Summary

1. Two new β-aminobenzylacetones have been prepared and procedures for preparing oximes of β-amino ketones discussed.

2. General methods for preparing β-amino alcohols and 1,3-diamino compounds from α,β-unsaturated ketones have been investigated.

3. Two new amino alcohols with their corresponding benzoates and two new 1,3-diamines with their corresponding benzamides have been prepared.

LINCOLN, NEBRASKA RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Studies on D-Galactosan$<1,5>\beta<1,6>$

BY RAYMOND M. HANN AND C. S. HUDSON

The hexose anhydride, D-galactosan$<1,5>\beta$-$<1,6>$, was first synthesized by Micheel[1] by the action of hot aqueous barium hydroxide upon 2,3,4,6-tetraacetyl-D-galactopyranosido-trimethyl-ammonium bromide; the over-all yield of the anhydride, based on the crystalline acetobromo-D-galactose employed, was 38%. Micheel also reported that he obtained a small amount of the same anhydride by the pyrolysis of β-D-galactose at temperatures of 270 to 360° and a pressure of 3 millimeters.[2] The $<1,5><1,6>$ structure was assigned by Micheel on the basis that acetobromo-D-galactose contains the 1,5 ring and that the 1,6 ring is probably more stable than the 1,3 and 1,4 rings; the $<1,5><1,6>$ structure was also the only probable one containing two adjacent hydroxyl groups in the *cis*-position, which seemed necessary in order to account for the ready formation of a monoacetone compound (m. p. 151–152°; $[\alpha]^{20}_{\mathrm{D}}$ $-73.3°$ in chloroform). These inferences of Micheel were proved to be correct by the work of McCreath and Smith[3]; they isolated as a by-product in the preparation of 1,2:3,4-diacetone galactose a monoacetone galactosan agreeing in physical properties with the one described by Micheel, and by methylation they converted it to a sirupy monomethyl-monoacetone-D-galactosan, which, upon hydrolysis with strong acid, formed the known crystalline 2-methyl-D-galactopyranose[4]; the monomethyl-monoacetone-D-galactosan, upon selective mild acid hydrolysis and subsequent methylation, formed a crystalline trimethyl-D-galactosan, which, upon complete acid hydrolysis, yielded crystalline 2,3,4-trimethyl-galactopyranose monohydrate. The ring structure of the parent galactosan is therefore $<1,5><1\ 6>$ and the β-configuration is assigned to the 1,6 ring, as first proposed by Micheel because the space formula indicates a high probability for this configuration. The monoacetone derivative is accordingly 3,4-isopropylidene-D-galactosan$<1,5>\beta<1,6>$, as originally inferred by Micheel.

Recently we[5] have found that the pyrolysis of α-lactose monohydrate, under the experimental conditions previously used for the preparation of D-mannosan$<1,5>\beta<1,6>$ from vegetable ivory, yields a distillate containing both levoglucosan and D-galactosan$<1,5>\beta<1,6>$. The anhydrides are readily separable through the fact that the galactosan, but not the glucosan, condenses with acetone; average yields of 12.3 g. of levoglucosan and 20.7 g. of 3,4-isopropylidene-D-galactosan$<1,5>\beta<1,6>$ have been obtained by the pyrolysis of a 200-g. charge of lactose monohydrate; economy in price of starting material, simplicity and speed of experimental procedures, and the relatively high yields of the desired products, thus combine to make this procedure of pyrolysis an excellent method for obtaining an abundant supply of these two sugar anhydrides at relatively low cost. In the case of the galactosan, such a result is of special importance; the galactosan and its acetone derivative are now inexpensive and readily accessible substances, suit-

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(1) Micheel, *Ber.*, **62**, 687 (1929).

