[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

N-(3,4,6-Triacetyl-D-glucosyl)-piperidine and Its Use in Preparing 2-Substituted Glucose Derivatives

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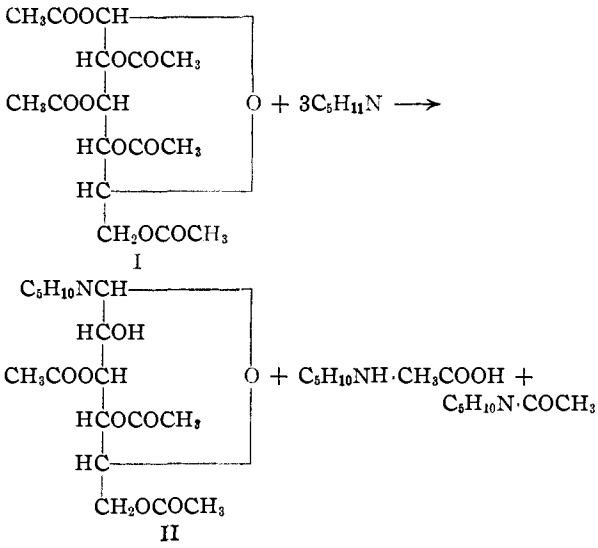
Crystalline N-(3,4,6-triacetyl-D-glucosyl)-piperidine has been isolated from the reaction of piperidine with pentaacetyl-D-glucopyranose, and the structure of this compound has been established. The substance is shown to provide a readily accessible starting product for the preparation of 2-substituted derivatives of D-glucose. A number of new compounds are reported.

Hans Vogel[2] studied the action of organic bases on sugars and sugar derivatives. For the reaction between piperidine and pentaacetyl-D-glucose he concluded that deacetylation on carbon atoms 1 and 2 occurred, since his tests for ene-diol formation in the mixture were positive. However, no crystalline products of the reaction were isolated.

We have isolated a new crystalline compound from the reaction of piperidine and pentaacetyl-(α or β)-D-glucopyranose (I) and have proved it to be N-(3,4,6-triacetyl-D-glucosyl)-piperidine (II). Since optimum yields were obtained by the use of 3 moles of piperidine for each mole of pentaacetyl-D-glucose, we have formulated the reaction thus



Crystalline piperidine acetate was isolated from the reaction mixture; however, no attempt was made to isolate the high-boiling liquid, N-acetylpiperidine. Since II was produced from 2,3,4,6-tetraacetyl-D-glucopyranose and piperidine, but not from N-(2,3,4,6-tetraacetyl-D-glucosyl)-piperidine, the separation of the acetyl group from the position of the second carbon atom must accompany or precede the formation of the glucosylamine linkage.

The structure of II was established by the following reactions: (1) The reaction of 1-chloro-3,4,6-triacetyl-D-glucopyranose[3] with piperidine at 0° produced II. (2) Methylation of II followed by deacetylation and hydrolysis gave the known 2-methyl-β-D-glucose in crystalline form. (3) Deacetylation of II in methanol–ammonia gave N-D-glucosylpiperidine.[4] (4) Acetylation of II in pyridine–acetic anhydride gave N-(2,3,4,6-tetraacetyl-D-glucosyl)-piperidine.[4,5] By these reactions the free hydroxyl group was shown to be on the second carbon atom, and the ring form to be pyranose. The question of the anomeric form (α or β) of II was not definitely settled. Since acetylation of II in pyridine–acetic anhydride at low temperature produced the same tetraacetate of N-D-glucosylpiperidine as was formed from 1-bromo-2,3,4,6-tetraacetyl-α-D-glucopyranose and piperidine[4,5] the β-form is indicated (provided that β-N-glycosides are formed, like β-O-glycosides, from tetraacetyl-α-D-glucosyl bromide).

Compound II offers an easily prepared starting material for the preparation of 2-substituted glucose derivatives. 2-Carbanilino-D-glucose, a new compound, and 2-methyl-D-glucose were easily prepared from II by acylation and alkylation, respectively, followed by deacetylation and hydrolysis. The 2-*p*-toluenesulfonyl derivative of II was also prepared and deacetylated to N-(2-*p*-toluenesulfonyl-D-glucosyl)-piperidine. The route of synthesis employed here is a general one and it is not unlikely that other 2-substituted aldoses could be prepared in the same way.

