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PREPARATION OF GLYCOSIDES OF 2-DEOXY-2-METHYLAMINO-D-MANNOSE, 2-DEOXY-2-METHYLAMINO-D-GLUCOSE, AND 2-DEOXY-2-METHYLAMINO-D-GALACTOSE OBSERVATIONS ON *N*-METHYLATION OF AMIDES*

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ABSTRACT

Benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-D-mannopyranoside (**10**) and its furanose isomer (**9**), the derived *N*-methyloxazolidinones **11** and **6**, benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-β-D-glucofuranoside (**15**) and methyl 2-deoxy-2-methylacetamido-β-D-galactofuranoside (**20**), were prepared from appropriate diethyl dithioacetals They were considered the most suitable starting materials for synthesis of *O*-methyl-2-deoxy-2-methylamino-hexoses because of their ease of prepraration and the presence of suitable blocking groups Oxazolidinones were prepared from *N*-benzyloxycarbonyl derivatives of 2-amino-2-deoxy-D-mannose by using methanolic sodium methoxide Their use in preparation of 2-deoxy-2-methylamino derivatives is discussed The Kuhn reagent was used in these syntheses for *N*-methylating amides However, certain amides containing comparatively bulky substituents in the vicinity of the NH group are resistant to methylation

INTRODUCTION

Methyl ethers of 2-deoxy-2-methylamino-D-glucose[1] and 2-deoxy-2-methylamino-D-galactose[2] have been prepared for use as chromatographic standards These can be used in identification of fragments arising from polysaccharides containing 2-acetamido-2-deoxy-D-glucopyranosyl and 2 acetamido-2-deoxy-D-galactopyranosyl residues, respectively, when the polysaccharides are successively methylated by the Kuhn[3] or Hakomori[4] procedure and hydrolysed This study is being extended to the preparation of methyl ethers that can arise, by a similar procedure, from 2-acetamido-2-deoxy-D-glucofuranose, 2-acetamido-2-deoxy-D-galactofuranose, 2-acetamido-2-deoxy-D-mannopyranose, and 2-acetamido-2-deoxy-D-mannofuranose residues The last two named are possible structures in 2-acetamido-2-deoxy-D-mannose-containing polysaccharides of bacteria[5,6] In order to prepare the methyl ethers it is necessary to obtain glycosides of corresponding 2-deoxy-2-methylamino-hexosides The experiments are presented as follows

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Preparation of the N-*methyl oxazolidinone* **11** *and benzyl* 2-[(*benzyloxycarbonyl*)-*methylamino*]-*2-deoxy-α-*D-*mannopyranoside* (**10**) — As the *N*-benzyloxycarbonyl derivative of 2-amino-2-deoxy-D-mannose (**2**) could not be prepared by the action of benzyl chloroformate on 2-amino-2-deoxy-D-mannose in aqueous sodium hydrogen carbonate, an alternative method of introducing the substituent was devised 2-[(Benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (**1**) was prepared by the reaction of 2-amino-2-deoxy-D-mannose hydrochloride with ethanethiol in the presence of hydrochloric acid (saturated at 0°) followed by treatment with benzyl chloroformate It was purified by chromatography on silicic acid and then converted into 2-[(benzyloxycarbonyl)amino]-2-deoxy-α,β-D-mannose (**2**) by using aqueous acetone–mercuric chloride in the presence of cadmium carbonate[7].