(2) Ordinary galactose is the α-form; we have shown (THIS JOURNAL, **63**, 2241 (1941)) that its pyrolysis gives good yields of D-galactosan$<1,5>\beta<1,6>$. We find that the yield of levoglucosan (D-glucosan$<1,5>\beta<1,6>$) is independent of the form of anhydrous glucose (α or β) that is pyrolyzed. The melting of such α- or β-forms establishes equilibrium between them, as may be inferred from an old record by C. Tanret (*Bull. soc. chim.*, [3] **13**, 734 (1895)). We have repeated his experiment under more precise control. The glassy melts which were obtained by heating samples of pure α- and β-D-glucose at 170° for fifteen minutes were cooled and then dissolved in water at 20°; the specific rotations after seven minutes were essentially alike (+53 and +50), representing the equilibrium rotation of glucose.

(3) McCreath and Smith, *J. Chem. Soc.*, 387 (1939).

(4) Oldham and Bell, THIS JOURNAL, **60**, 323 (1938).

(5) Hann and Hudson, *ibid.*, **63**, 1484 (1941).

able for synthetic studies in the preparation of new compound sugars possessing a linkage at the second carbon atom of galactose.

Although the structure of D-galactosan<1,5>-β<1,6> has been firmly established through the methylation studies of McCreath and Smith, it seemed desirable to seek confirmation of it by application of the periodate methods previously employed in this Laboratory in studies on D-glucosan (levoglucosan),[6] D-altrosan,[7] and D-mannosan.[8] It was found that the oxidation of the anhydride by per-iodic acid or sodium metaperiodate proceeded with the reduction of two molecular equivalents of the oxidant and the generation of a molecular equivalent each of formic acid and L′-oxy-D-methylene-diglycolic aldehyde; the latter compound, upon further oxidation with bromine water in the presence of strontium carbonate, formed strontium L′-oxy-D-methylene-diglycolate, the same crystalline salt that had been obtained previously from D-glucosan, D-altrosan and D-mannosan. This result proves that the same structure and β<1,6> configuration are common to the four hexose anhydrides; the galactosan is therefore D-galactosan<1,5>β<1,6>, and the conclusions of the previous investigators are confirmed by this independent method.

The present investigation has been extended to include the preparation of several new derivatives of D-galactosan<1,5>β<1,6>; by customary procedures 3,4-isopropylidene-D-galactosan<1,5->β<1,6> has been converted into its 2-substituted acetyl, benzoyl and tosyl derivatives, all of which are crystalline; by selective mild acid hydrolysis the isopropylidene group of these compounds is removed and, although the 2-acetyl-D-galactosan<1,5>β<1,6> could not be crystallized, it was possible to crystallize 2-benzoyl- and 2-tosyl-D-galactosan<1,5>β<1,6>; migration of the acyl groups does not appear to occur under the experimental conditions of the hydrolysis since the monobenzoate, upon treatment with acetone and anhydrous copper sulfate, regenerates 2-benzoyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6> in high yield. The 2-benzoyl-D-galactosan<1,5>β<1,6> yielded by suitable reactions, crystalline 3,4-diacetyl and 3,4-ditosyl derivatives; by treatment with benzoyl chloride, it formed a crystalline 2,3,4-tribenzoyl-D-galactosan<1,5>β<1,6>, which was identical with the tribenzoate obtained by direct benzoylation of D-galactosan<1,5>β<1,6>. The 2-tosyl-D-galactosan<1,5>β<1,6> is a compound of particular interest, since studies now in progress indicate that upon detosylation it forms a compound (m. p. 132–133°; $[\alpha]^{20}\text{D}$ $-84°$ in water), which gives correct carbon and hydrogen analyses for an anhydro-D-galactosan<1,5>β-<1,6>; its behavior thus parallels that of 4-tosyl-D-mannosan<1,5>β<1,6>, which is known[9] to form an anhydro-D-mannosan<1,5>-β<1,6>, presumably 3,4-anhydro-D-talosan <1,5>β<1,6>, upon detosylation.

We express our appreciation to Dr. A. T. Ness for performing the microchemical analyses in connection with this study.

