[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF THE UNIVERSITY OF ST. ANDREWS, SCOTLAND]

The Synthesis of Amino Sugars. I

BY W. H. MYERS* AND THE LATE G. J. ROBERTSON

During recent years, a series of papers[1] from this Laboratory has shown that derivatives of glucose may be converted smoothly into derivatives of altrose, galactose and gulose by means of optical inversion within the molecule. In each case, the key substance to such a conversion has been an anhydro compound of the ethylene oxide type, in which the ring is broken under the influence of alkali. For example, 4,6-benzylidene-2,3-anhydro-α-methylalloside and 4,6-benzylidene-2,3-anhydro-α-methylmannoside, in our experience, invariably yield derivatives of altrose when treated with alcoholic potash or sodium methoxide solution.

As already announced,[2] we have extended our researches to the action of ammonia and certain amines as well as other alkaline reagents on 4,6-benzylidene-2,3-anhydro-α-methylalloside, the corresponding mannoside and the guloside (or taloside) and chlorohydrins derived from these substances.

Whenever rupture of the anhydro ring was effected as the result of treatment with one of these reagents, two isomers were formed, one of which greatly predominated, making the isolation of the lesser constituent difficult. Inversion of the carbon atom to which the amino group attached itself was the invariable result, when anhydro compounds were treated. The mechanism involved when chlorohydrins were used is not yet clear. Our work is in agreement with that of Peat and Wiggins,[3] although their ratio of products obtained was different from ours. Reaction of ammonia with 4,6-benzylidene-2,3-anhydro-α-methylalloside gave a mixture of amino glycosides.[3] Treatment of an acetone solution of the mixture with dilute hydrochloric acid resulted in the crystallization of very pure 4,6-benzylidene-2-amino-α-methylaltroside hydrochloride. The hydrochloride of the minor constituent was not isolated. Warming a solution of the altroside salt with hydrochloric acid, cooling and neutralizing resulted in the formation of 2-amino-α-methylaltroside. This was acetylated to form 3,4,6-triacetyl-2-acetamido-α-methylaltroside. A diacetate of the 2-amino-altroside was prepared by acetylating 4,6-benzylidene-2-amino-α-methylaltroside, then removing the benzylidene group with dilute hydrochloric acid, to give 3-acetyl-2-acetamido-α-methylaltroside.

An unpublished method by Robertson and Whitehead was used in forming 4,6-benzylidene-2,3-anhydro-α-methylmannoside. Treatment of this material with aqueous ammonia in sealed tubes produced two new amino derivatives which were separated by repeated crystallization after acetylation. As in the reaction of ammonia with the anhydro alloside compound, one isomer greatly predominated and, since altrosides were favored by this anhydro ring rupture, it was reasonable to assume its configuration to be that of 2-acetyl-4,6-benzylidene-3-acetamido-α-methylaltroside. This was confirmed when "methyl epiglucosamine hydrochloride" (3-amino-β-methylaltroside hydrochloride) was formed by removal of the benzylidene group with hydrochloric acid before acetylation.

It will be noted that the hydrochloric acid boil, used to remove the benzylidene group, seems to have caused inversion of the first carbon atom to give the β-configuration. The only evidence for this is the identity of the constants of the hydrochloride with those of methyl epiglucosamine prepared by other workers, where the β-configuration is unquestioned. Examination of the rotations of the other compounds described in this paper did not lead to a definite conclusion whether or not hydrolysis caused inversion in other instances. Therefore, lacking reference compounds and definite proof to the contrary, these other compounds are tentatively assigned the α-configuration until the contrary is proved. By elimination, the minor isomer must be the only remaining 2,3-*trans*-isomer of the four possible configurations, since three such isomers had already been isolated, and the constants of the new compound did not correspond to any of them. Therefore, it was designated as 3-acetyl-4,6-benzylidene-2-acetamido-α-methylglucoside.

* Present address: Hercules Experiment Station, Hercules Powder Company, Wilmington, Delaware.