Experimental[6]

Materials.—A "Practical" grade of piperidine was dried over sodium hydroxide pellets and fractionally distilled. The fraction boiling from 105.5–107° was taken. Pentaacetyl-α-D-glucopyranose, m.p. 112°, and pentaacetyl-β-D-glucopyranose, m.p. 131°, were obtained by recrystallizing commercial preparations from ethanol.

N-(3,4,6-Triacetyl-D-glucosyl)-piperidine.—(a) Pentaacetyl-β-D-glucopyranose, 117 g. (0.30 mole) and piperidine, 77 g. (0.90 mole), were stirred together in a flask. After about 3 minutes, as soon as warming of the mixture was detected, the flask was cooled in an ice-water-bath at intervals to keep the mixture at 25 ± 5°. After about 8 minutes from the time of mixing, the original pasty mass had become fluid and nearly clear. Only a pale yellow color developed. A few minutes later crystallization of the product began. Stirring was continued for several minutes while diethyl ether (100 ml.) was added. The flask was kept at 0° for an hour, then the white crystals were collected on a buchner funnel, washed with ether, and dried *in vacuo* over calcium chloride; yield 49.3 g. The yellow filtrate from the first batch of crystals was diluted with ether and kept at 0° overnight; yield 19.7 g. The two batches combined gave 69.0 g. (62%) of white, crude product; m.p. 119° with decomposition. The crude product was purified (removing piperidine acetate) by stirring it in 150 ml. of absolute ethanol for 10 minutes, filtering, washing with absolute ethanol and ether, and drying; yield 40 g. (36%); white needles, m.p. 125° (dec.); $[\alpha]^{25}D$ +31.6° (*c* 4.0, chloroform).

The compound is soluble in chloroform, ethylene chloride, acetone, dioxane, pyridine and hot alcohols; it is only

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(2) H. Vogel, *Ber.*, **70**, 1193 (1937).

(3) P. Brigl, *Z. physiol. Chem.*, **116**, 20 (1921).

(4) J. E. Hodge and C. E. Rist, THIS JOURNAL, **74**, 1494 (1952).

(5) J. W. Baker, *J. Chem. Soc.*, 1205 (1929).

(6) All melting and boiling points are corrected.

slightly soluble in cold water, cold alcohols, ethyl acetate, benzene, ether and carbon tetrachloride. In glacial acetic acid it dissolves and undergoes decomposition with browning of the solution. The compound reduces hot Fehling solution.

(b) Pentaacetyl-α-D-glycopyranose, 19.6 g. (0.050 mole), was suspended in 50 ml. of dry ether, and piperidine, 17.0 g. (0.20 mole), was added. There was a cooling effect on adding the piperidine, but after 20 minutes at 25° heat was produced, and the pentaacetyl-α-D-glucose dissolved completely. No color developed. Light petroleum ether, 30 ml., was added, and the flask was cooled at 1° for 4 hours. The white crystals which formed were filtered off and dried; yield 7.0 g. The product was purified by stirring with 80 ml. of absolute ethanol, filtering, and recrystallizing the washed crystals from 80 ml. of absolute methanol; yield 4.75 g. (25%), m.p. 122–123° (dec.). The melting point of the pure compound was sharp, but varied between 121 and 126°, depending upon the manner and rate of heating. The crystals turned brown several degrees before the melting point was reached; $[\alpha]^{25}D$ +31.7 (*c* 4.0, chloroform).

Anal. Calcd. for $C_{11}H_{18}O_5N(COCH_3)_3$: C, 54.7; H, 7.29; N, 3.75; $COCH_3$, 34.6. Found: C, 54.7; H, 7.21; N, 3.94; $COCH_3$, 34.7.

Other solvents (chloroform, acetone, benzene, pyridine, methanol and ethanol) were tried as reaction media, but the yields were lower (10–20%) and in most cases considerable browning of the reaction mixtures occurred.

(c) 1-Chloro-3,4,6-triacetyl-D-glycopyranose was prepared by the method of Brigl.[3] The glistening needles, m.p. 133–135° (probably a mixture of α- and β-forms), 2.5 g., were treated with 1.5 g. of piperidine at 0° for 6 days. To the matrix of crystals which formed were added 5-ml. portions of absolute ethanol. Decanting through a filter yielded 1.0 g. (35%) of white, needle crystals, m.p. 123° (dec.). After recrystallization from 10 ml. of absolute ethanol, the yield was 0.8 g., m.p. 123° (dec.); $[\alpha]^{21}D$ +31.4° (*c* 2.3, chloroform).