Experimental

D-Glucosan<1,5>β<1,6> and 3,4-Isopropylidene-D-galactosan<1,5>β<1,6> from α-Lactose Monohydrate.—Three successive charges of 75, 65 and 60 g. of α-lactose monohydrate were pyrolyzed in the apparatus and under the experimental condition specified[8] for the preparation of D-mannosan<1,5>β<1,6> from vegetable ivory. The combined pyrolysates, a dark colored sirup, was dissolved in 200 cc. of water and the solution, after clarification by filtration through a layer of 45 g. of decolorizing carbon on a Büchner funnel of 171 mm. diameter, was concentrated *in vacuo* to a thick sirup; a solution of the sirup in 75 cc. of acetone was poured in a thin stream into an additional 325 cc. of acetone, and, after decantation from a small amount of precipitated gum, the acetone solution was agitated with 40 g. of anhydrous copper sulfate for twenty-four hours; the copper sulfate was removed by filtration and the filtrate was concentrated *in vacuo* to a magma of the consistency of honey; the magma was thinned with 25 cc. of isopropyl alcohol and the crystalline product (24.0 g.), which was mainly 3,4-isopropylidene-D-galactosan-<1,5>β<1,6>, was separated by filtration and preserved for final purification as described later in this paragraph. The filtrate was concentrated *in vacuo* to remove the isopropyl alcohol, and the resulting sirup was transferred to a crystallizing dish with the aid of 20 cc. of warm acetone; crystallization, which occurred spontaneously as the solution cooled, was allowed to progress for twenty-four hours in the refrigerator and the precipitate (13.6 g.), which was nearly all levoglucosan, was then separated by filtration. The further purification of the products was conducted as follows: the levoglucosan fraction was refluxed for ten minutes with 5 parts of chloroform, in which 3,4-isopropylidene-D-galactosan<1,5>β<1,6> is readily soluble and levoglucosan practically insoluble, and the crystalline levoglucosan was removed by filtration; to the chloroform filtrate the 3,4-isopropylidene-D-galactosan<1,5>β-<1,6> fraction previously isolated and additional chloroform to maintain a volume of 5 cc. of solvent for each gram of solid were added and the mixture was refluxed for ten

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[6] Jackson and Hudson, THIS JOURNAL, **62**, 958 (1940).

[7] Richtmyer and Hudson, *ibid.*, **62**, 961 (1940).

[8] Knauf, Hann and Hudson, *ibid.*, **63**, 1447 (1941).

[9] Hann and Hudson, *ibid.*, **64**, 925 (1942).

minutes, and then allowed to stand for several hours at room temperature; the levoglucosan was removed by filtration and the 3,4-isopropylidene-D-galactosan <1,5>β-<1,6> was recovered by concentration of the chloroform filtrate. The average yield of levoglucosan from 200 g. of lactose monohydrate was 12.3 g. (13%) and that of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> was 20.7 g. (18%). The latter compound may be crystallized from 3 parts of water or 5 parts of ethyl acetate; it melted at 151–152° and showed a specific rotation[10] of −72.9° in chloroform (*c*, 0.87). Micheel[1] records a melting point of 151–152° and a specific rotation of −73.3° in chloroform (*c*, 1.4), and McCreath and Smith[3] record the same melting point and a specific rotation $[\alpha]^{19}\text{D}$ of −72.5° in chloroform (*c*, 1.7) for 3,4-isopropylidene-D-galactosan <1,5>β-<1,6>.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.41; H, 6.88.

2-Acetyl-3,4-isopropylidene-D-galactosan<1,5>β-<1,6>.—A solution of 2.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in a mixture of 10 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand overnight at room temperature and then poured upon crushed ice. The crystalline acetyl derivative (2.0 g.; 83%) which separated was recrystallized from 50 parts of boiling water and obtained as colorless plates, which melted at 136–137° and had a specific rotation of −51.4° in chloroform (*c*, 0.88).

