethyl acetate-pyridine-water (10:4:3 v./v.). Spray indicators employed were C, potassium permanganate-periodate, and D, an acetone solution of silver nitrate, followed by an ethanolic sodium hydroxide solution.[15] Purity of crystalline products were determined by thin layer chromatography on 1 × 3 in. silica gel G[16]-coated microscope slides irrigated with E, 1-butanol saturated with water, or F, chloroform-acetone (1:1 v./v.). Plates were sprayed with a dilute ethanolic solution containing 5% sulfuric acid and charred at 110° until permanent spots were visible. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were done at reduced pressure.

5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (I).—Compound I was prepared by the method described in "Methods in Carbohydrate Chemistry," Vol. II.[17] However, the starting material, namely 1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose, for the preparation of I was scaled up by a modified procedure. The chloroform solution containing the 6-*O*-tosyl derivative was extracted with an aqueous solution of copper sulfate until the color of the extract changed from a prussian blue to an azure blue. The chloroform phase was washed successively with two portions of water, a dilute chilled solution of acetic acid, and finally with water, after which it was dried over anhydrous sodium sulfate, filtered, and evaporated below 40°. The 6-*O*-tosyl derivative crystallized from a solution of ether and petroleum ether (b.p. 40-60°) in 63% yield and had a melting point of 108°.

6-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (II).—Compound I (36 g.) was added slowly to 400 ml. of a cooled, continuously stirred solution of benzyl alcohol which contained 4 g. sodium. The solution was maintained at 25° for 3 days and then slowly neutralized with a chilled dilute solution of sulfuric acid. Sodium sulfate was filtered from solution and washed with two 20-ml. portions of benzyl alcohol. Combined washings and filtrate were extracted with two 50-ml. portions of water. The aqueous phase was made alkaline with a 40% solution of potassium hydroxide and extracted with diethyl ether. Both ether extracts and benzyl alcohol filtrates were combined and dried over anhydrous sodium sulfate. After filtration, ether was removed under reduced pressure and the remaining benzyl alcohol was removed by high vacuum distillation. Compound II, contained in the residue, crystallized from a mixture of ether-petroleum ether to yield 45 g. (80%), m.p. 74-75°. Compound II was recrystallized from ethyl acetate and petroleum ether to give m.p. 79°, $[\alpha]^{25}\text{D}$ −3.5° (*c* 0.97, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.14. Found: C, 61.74; H, 7.12.

6-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (III).—A solution containing 30 g. of II dissolved in 100 ml. of pyridine was cooled with stirring to −5°. A one-half portion of 18.42 g. of tosyl chloride (*p*-toluenesulfonyl chloride) was added to the solution over a period of 2 hr. The solution was maintained at 25° for 5 hr., cooled again to −5°, and the remaining half portion of tosyl chloride was added as before. After 10 hr. at 25°, the reaction mixture was treated with ice and stirred for 0.5 hr., after which 100 ml. of chloroform was added, and the total mixture was poured into ice-water. The chloroform layer was washed sequentially with water, an ice-cold solution of aqueous hydrochloric acid until slightly acidic (pH 4.0), and an aqueous solution of sodium bicarbonate until neutral. After several washings with water, the chloroform layer was dried over sodium sulfate, filtered, and evaporated below 40° to a sirup which crystallized from a benzene-petroleum ether mixture. Compound III was obtained as long needles; the yield was 23 g. (50%), m.p. 130-131°, $[\alpha]^{25}\text{D}$ −10.1° (*c* 1.15, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_8S$ (464.53): C, 59.47; H, 6.07; S, 6.90. Found: C, 59.56; H, 6.09; S, 7.06.

1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose.—Compound III (1 g.) was dissolved in 25 ml. of absolute ethanol containing 5 g. of 5% palladium on carbon. The mixture was subjected to 50 p.s.i. of hydrogen in a Parr hydrogenation apparatus and shaken at 25° for 10 hr. Filtration and evaporation of the solution gave a sirup which readily crystallized from benzene-petroleum ether to yield 716 mg. (88%) of product, m.p. 124°, $[\alpha]^{25}\text{D}$ +8.0° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_8S$ (374.4): C, 51.33; H, 5.92; S, 8.56. Found: C, 51.38; H, 5.86; S, 8.41.