Anal. Calcd. for $C_{11}H_{18}O_5N(COCH_3)_3$: N, 3.75; $COCH_3$, 34.6. Found: N, 3.76; $COCH_3$, 34.2.

(d) 1-Chloro-2-trichloroacetyl-3,4,6-triacetyl-D-glucopyranose,[3] m.p. 140°, 1.75 g., was suspended in dry ether (10 ml.) at 0°. Piperidine, 0.95 g., was added, and the mixture was kept at 0° for 4 days. No color developed and a white, crystalline precipitate was formed; yield 1.2 g. (86%); m.p. 120° (dec.). Recrystallized from 10 ml. of absolute ethanol, the compound melted and decomposed sharply at 124°, and a mixture with the product described in paragraph (b) above showed no lowering of the decomposition point; $[\alpha]^{25}D$ +31.7° (*c* 2.0, chloroform).

(e) Tetraacetyl-β-D-glucopyranose, 1.0 g., and piperidine 0.85 g., were stirred together and allowed to stand at 25° for several days. The solution was diluted with ether and cooled to 0°, producing 0.15 g. of white needle crystals. After two recrystallizations from absolute ethanol, the product melted at 122° (dec.). A mixture with the product obtained above, paragraph (b), showed no lowering of the decomposition point.

Anal. Calcd. for $C_{11}H_{18}O_5N(COCH_3)_3$: N, 3.75. Found: N, 3.76.

(f) An attempt to prepare N-(3,4,6-triacetyl-D-glucosyl)-piperidine from N-(2,3,4,6-tetraacetyl-D-glucosyl)-piperidine[4] and piperidine under the conditions given in paragraph (e) resulted only in the recovery of the starting material (50%). None of the compound melting with decomposition in the range 121–126° could be isolated.

Acetylation of N-(3,4,6-Triacetyl-D-glucosyl)-piperidine.—N-(3,4,6-Triacetyl-D-glucosyl)-piperidine, 2.2 g., was added in portions to a mixture of 9 ml. of dry pyridine and 2 ml. of acetic anhydride previously cooled to 0°. The mixture was kept at 0° for 16 hours and at 27° for 4 hours. The resulting solution was concentrated *in vacuo* yielding a dry, crystalline residue. Addition of 10 ml. of ethanol, cooling to 0°, filtering, and washing with cold ethanol gave 2.2 g. of fine white needles, m.p. 122° without decomposition. Recrystallization from 20 ml. of absolute ethanol gave 2.0 g., m.p. 123°, $[\alpha]^{26}D$ −3.5° (*c* 5.1, chloroform). A mixture with authentic N-(2,3,4,6-tetraacetyl-D-glucosyl)-piperidine[4] also melted sharply at 123°.

Deacetylation of N-(3,4,6-Triacetyl-D-glucosyl)-piperidine.—N-(3,4,6-Triacetyl-D-glucosyl)-piperidine, 2.15 g., was suspended in 25 ml. of ammoniacal methanol (14% NH_3), and the mixture was kept at 0° for 28 hours. The solution was concentrated *in vacuo* with the addition of methanol to a clear, amber sirup. Ethyl acetate was added and, after seeding with N-D-glucosylpiperidine,[4] crystallization occurred. The crystals were filtered, washed with hot ethyl acetate and dried *in vacuo* over calcium chloride; yield 1.1 g. (77%); m.p. 123° (dec.). Recrystallized from ethanol–acetone the crystals, 0.7 g., melted at 128–129° (dec.); $[\alpha]^{25}D$ +8.4°, without mutarotation (*c* 5.0, pyridine). The constants are the same as those of N-D-glucosylpiperidine.[4]