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; CH_3CO, 17.6. Found: C, 54.36; H, 6.49; CH_3CO, 17.5.

2-Benzoyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>.—To an ice-cold solution of 3.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 10 cc. of pyridine, benzoyl chloride (1.9 cc.; 1.1 molecular equivalents) was added dropwise; the reaction mixture was allowed to stand overnight at room temperature and then poured upon crushed ice to precipitate the crystalline benzoyl derivative. The yield was 3.7 g. (82%). The substance deposited from its solution in 5 parts of alcohol in fine needles which melted at 119–120° and exhibited a specific rotation of +6.3° in chloroform (*c*, 0.84).

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; C_6H_5CO, 34.3. Found: C, 62.96; H, 5.92; C_6H_5CO, 34.7.

2-Tosyl-3,4-isopropylidene-D-galactosan<1,5>β<1,6>.—This compound was obtained in quantitative yield by the action of *p*-toluene-sulfonyl chloride (1.4 g.; 1.5 molecular equivalents) on a solution of 1.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 6 cc. of pyridine. It was recrystallized from 8 parts of alcohol in the form of quadrilateral plates, which melted at 118–119° and showed a specific rotation of −63.7° in chloroform (*c*, 0.92).

Anal. Calcd. for $C_{16}H_{20}O_7S$: C, 53.92; H, 5.66. Found: C, 53.85; H, 5.61.

D-Galactosan<1,5>β<1,6> from 3,4-Isopropylidene-D-galactosan<1,5>β<1,6>.—A solution of 20.0 g. of 3,4-isopropylidene-D-galactosan <1,5>β<1,6> in 220 cc. of 0.1 *N* hydrochloric acid was allowed to stand for twenty-four hours at 20°, during which period the specific rotation reached a constant value of −17.9°, equivalent to a rotation of −22.4° for D-galactosan <1,5>β<1,6>. The solution, which was devoid of reducing power (negative Fehling test), was treated with silver carbonate to remove the hydrochloric acid and then concentrated *in vacuo* to dryness. The yield of D-galactosan <1,5>β<1,6> was 14.5 g. (91%) and this material required no further purification for use in synthetic work. After recrystallization to constant physical properties from 5 parts of alcohol, it melted at 223–224° and showed a specific rotation of −22.0° in water (*c*, 1.96). Micheel[1] records a melting point of 220–221° and a specific rotation $[\alpha]^{21}\text{D}$ of −21.9° in water (*c*, 2.14).

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.51; H, 6.28.

Per-iodic Acid Oxidation of D-Galactosan<1,5>β-<1,6>.—A solution of 5.6199 g. of D-galactosan<1,5>β-<1,6> in 75 cc. of water was cooled in an ice-bath and 122 cc. of 0.625 *M* aqueous per-iodic acid (2.2 molecular equivalents) was gradually added. The oxidation was allowed to proceed at 20° for twenty-four hours and the volume was adjusted to 250 cc. by the addition of water. The titration of a 5-cc. aliquot for excess per-iodic acid revealed that 2.02 molecular equivalents of oxidizing agent had been reduced. The specific rotation of the oxidation product, calculated as L′-oxy-D-methylene-diglycolic dialdehyde, was −13.9°. This value is in good agreement with those reported for the per-iodic acid oxidation of levoglucosan,[6] D-altrosan <1,5>β<1,6>[7] and D-mannosan <1,5>β-<1,6>,[8] namely, −15.0°, −14.5° and −14.9°, and −14.2°, respectively. The sirupy aldehyde was isolated and further oxidized by bromine water in the presence of strontium carbonate in the usual way; crystalline strontium L′-oxy-D-methylene-diglycolate pentahydrate was obtained in a yield of 4.7 g. (38%). This salt, after two recrystallizations from water, gave a specific rotation of +27.7° (*c*, 0.6), a value near that of +28.1° recorded by Richtmyer and Hudson for the same salt obtained from D-altrosan <1,5>β<1,6>. When 0.5731 g. of the pentahydrate was dissolved in 25 cc. of *N* hydrochloric acid the specific rotation of the resulting solution of free L′-oxy-D-methylene-diglycolic acid was +7.9°, in close agreement with the values of +8.0°,[6] +7.9°,[7] and +7.8°[8] previously reported.