(1) Mathers and Robertson, *J. Chem. Soc.*, 1076 (1933); Robertson and Griffith, *ibid.*, 1193 (1935); Oldham and Robertson, *ibid.* 685 (1935).

(2) Robertson, Myers and Tetlow, *Nature*, **142**, 1077 (1938); Robertson and Myers, *ibid.*, **143**, 640 (1939).

(3) Peat and Wiggins, *J. Chem. Soc.*, 1810 (1938).

Treatment of the original mixture of amino isomers with cold dilute hydrochloric acid in acetone solution caused crystallization of 4,6-benzylidene-3-amino-α-methylaltroside hydrochloride. The diacetates were formed by acetylation of the amino isomers followed by removal of the benzylidene groups with warm hydrochloric acid. Subsequent acetylation of these derivatives gave the tetraacetates.

It was a matter of historical interest to compare these glucosamine derivatives with those prepared by Irvine and Hynd thirty years ago.[4]

Specimens of their products were acetylated, and tested for physical constants. They were not in agreement with those found for the α-forms prepared in the present work, so they were assumed to be of the β-configuration. This is in agreement with the results of Moggridge and Newberger,[5] and of Haworth, Lake and Peat.[6]

The 4,6-benzylidene-2,3-anhydro-α-methylguloside (or taloside), first prepared by Robertson and Tetlow (unpublished result), also gave two amino derivatives which could be separated after acetylation. Unpublished results of Robertson, Tetlow and Robson showed that the anhydro ring of this guloside (or taloside) ruptured under alkaline influence to give idose derivatives. It was, therefore, reasonable to assume that the predominating isomer was 2(or 3-)-acetyl-4,6-benzylidene-3(or 2-)-acetamido-α-methylidoside and that the minor constituent was 3(or 2-)-acetyl-4,6-benzylidene-2(or 3-)-acetamide-α-methylgalactoside. Additional results will be given in a later paper.

Thanks are due to Vice Chancellor Sir James Irvine and Professor John Read for their direction and advice after the death of the senior author.

Experimental

Action of Ammonia on 4,6-Benzylidene-2,3-anhydro-α-methylalloside.—The starting material was prepared by the method of Robertson and Griffith.[1] The anhydro sugar (2 g.) was heated with aqueous concentrated ammonia (50 cc.) in a sealed tube at 100° for thirty hours. Long needles crystallized on cooling. This mixture of isomers could not be separated in this form. The theoretical yield was obtained, the product having m. p. 168° and $[\alpha]^{18}D$ +104.7° (*c* 1.35, chloroform) and its analysis corresponded to an aminobenzylidene-α-methylhexoside. (Found: C, 59.7; H, 6.6; N, 5.0. $C_{14}H_{19}O_5N$ requires C, 60.0; H, 6.7; N, 5.0.) Acetylation of the mixture by treatment with acetic anhydride in pyridine gave 3-acetyl-4,6-benzylidene-2-acetamido-α-methylaltroside (60% yield).[3]

Partial Hydrolysis of 3-Acetyl-4,6-benzylidene-2-acetamido-α-methylaltroside.—The amino altroside (2 g.) was refluxed with 0.5% methyl alcoholic hydrochloric acid (100 cc.) to a constant rotation (two hours). The solvent was removed by distillation under reduced pressure, leaving a sirup which crystallized in 60% yield from acetone–alcohol. It was **3-acetyl-2-acetamido-α-methylaltroside,** having m. p. 189° with decomposition and $[\alpha]^{16}D$ +7.3° (*c* 4.1, methyl alcohol). (Found: N, 5.0. $C_{11}H_{19}O_7N$ requires N, 5.0.)

Triacetyl-2-acetamido-α-methylaltroside.—The diacetyl derivative (2 g.) was boiled with acetic anhydride (30 cc.) and fused sodium acetate (8 g.). On initial heating a vigorous action took place and boiling was continued for five minutes. The dark reaction mixture was poured into water (150 cc.) and extracted with chloroform (6 × 100 cc.). The extracts were washed with 5% sulfuric acid, saturated sodium bicarbonate solution and water, then dried with sodium sulfate and the solvent removed under diminished pressure, leaving a sirup which crystallized from alcohol in 65% yield. It was triacetyl-2-acetamido-α-methylaltroside having m. p. 176° and $[\alpha]^{20}D$ +110° (*c* 1.7, chloroform). (Found: N, 3.8. $C_{15}H_{23}O_9N$ requires N, 3.9.)