N-(2-Methyl-3,4,6-triacetyl-D-glucosyl)-piperidine.—N-(3,4,6-Triacetyl-D-glucosyl)-piperidine, 20.2 g. (0.054 mole), was suspended in methyl iodide, 71 g. (0.50 mole), and the mixture was allowed to stand for 30 minutes. Freshly prepared moist silver oxide, 15 g., was then added in portions over 30 minutes with constant shaking. (Old, nearly dry silver oxide gave a much lower yield than the freshly prepared silver oxide which contained 10.5% H_2O.) Toward the end of the addition, the viscosity of the slurry decreased noticeably and the mixture became warm. After shaking mechanically for 30 minutes more and standing at room temperature for one hour, the mixture was filtered to remove the silver compounds. The filtrate was concentrated to dryness *in vacuo*, yielding a crystalline residue. This crude product (19.5 g.) was recrystallized from hot *n*-butyl ether, yielding 17.5 g. (84%) of dense, colorless needles of m.p. 109–110°. A second recrystallization gave the pure product which melted without discoloration at 113°; $[\alpha]^{25}D$ +23° (*c* 3, chloroform).

Anal. Calcd. for $C_5H_{10}N{\cdot}C_6H_7O_4(COCH_3)_3{\cdot}OCH_3$: OCH_3, 8.0; $COCH_3$, 33.3. Found: OCH_3, 8.2; $COCH_3$, 33.0.

N-(2-Methyl-D-glucosyl)-piperidine.—N-(2-Methyl-3,4,6-triacetyl-D-glucosyl)-piperidine, 4 g., m.p. 113°, was dissolved in 25 ml. of absolute methanol, and the solution was added to a saturated, anhydrous solution of ammonia in methanol, 50 ml., prepared at 0°. The combined solutions were held at 0° while dry ammonia gas was bubbled through for 45 minutes. The clear, colorless solution so obtained was concentrated *in vacuo* to a sirup. The sirup was taken up in diethyl ether, and soon thereafter, crystals of the product formed; yield 1.5 g. (56%); m.p. 112°. Recrystallization from ethyl acetate gave the pure product; m.p. 114°; $[\alpha]^{25}D$ −2.5° (initial) → −6.0° (final) constant after 16 hours (*c* 2.0, pyridine); $[\alpha]^{25}D$ −11° (4 minutes) → −16.5° (constant from one hour to 6 days, *c* 2.9, methanol). The slight mutarotation noted for this 2-methyl derivative in pyridine stands in contrast to the behavior of N-D-glucosylpiperidine for which no change in rotation could be observed.[4]

Anal. Calcd. for $C_5H_{10}N{\cdot}C_6H_{10}O_4{\cdot}OCH_3$: N, 5.36; OCH_3, 11.9. Found: N, 5.35; OCH_3, 12.0.

2-Methyl-β-D-glucose.—N-(2-Methyl-D-glucosyl)-piperidine, m.p. 114°, 1.0 g., was dissolved in 25 ml. of 1.0 *N* sulfuric acid, and the solution was heated in a steam-bath for 90 minutes. The acid solution was neutralized with an excess of barium carbonate, then filtered. The neutral filtrate, free of sulfate ion, was concentrated *in vacuo* to a sirup. The sirup was dissolved in a little ethanol, then ethyl acetate was added to the point of incipient turbidity. On cooling to 0°, the product crystallized; yield 0.45 g. (61%); m.p. 154–156°. After two recrystallizations from absolute ethanol, 0.2 g. of white, dense, prismatic crystals was obtained; m.p. 160°; $[\alpha]^{25}D$ +21° (5 minutes) → +66° (constant value after 7 hours, *c* 1.5, water).

Anal. Calcd. for $C_6H_{11}O_5{\cdot}OCH_3$: C, 43.4; H, 7.27; OCH_3, 16.0. Found: C, 43.3; H, 7.26; OCH_3, 16.3.

The melting point, specific rotation, and analysis indicated the final product to be 2-methyl-β-D-glucose.[7] The identity of the 2-methyl-β-D-glucose was confirmed by preparing the known phenylhydrazone derivative.[8] Crystalline 2-methylglucose, 0.2 g., was dissolved in methanol and 3 drops of phenylhydrazine was added. After evaporation on the steam-bath, a crystalline residue remained. Recrystallization from ethanol yielded brilliant platelets of

(7) J. W. H. Oldham and J. K. Rutherford, THIS JOURNAL, **54**, 1086 (1932).

(8) P. A. Levene, G. M. Meyer and A. L. Raymond, *J. Biol. Chem.*, **91**, 497 (1931).

m.p. 176–177°; $[\alpha]^{25}D$ −10° (8 to 30 minutes after dissolving, *c* 1, pyridine).