Anal. Calcd. for $C_5H_4O_6Sr \cdot 5H_2O$: C, 17.78; H, 1.19; Sr, 25.94; H_2O, 26.67. Found: C, 17.67; H, 1.16; Sr, 25.90; H_2O, 26.45.

Sodium Metaperiodate Oxidation of D-Galactosan-<1,5>β<1,6>.—To an ice-cold solution of 0.5900 g. of D-galactosan <1,5>β<1,6> in 25 cc. of water, 20 cc. of 0.546 *M* aqueous sodium periodate (3.00 molecular equivalents) was added and the oxidation reaction allowed to proceed at 20° for twenty-four hours. The volume was adjusted to 50 cc. with water and a 5-cc. aliquot, upon analysis, indicated the consumption of 2.00 molecular equivalents of the periodate during the oxidation; the titration of a further 10-cc. aliquot with 0.1 *N* sodium hydroxide, using methyl red as an indicator, consumed 7.15 cc. of alkali, equivalent to the production of 0.98 molecular equivalent of formic acid as a product of the oxidation. D-Galactosan <1,5>β<1,6> would be expected to reduce

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[10] All of the crystalline compounds described in the experimental part were recrystallized to constant melting point (cor.) and specific rotation $[\alpha]^{20}\text{D}$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

two equivalents of periodate and form one equivalent of formic acid.

2,3,4-Tribenzoyl-D-galactosan$<1,5>\beta<1,6>$.—A solution of 1.0 g. of D-galactosan $<1,5>\beta<1,6>$ in 10 cc. of pyridine was cooled in an ice–salt bath and 2.35 cc. (3.3 molecular equivalents) of benzoyl chloride was added dropwise. The reaction mixture was allowed to stand at room temperature for twenty-four hours and poured upon crushed ice; the crystallization of the thick sirup which precipitated was difficult but was finally attained by the alternate addition and slow evaporation of small amounts of methyl alcohol. The tribenzoate deposited from its solution in 20 parts of methyl alcohol in the form of glistening prisms, which melted at 89–90° and showed a specific rotation of +84.8° in chloroform (*c*, 1.05).

Anal. Calcd. for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67; C_6H_5CO, 66.5. Found: C, 68.41; H, 4.63; C_6H_5CO, 66.2.

2,3,4-Tritosyl-D-galactosan$<1,5>\beta<1,6>$.—To an ice-cold solution of 2.0 g. of D-galactosan $<1,5>\beta<1,6>$ in 20 cc. of pyridine, 7.8 g. of tosyl chloride (3.3 molecular equivalents) was added and the reaction mixture allowed to stand for twenty-four hours at room temperature. The gum which separated upon addition of the pyridine solution to water gradually crystallized over a period of two weeks and yielded 6.3 g. of a granular powder. By fractional crystallization, first from aqueous acetic acid and finally from alcohol, a yield of 2.0 g. (26%) of tritosyl-D-galactosan $<1,5>\beta<1,6>$ was separated from the mixture of partially tosylated galactosans. The tritosyl compound deposited from its solution in 4 parts of alcohol in the form of small needles which melted at 103–104° (cor.) and showed a specific rotation of −51.1° in chloroform (*c*, 1.26). These constants were not changed by further recrystallization.

Anal. Calcd. for $C_{27}H_{28}O_{11}S_3$: C, 51.91; H, 4.52; S, 15.40. Found: C, 51.76; H, 4.70; S, 15.31.