Hydrochloride Salt of 2-Amino-4,6-benzylidene-α-methylaltroside.—The mixture of isomers (0.5 g.) was dissolved in ice-cold acetone (25 cc.). Aqueous hydrochloric acid (2 cc. of 2 *N*) was added, with immediate crystallization of the hydrochloride salt in fine needles. As only a 93% yield was obtained, it is assumed that only the altroside form crystallized; constants were identical for a number of preparations. It gave positive tests for benzaldehyde, nitrogen and chlorine. It was therefore the **hydrochloride salt of 2-amino-4,6-benzylidene-α-methylaltroside,** having m. p. 96° and $[\alpha]^{21}D$ +85.5° (*c* 0.3, chloroform). (Found: Cl, 11.1. $C_{14}H_{18}O_5NCl$ requires Cl, 11.2.)

Action of Ammonia on 4,6-Benzylidene-2,3-anhydro-α-methylmannoside.—The anhydro mannoside (prepared by the method of Robertson and Whitehead, unpublished result) was treated in the manner described above for the alloside except that it was necessary to heat for only six hours. The theoretical yield of a mixture of isomers was obtained, in long needles, which could not be separated in this form. The material, proved by the reactions below to contain **4,6-benzylidene-3-amino-α-methylaltroside** (99%) and **4,6-benzylidene-2-amino-α-methylglucoside** (1%), had m. p. 188° and $[\alpha]^{19}D$ +88.9° (*c* 0.5, chloroform). (Found: C, 59.7; H, 6.5; N, 5.2. $C_{14}H_{19}O_5N$ requires C, 60.0; H, 6.7; N, 5.0.)

The mixture was separated by acetylation. The crystalline mixture obtained was fractionally crystallized from methyl alcohol and ether, giving a 60% yield of **2-acetyl-4,6-benzylidene-3-acetamido-α-methylaltroside** in small prisms having m. p. 201° and $[\alpha]^{12}D$ +14.6° (*c* 2.3, chloroform). (Found: N, 3.9. $C_{18}H_{23}O_7N$ requires N, 3.9.) Also, a 1% yield of **3-acetyl-4,6-benzylidene-2-acetamido-α-methylglucoside** was isolated in short needles having m. p. 235° and $[\alpha]^{12}D$ +45.5° (*c*, 2, chloroform). (Found: N, 3.9.)

(4) Irvine and Hynd, *J. Chem. Soc.*, 698 (1914).
(5) Moggridge and Newberger, *ibid.*, 748 (1938).
(6) Haworth, Lake and Peat, *ibid.*, 271 (1939).

Hydrochloride Salt of 3-Amino-4,6-benzylidene-α-methylaltroside.—The mixture of isomers (0.5 g.) was dissolved in chilled acetone (50 cc.) and aqueous hydrochloric acid (2 cc. of 2 *N*) was added. As no crystallization took place, the solution was warmed at 50° for five minutes, when the hydrochloride salt (needles) crystallized out (88% yield). From the yield obtained and from the fact that the constants were identical for several preparations, it is assumed that only the altroside form crystallized. It melted with decomposition at 183° and had $[\alpha]^{19}D$ +83.5° (*c* 1, water). Its analysis proved it to be the **hydrochloride salt** of **4,6-benzylidene-3-amino-α-methylaltroside.** (Found: Cl, 11.3. $C_{14}H_{20}O_5NCl$ requires Cl, 11.2.)

Partial Hydrolysis of 2-Acetyl-4,6-benzylidene-3-acetamido-α-methylaltroside.—The 3-amino-altroside (2 g.) was dissolved in 0.5% methyl alcoholic hydrogen chloride (100 cc.) and warmed at 55° to a constant rotation (two hours). The solvent was removed by distillation under diminished pressure, leaving a sirup which crystallized from acetone–alcohol in 60% yield. It was **2-acetyl-3-acetamido-α-methylaltroside** having m. p. 174° and $[\alpha]^{16}D$ +106.2° (*c* 1.1, chloroform). (Found: N, 5.1. $C_{11}H_{19}O_7N$ requires N, 5.0.)