Anal. Calcd. for $C_{12}H_{17}O_4N_3 \cdot OCH_3$: N, 9.86; OCH_3, 10.9. Found: N, 9.64; OCH_3, 11.0.

An attempt to prepare 2-methyl-D-glucose directly from N-(2-methyl-3,4,6-triacetyl-D-glucosyl)-piperidine by acid hydrolysis resulted in the formation of a sirupy product that could not be crystallized. However, acetylation of the sirup in pyridine–acetic anhydride yielded a monomethyl-tetraacetyl hexose (6%), probably 2-methyl-tetraacetyl-D-glucose, as fine, white needles, m.p. 109°; $[\alpha]^{25}D$ +21° (*c* 0.4, chloroform).

Anal. Calcd. for $C_6H_7O_3(COCH_3)_4 \cdot OCH_3$: $COCH_3$, 47.5; OCH_3, 8.6. Found: $COCH_3$, 47.5; OCH_3, 9.1.

N-(2-Carbanilino-3,4,6-triacetyl-D-glucosyl)-piperidine.—N-(3,4,6-Triacetyl-D-glucosyl)-piperidine, 11.2 g. (0.030 mole) was suspended and nearly completely dissolved in 70 ml. of dry pyridine in a stoppered flask. To this mixture was added 4.6 g. (0.039 mole) of phenyl isocyanate. The mixture became slightly warm and the remaining crystals dissolved within 15 minutes. After standing at room temperature for 16 hours, the flask was heated on a steam-bath for 15 minutes. The color of the solution turned from pale yellow to deep orange-red during the heating period. After the solution was cooled to about 40°, methanol (50 ml.) was added. The solution was then poured into 50% aqueous methanol (150 ml.). The crystalline product which formed was filtered off, washed with methanol and ether, and dried. Additional crops of crystals were isolated by concentrating the mother liquor and washings; combined yield 12.2 g. (83%); m.p. 163°. Recrystallized from methanol, the pure white product melted and decomposed at 164°; $[\alpha]^{25}D$ +37° (*c* 2.0, chloroform).

Anal. Calcd. for $C_{24}H_{32}O_9N_2$: C, 58.5; H, 6.55; N, 5.69; $COCH_3$, 26.2. Found: C, 58.8; H, 6.20; N, 5.72; $COCH_3$, 26.2.

N-(2-Carbanilino-D-glucosyl)-piperidine.—Crude crystalline N-(2-carbanilino-3,4,6-triacetyl-D-glucosyl)-piperidine, 17.5 g., was deacetylated in 350 ml. of methanol which was saturated with anhydrous ammonia at −5°. The mixture was kept at 0° for 23 hours. Concentration of the solution *in vacuo* produced a dry mass of white crystals. The residue was stirred with 100 ml. of ethyl acetate, and the crystals remaining were filtered off, washed with ethyl acetate and dried; yield 11.8 g. (91%). The product was recrystallized from methanol, yielding clumps of fine, white, slightly hygroscopic crystals, m.p. 152° (dec.); $[\alpha]^{25}D$ +63° (*c* 0.9, pyridine).

Anal. Calcd. for $C_{18}H_{26}O_6N_2$: C, 59.0; H, 7.15; N, 7.65. Found: C, 59.0; H, 7.35; N, 7.49.

2-Carbanilino-D-glucose.—N-(2-Carbanilino-D-glucosyl)-piperidine, 2.5 g., m.p. 150°, was shaken with 100 ml. of 0.10 *N* hydrochloric acid, and the mixture was allowed to stand at 25° for 4 days. The flask then contained 0.3 g. of carbanilide, m.p. 237°, which remained insoluble and was filtered from the reaction mixture. The filtrate was neutralized with 0.6 g. of silver carbonate, the silver residues were filtered off, and the final filtrate was concentrated *in vacuo* to a sirup. Taken up in hot 1:1 ethanol–ethyl acetate, the sirup solution on cooling gave 0.6 g. of needle crystals, m.p. 165–166°. Recrystallization from 10 ml. of absolute ethanol gave white prismatic needles, 0.45 g., m.p. 165–166°; $[\alpha]^{25}D$ +43° (initial) → +46° (constant after 7 hours, *c* 1.0, water). The compound was soluble in water, pyridine, hot alcohol and hot acetone; it was nearly insoluble in ether and ethyl acetate. It reduced hot Fehling solution slowly.