2-Benzoyl-D-galactosan$<1,5>\beta<1,6>$.—A solution of 2.5 g. of 2-benzoyl-3,4-isopropylidene-D-galactosan $<1,5>$-$\beta<1,6>$ in 25 cc. of 20% acetic acid was refluxed for two and one-half hours; upon cooling, the solution deposited 1.5 g. (68%) of 2-benzoyl-D-galactosan. The benzoate was recrystallized from 5 parts of alcohol or 15 parts of 20% acetic acid; it formed prisms which melted at 164–165° and had a specific rotation of +47.2° in chloroform (*c*, 0.8). The presence of other monobenzoylated-D-galactosans in the product, as a result of a conceivable acyl migration, would seem to be excluded, since (as described in the following paragraph) a nearly quantitative yield of authentic 2-benzoyl-3,4-isopropylidene-D-galactosan $<1,5>\beta<1,6>$ may be obtained from it by treatment with acetone and anhydrous copper sulfate. Upon further benzoylation, the 2-benzoyl-galactosan yields the 2,3,4-tribenzoyl-D-galactosan $<1,5>\beta<1,6>$ previously described.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30; C_6H_5CO, 39.5. Found: C, 58.68; H, 5.23; C_6H_5CO, 39.2.

2-Benzoyl-3,4-isopropylidene-D-galactosan$<1,5>\beta<1,6>$ from 2-Benzoyl-D-galactosan$<1,5>\beta<1,6>$.—A solution of 1.0 g. of the 2-benzoyl-D-galactosan $<1,5>\beta$-$<1,6>$ in 25 cc. of acetone was refluxed with 5.0 g. of anhydrous copper sulfate for three hours. The copper sulfate was separated by filtration and the filtrate was concentrated to a dry crystalline residue. The reaction product was recrystallized from 5 cc. of alcohol and gave a yield of 1.0 g. (91%) of 2-benzoyl-3,4-isopropylidene-D-galactosan $<1,5>\beta<1,6>$, identical in melting point and specific rotation with the substance obtained by direct benzoylation of 3,4-isopropylidene-D-galactosan $<1,5>\beta<1,6>$. A mixed melting point showed no depression.

2-Benzoyl-3,4-diacetyl-D-galactosan$<1,5>\beta<1,6>$.—A solution of 1.0 g. of 2-benzoyl-D-galactosan $<1,5>\beta$-$<1,6>$ in a mixture of 10 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand at room temperature for eighteen hours and then poured upon crushed ice. The precipitated 2-benzoyl-3,4-diacetyl-D-galactosan (1.3 g., quantitative) was separated by filtration and recrystallized from 10 parts of alcohol. It formed needles which melted at 103–104° and rotated +85.4° in chloroform (*c*, 0.9).

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.48; H, 5.13.

2-Benzoyl-3,4-ditosyl-D-galactosan$<1,5>\beta<1,6>$.—This substance was obtained by tosylation of the monobenzoyl-D-galactosan $<1,5>\beta<1,6>$ by the usual method; recrystallized from 5 parts of alcohol, it was obtained in prisms which melted at 119–120° and rotated +78.0° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{27}H_{26}O_{10}S_2$: C, 56.42; H, 4.55; S, 11.16. Found: C, 56.43; H, 4.56; S, 11.07.

Summary

The pyrolysis of α-lactose monohydrate under reduced pressure forms a sirup from which, after condensation with acetone, yields of 13% of levoglucosan and 17.5% of 3,4-isopropylidene-D-galactosan $<1,5>\beta<1,6>$ were obtained. Selective mild acid hydrolysis converts the latter compound into the known D-galactosan $<1,5>\beta$-$<1,6>$. Confirmation of the ring structure and configuration of the galactosan was obtained by periodate oxidative procedures. A number of new derivatives of 3,4-isopropylidene-D-galactosan $<1,5>\beta<1,6>$ and of D-galactosan $<1,5>$-$\beta<1,6>$ have been prepared and described.

BETHESDA, MD. RECEIVED JULY 31, 1942