Triacetyl-3-acetamido-α-methylaltroside.—The diacetyl derivative was acetylated and isolated as described for 2-acetamido-α-methylaltroside. It crystallized in small cubes from alcohol, having m. p. 177°, and $[\alpha]^{18}D$ +34.1° (*c* 1.2, chloroform). It was **triacetyl-3-acetamido-α-methylaltroside.** (Found: N, 4.0. $C_{15}H_{23}O_9N$ requires N, 3.9.)

Partial Hydrolysis of 4,6-Benzylidene-2-amino-α-methylaltroside.—The mixture of amino isomers (2 g.) was dissolved in water (400 cc.) containing 2 *N* hydrochloric acid (19 cc.). The solution was refluxed to a constant rotation (two and one-half hours), washed with chloroform to remove benzaldehyde and taken to dryness under reduced pressure, yielding **2-amino-α-methylaltroside hydrochloride** (sirup, $[\alpha]^{22}D$ +39.7° (*c* 3.1, chloroform). Found: Cl, 15.6. $C_7H_{16}O_5NCl$ requires Cl, 15.5).

In a subsequent preparation, after the hydrolysis as above, the solution was neutralized with barium carbonate, filtered and taken to dryness under diminished pressure at 50°. The residue was extracted with acetone and on concentration of the solution needles crystallized (70% yield) and were recrystallized from alcohol. The substance was **2-amino-α-methylaltroside,** m. p. 193°, $[\alpha]^{20}D$ +107° (*c* 0.3, chloroform). (Found: OCH_3, 16.1. $C_7H_{15}O_5N$ requires OCH_3, 16.1.) No trace of the other isomer could be isolated in this form.

Partial Hydrolysis of 4,6-Benzylidene-3-amino-α-methylaltroside.—The mixture of amino isomers (1.8 g.) was dissolved in aqueous 1% hydrochloric acid (200 cc.) and the solution refluxed to a constant rotation (eighteen hours). The dark solution was decolorized with norit, washed with chloroform to remove benzaldehyde and taken to dryness under diminished pressure at 50°, leaving a 76% yield of the hydrochloride of 3-amino-β-methylaltroside (needles, m. p. 209° with decomposition; $[\alpha]^{18}D$ −149° (*c* 1, water). (Found: N, 6.2; Cl, 15.4. $C_7H_{16}O_5NCl$ requires N, 6.1; Cl, 15.5.) These constants identify the compound as "methyl epiglucosamine hydrochloride."[7,8]

(7) Fisher, *Ber.*, **53**, 540 (1920).

(8) Levene and Meyer, *J. Biol. Chem.*, **53**, 221 (1923).

Action of Ammonia on 2,3-Anhydro-α-methylalloside.—2,3-Anhydro-α-methylalloside (prepared by the method of Robertson and Dunlop[9]) was treated with ammonia by the previously described method, heating being continued for twenty hours. The resultant sirup was acetylated with acetic anhydride and sodium acetate, giving **triacetyl-2-acetamido-α-methylaltroside** (68% yield). No glucose derivative was isolated.

Partial Hydrolysis of 4,6-Benzylidene-2,3-anhydro-α-methylmannoside.—The material (3 g.) was dissolved in acetone (270 cc.) containing an aqueous solution of oxalic acid (9 g. in 30 cc.) and the solution was boiled for twelve hours. After neutralization with barium carbonate and filtration the acetone was removed under diminished pressure, leaving an aqueous solution which was washed with ether to remove benzaldehyde, then evaporated to dryness under diminished pressure at 50°. The residue was extracted several times with acetone, and the combined extracts, on evaporation, yielded a colorless sirup which crystallized (80% yield) from acetone-alcohol on long standing in needles of **2,3-anhydro-α-methylmannoside** (m. p. 67°; $[\alpha]^{20}D$ +44.6° (*c* 1.4, chloroform). Found: C, 48.0; H, 6.7; OCH_3, 17.3. $C_7H_{12}O_5$ requires C, 47.7; H, 6.8; OCH_3, 17.6).