Anal. Calcd. for $C_{13}H_{17}O_7N$: C, 52.2; H, 5.73; N, 4.68. Found: C, 52.3; H, 5.73; N, 4.67.

N-(2-*p*-Toluenesulfonyl-3,4,6-triacetyl-D-glucosyl)-piperidine.—N-(3,4,6-Triacetyl-D-glucosyl)-piperidine, 11.2 g. (0.030 mole), was dissolved in dry pyridine (100 ml.) and *p*-toluenesulfonyl chloride, 6.3 g. (0.033 mole), was dissolved in dry chloroform (25 ml.). The solutions were cooled to 0° then mixed and allowed to stand at 0° for 3 days. A dark red-brown color developed. Water (1 ml.) was added and, after 1 hour, 100 ml. of chloroform. The solution was extracted twice with an equal volume of ice-water, then the chloroform layer was dried over potassium carbonate. On concentration of the chloroform solution to dryness, a sirup was obtained which soon crystallized. The product was isolated and washed with absolute ethanol. After drying, the yield was 6.6 g. (42%); m.p. 151–152° (dec.). Recrystallized from 170 ml. absolute ethanol, 5.5 g. was obtained as white, felted needles; m.p. 154° (dec.); $[\alpha]^{25}D$ +17° (*c* 2.1, chloroform).

Anal. Calcd. for $C_{24}H_{33}O_{10}NS$: S, 6.1; $COCH_3$, 24.5. Found: S, 6.0; $COCH_3$, 25.0.

N-(2-*p*-Toluenesulfonyl-D-glucosyl)-piperidine.—N-(2-*p*-Toluenesulfonyl-3,4,6-triacetyl-D-glucosyl)-piperidine, 2.4 g., was deacetylated with sodium methoxide, 0.25 g., in methanol (150 ml.) by the method of Zemplén[9] (*cf.* Reynolds[10]). White, needle crystals, 1.3 g. (70%), were obtained, m.p. 111–112° (dec.); $[\alpha]^{25}D$ +4° (*c* 2, pyridine). The crystals were insoluble in cold water, soluble in hot water, very soluble in alcohols and pyridine. Hot Fehling solution was reduced by the compound.

Anal. Calcd. for $C_{18}H_{27}O_7NS$: C, 53.9; H, 6.78; N, 3.49; S, 7.99. Found: C, 54.2; H, 6.90; N, 3.61; S, 7.91.

N-(2-*p*-Toluenesulfonyl-3,4,6-triacetyl-D-glucosyl)-piperidine was also deacetylated at 0° in methanol saturated with ammonia[11] with 72% yield of N-(2-*p*-toluenesulfonyl-D-glucosyl)-piperidine, m.p. 110°. An attempt to make 2-*p*-toluenesulfonyl-D-glucose by adding one equivalent of dilute mineral acid to the compound isolated above did not succeed in producing a crystalline compound.

N-(2-*p*-Nitrobenzoyl-3,4,6-triacetyl-D-glucosyl)-piperidine.—*p*-Nitrobenzoyl chloride, 1.0 g. (5.4 millimoles), was dissolved in 15 ml. of dry pyridine, and N-(3,4,6-triacetyl-D-glucosyl)-piperidine, 1.8 g. (4.8 millimoles), was added. After standing 2.5 hours the red-brown solution was poured into cold 40% aqueous ethanol (40 ml.) yielding a crystalline product. Recrystallization from absolute ethanol (20 ml.) gave 1.3 g. (52%) white needles, m.p. 158–159° (dec.); $[\alpha]^{25}D$ +52.3° (*c* 2.0, chloroform).

Anal. Calcd. for $C_{24}H_{30}O_{11}N_2$: N, 5.36; $COCH_3$, 24.7. Found: N, 5.18; $COCH_3$, 25.0.

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(9) G. Zemplén, *Ber.*, **59**, 1254 (1926).

(10) T. M. Reynolds, *J. Chem. Soc.*, 223 (1933).

(11) E. W. Bodycote, W. N. Haworth and E. L. Hirst, *ibid.*, 151, (1934).