5,6-Anhydro-1,2-*O*-isopropylidene-β-L-idofuranose.—A solution containing 500 mg. of 1,2,-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose dissolved in 0.5 ml. of alcohol-free chloroform was chilled to −15° and a 0.25-ml. portion of methanol containing 60 mg. of sodium was added. After the reaction mixture was maintained at 0° for 3 hr., 0.2 ml. of a saturated solution of potassium bicarbonate was added. The mixture was evaporated at 0° to remove methanol, extracted with three portions of chloroform, and dried over anhydrous magnesium

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(15) W. E. Trevelyan, P. D. Proctor, and S. J. Harrison, *Nature*, **166**, 444 (1950).

(16) Brinkman Instruments, Inc., Great Neck, L. I., N. Y.

(17) R. L. Whistler and M. L. Wolfrom, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p. 190.

sulfate. After filtration and evaporation of solution, a crystalline product obtained from a benzene–petroleum ether mixture was identical with 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose,[9] since the melting point of 74° remained undepressed when admixed with an authentic sample.

Reduction of Compound III.—After 2 g. of III was dissolved in 25 ml. of anhydrous tetrahydrofuran and cooled to 0°, 1 g. of lithium aluminum hydride was added. Within 0.5 hr. the mixture was warmed to 25°, then stirred for 2 hr., and refluxed an additional 48 hr. Excess hydride was destroyed carefully by a slow addition of water. After 100 ml. of a saturated aqueous sodium sulfate solution was added, the mixture was poured into a separatory funnel and mixed with a dilute chilled hydrochloric acid solution until the solids were dissolved. The tetrahydrofuran layer was drawn off, and the remaining aqueous phase was extracted with four 20-ml. portions of chloroform. The chloroform extracts were combined with the tetrahydrofuran layer, washed three times with water, and dried over anhydrous magnesium sulfate. A sirupy product obtained after filtration and evaporation of solvent was dissolved in 25 ml. of absolute ethanol and hydrogenated at 50 p.s.i. for 10 hr. at 25° with palladium on carbon. A portion of the sirupy product obtained after hydrogenation crystallized from a benzene–petroleum ether mxiture as long needles; the yield was 150 mg., m.p. 95°, $[\alpha]^{25}\text{D}$ −9.0 (*c* 0.50, chloroform).

A mixture melting point of this product and an authentic sample of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose remained undepressed.

Anal. Calcd. for $C_9H_{16}O_5$ (204.22): C, 52.94; H, 7.89. Found: C, 53.14; H, 7.79.

6-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose (IV).—Compound III (2 g.) was dissolved in 15 ml. of alcohol-free chloroform. The mixture was cooled to −5° and 8 ml. of methanol containing 12.5% sodium methylate was added. The solution was stirred for 1 hr. at 0° and then at 25° for an additional 16 hr. A saturated solution of potassium bicarbonate was added, and the mixture was evaporated to remove methanol. The residue was extracted four times with 25-ml. portions of chloroform and dried over anhydrous magnesium sulfate. The solution was filtered and evaporated under reduced pressure to a sirup which crystallized from a mixture of benzene–petroleum ether in long fine needles to yield 1.25 g. (95%) of product with m.p. 113°, $[\alpha]^{25}\text{D}$ −47.3° (*c* 1.15, chloroform). Paper chromatograms of IV in irrigants A and B when sprayed with indicator C revealed a single component. Thin layer chromatograms in irrigants E and F indicated that IV was not contaminated with any foreign organic material. It absorbed bromine from a bromine–carbon tetrachloride solution and instantaneously decolorized a potassium permanganate solution indicating unsaturation; $\nu_{\max}^{\text{KBr}}$ 1310 (m) and 975 (s), *trans* double bond; and 810 and 948 cm.$^{-1}$, vinyl ether.

Anal. Calcd. for $C_{16}H_{20}O_5$ (292.33): C, 65.74; H, 6.89. Found: C, 65.92; H, 6.82.