Action of Ammonia on 2,3-Anhydro-α-methylmannoside.—The material was treated with ammonia, heating for ten hours, yielding a sirup which was acetylated by the usual method to give a mixture of **triacetyl-3-acetamido-α-methylaltroside** (65%) and **triacetyl-2-acetamido-α-methylglucoside** (**tetraacetyl-α-methylglucosamine**) (2%) which were separated by fractional crystallization from chloroform–ether. The latter had m. p. 132°; $[\alpha]^{20}D$ +44.6° (*c* 1.4, chloroform). (Found: N, 4.0. $C_{15}H_{23}O_9N$ requires 3.9% nitrogen.)

Acetylation of 4,6-Benzylidene-2-amino-β-methylglucoside.—Through the kindness of Principal Sir James Irvine a sample of this material, prepared in 1914, was provided. It was acetylated with acetic anhydride in pyridine by the usual method, and the sirup isolated crystallized (needles) from alcohol (75% yield) to give **3-acetyl-4,6-benzylidene-2-acetamido-β-methylglucoside** (m. p. 158°; $[\alpha]^{20}D$ −12.9° (*c* 0.9, chloroform). Found: N, 3.8. $C_{18}H_{23}O_7N$ requires N, 3.9). This derivative was prepared to confirm the supposition that Irvine and Hynd[4] were working with β-methylglucosamine.

Partial Hydrolysis of 3-Acetyl-4,6-benzylidene-2-acetamido-β-methylglucoside.—The material was partially hydrolyzed, giving an uncrystallizable sirup which was acetylated in the usual way from acetone–alcohol (70% yield) to give **triacetyl 2-acetamido-β-methylglucoside;** m. p. 238° with decomposition; $[\alpha]^{20}D$ −23.0° (*c* 0.3, chloroform). (Found: N, 3.9. $C_{15}H_{23}O_9N$ requires N, 3.9.)

Action of Ammonia on 4,6-Benzylidene-2,3-anhydro-α-methylguloside (or taloside).—The starting material, prepared from galactose by the method of Robertson and Tetlow (unpublished result), was treated with ammonia by the usual method, heating being continued for ten hours at 110°. An 80% yield of isomers was obtained, having m. p. 128–130° and $[\alpha]^{20}D$ +60.6° (*c* 0.9, chloroform). (Found: N, 5.1; OCH_3, 11.0. $C_{14}H_{19}O_5N$ requires N,

(9) Robertson and Dunlop, *J. Chem. Soc.*, 472 (1938).

5.0; OCH_3 11.0.) The product was acetylated in the usual manner to yield on crystallization from alcohol and ether **3(or 2)-acetyl-4,6-benzylidene-2(or 3)-acetamido-α-methylidoside** (55% yield); m. p. 188°; $[\alpha]^{12}D$ +43.4° (*c* 1.3, chloroform) (Found: N, 3.8. $C_{18}H_{23}O_7N$ requires N, 3.9) and **3(or 2)-acetyl-4,6-benzylidene-2(or 3)-acetamido-α-methylgalactoside** (8% yield; m. p. 260°; $[\alpha]^{12}D$ +70.3° (*c* 0.8, chloroform). Found: N, 3.9).

Partial Hydrolysis of 3(or 2)-Acetyl-4,6-benzylidene-2-(or 3)-acetamido-α-methylidoside.—The material was treated with warm hydrochloric acid, heating being continued for two hours, to give an 81% yield of **3(or 2)-acetyl 2(or 3)-acetamido-α-methylidoside** (sirup, $[\alpha]^{16}D$ −36.0° (*c* 3.3, methyl alcohol). (Found: N, 4.9. $C_{11}H_{10}O_7N$ requires N, 5.0.)