Reductive Ozonolysis of IV.—A 20-ml. portion of purified ethyl acetate was cooled to −70° in a Dry Ice–acetone bath and ozone was bubbled through the solution until a permanent blue color was maintained. A solution containing 30 mg. of IV, dissolved in 1 ml. of cold ethyl acetate, was added to the ozone-saturated ethyl acetate solution. Excess ozone was immediately evaporated and the remaining ethyl acetate solution containing the respective ozonide was concentrated nearly to dryness. After a 10-ml. portion of methylene chloride and 50 mg. of Lindlar catalyst[18] were added to the ozonide, the mixture was agitated for 0.5 hr. in a hydrogen atmosphere. Filtration and evaporation of the hydrogenated solution gave a sirupy product which, on paper chromotography in irrigants A and B, developed with indicator D, migrated identically with 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[13] (V). The latter was converted to 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose phenylhydrazone[13,14] (VI), m.p. 140°, $[\alpha]^{25}\text{D}$ −42.0° (*c* 2.0, chloroform).

3-*O*-Acetyl-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose.—A 300-mg. portion of IV was dissolved in 3 ml. of pyridine, cooled to 0°, and 1 ml. of acetic anhydride was added. After 10 hr. at 0°, the reaction mixture was warmed to 25° for an additional 9 hr., then poured into ice–water, and stirred until the gummy acetate settled. A chloroform solution containing the acetyl derivative was washed with water and dried over anhydrous sodium sulfate. After filtration and evaporation of solution, the acetyl derivative, obtained as a semisolid, crystallized from benzene–petroleum ether to give a product with m.p. 78°, $[\alpha]^{25}\text{D}$ −34.5° (*c* 1.05, chloroform).

Anal. Calcd. for $C_{18}H_{22}O_6$ (334.36): C, 64.66; H, 6.63; CH_3CO, 12.87. Found: C, 64.83; H, 6.72; CH_3CO, 12.63.

5-Deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.—Compound IV (200 mg.) was dissolved in 20 ml. of absolute ethanol containing 1 g. of palladium on carbon. The mixture was subjected to 50 p.s.i. of hydrogen pressure in a Parr hydrogenation apparatus and shaken at 25° for 8 hr. Filtration of the reaction mixture and evaporation of solvent gave a sirup, which spontaneously crystallized from a mixture of benzene–petroleum ether to yield 130 mg. (90%) of product with m.p. 95°, $[\alpha]^{25}\text{D}$ −10.0° (*c* 0.71, in chloroform). An X-ray powder diffraction pattern of the crystalline product was identical with an authentic sample of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.

Anal. Calcd. for $C_9H_{16}O_5$ (204.22): C, 52.94; H, 7.89. Found: C, 53.05; H, 7.98.

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[18] H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

6-Deoxy-6-hydrazinoamylitol and 6-Deoxy-6-hydrazinocellulose[1]

ROY L. WHISTLER AND BARUCH SHASHA

Department of Biochemistry, Purdue University, Lafayette, Indiana

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Direct tosylation of amylitol and cellulose to (degree of substitution) 0.65 and 0.64, respectively, and reaction with hydrazine leads to 6-deoxy-6-hydrazinoamylitol of D.S. 0.40 and 6-deoxy-6-hydrazinocellulose of D.S. 0.50. Different oxidants remove the hydrazino groups with formation of 6-deoxyglycans which on hydrolysis produce D-glucose and D-quinovose. Reaction of the 6-deoxy-6-hydrazinoglycans with D-glucose or D-glucono-1,4-lactone produces the appropriate derivatives in quantitative yields.

Introduction of hydrazino groups into the linear polysaccharides amylose and cellulose is undertaken to make available reactive groups that may be used as attachment points for sugars or sugar derivatives. In this way it is possible to construct molecules with sugar size chains of controlled lengths. By insertion of the hydrazino groups, used for coupling, at the C-6 position, side chains are uniformly located. Such definite compounds are of value in establishing the relationship between molecular architecture and physical properties of high polymeric hydrophilic molecules. Previously, this laboratory[2] made 6-amino-6-deoxy-

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[2] R. L. Whistler and D. G. Medcalf, presented in part before the Carbohydrate Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962; *Arch. Biochem. Biophys.*, **104**, 150 (1964).