Summary

A number of new amino sugar derivatives have been prepared by action of aqueous ammonia on the 2,3-anhydro ring of allose, mannose and gulose (or talose) derivatives. In each case, two *trans* isomers were formed, the altroside configuration greatly predominating in reactions with the first two compounds.

WILMINGTON, DEL. RECEIVED OCTOBER 2, 1942

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Synthesis of Polyenes. III. A New Synthesis of Diethylstilbestrol

BY M. S. KHARASCH AND MORTON KLEIMAN[1]

The *trans*-4,4′-dihydroxy-α,α′-diethylstilbene, now commonly referred to as diethylstilbestrol, was first synthesized in 1938 by Dodds and co-workers[2] by the following series of reactions

Anisaldehyde $\xrightarrow{KCN}$ Anisoin $\xrightarrow[\text{acetic acid, 100°, 24 hr.}]{Zn\ dust}$

Desoxyanisoin $\xrightarrow[EtI]{EtONa}$ Ethyl desoxyanisoin $\xrightarrow{EtMgBr}$

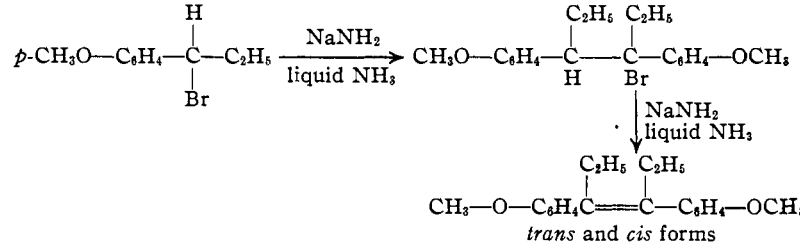
3,4-Bis-(*p*-anisyl)-3-hexanol $\xrightarrow[\text{or } KHSO_4]{PBr_3}$

Diethylstilbestrol dimethyl ether $\xrightarrow[\text{alcohol, 205°}]{KOH}$ Diethylstilbestrol

Numerous workers[3] have since attempted to improve upon this method of preparation; however, all the other suggested syntheses are equally laborious and, in our estimation, inferior to Dodds' method from a practical standpoint (availability of raw materials, etc.).

In this Laboratory, the condensation of allyl chloride and β-methylallyl chloride to hexatriene[4a] and 2,5-dimethylhexatriene,[4b] respectively, under the influence of sodamide in liquid ammonia has been studied exhaustively. The hypothesis evolved to account for these reactions suggested that a molecule such as anethole hydrobromide should react with sodamide or potassium amide to yield the products shown below.

Because of the possibility of side reactions, it was considered desirable to establish first the validity of the general method by the syntheses of the α,α′-dimethyl- and α,α′-diethylstilbenes from α-chloroethylbenzene and α-chloropropylbenzene, respectively.



trans and *cis* forms

α-Chloroethylbenzene, obtained by the addition of dry hydrogen chloride to styrene at low temperature, was treated with sodamide in liquid ammonia solution. When the sodamide was present in large excess, as was the case when the organic reactant was slowly added to the suspension of sodamide in liquid ammonia, a 40% yield of *cis*-dimethylstilbene was isolated. High boiling oils, the products of side reactions and poly-

(1) This paper is part of a dissertation submitted by Morton Kleiman to the Faculty of the Division of the Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy, March, 1942.

(2) Dodds, Goldberg, Lawson and Robinson, *Nature*, **141**, 247 (1938).

(3) (a) Kerschbaum, Kleedorfer, Prillinger, Wessely and Zajic, *Naturwiss.*, **27**, 131 (1939); (b) Wessely and Kleedorfer, *ibid.*, **27**, 567 (1939); (c) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940); (d) Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 93 (1940); (e) Kuwada, Sasagawa and Nisikawa, *ibid.*, **60**, 553 (1940); (f) Peteri, *J. Chem. Soc.*, 833 (1940).

(4) (a) Kharasch and Sternfeld, THIS JOURNAL, **61**, 2318 (1939); (b) Kharasch, Nudenberg and Sternfeld, *ibid.*, **62**, 2034 (1940).