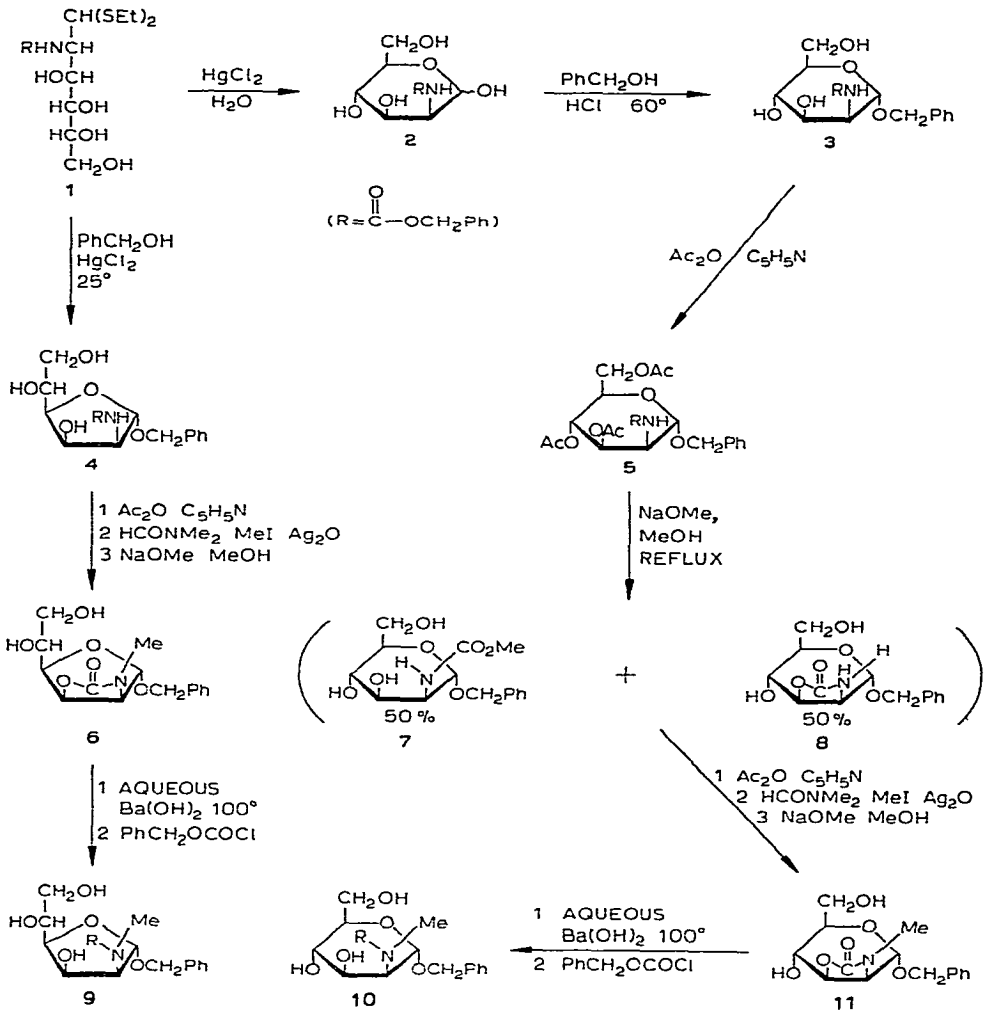
The *N*-benzyloxycarbonyl derivative **2** was converted into benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannopyranoside (**3**) by the action of benzyl alcohol–hydrogen chloride at 60° The product (**3**) was purified by chromatography on silicic acid, and converted into its crystalline triacetate **5** (30% yield based on 2-amino-2-deoxy-D-mannose hydrochloride) Deacetylation gave **3**, whose specific rotation of +64° corresponded to an α anomer The tri-*O*-acetyl derivative proved resistant to *N*-methylation by the Kuhn procedure*, and it was necessary to find another route for introducing the *N*-methyl group

Compound **3** was prepared[8] from 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (**1**) with benzyl alcohol–mercuric chloride at 60°, but t l c showed several components, and column chromatography gave an incomplete separation. The product had a specific rotation of +50° and thus was not pure

The acetate **5**, or its parent glycoside **3**, was treated with refluxing methanolic sodium methoxide Benzyl alcohol was eliminated and a mixture of the *N*-methoxycarbonyl derivative **7** and the oxazolidinone **8** was obtained After resolution of a portion of the mixture, p m r spectra of the products were obtained and found to be in accord with the proposed structures The acetates obtained by acetylation of the mixture both underwent *N*-methylation when treated with *N,N*-dimethylformamide–methyl iodide–silver oxide as the *N*-methyloxazolidinone **11** was obtained in 70% yield on treatment of the product with methanolic sodium methoxide The *N*-methoxycarbonyl-*N*-methyl intermediate obtained from **7** apparently underwent a facile cyclisation to give the same product as that obtained from the oxazolidinone **8**

The *N*-methyloxazolidinone **11** was converted into benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-D-mannopyranoside (**10**) as follows The oxazolidinone ring was split by hot aqueous barium hydroxide, the formation of carbon dioxide from the intermediate carbamic acid being evident by the production of a precipitate of barium carbonate This method of scission was easier to control than that of Gross *et al* [9], who used hot aqueous *p*-dioxane containing potassium hydroxide, as the former reagent is more readily removed The resulting benzyl 2-deoxy-2-methyl-

*The tri-*O*-acetyl derivative of benzyl 2-acetamido-2-deoxy-α-D-mannopyranoside was similarly resistant to *N*-methylation



Scheme 1 Reaction scheme for preparation of benzyl glycosides based on 2-deoxy-2-methylamino-D-mannose

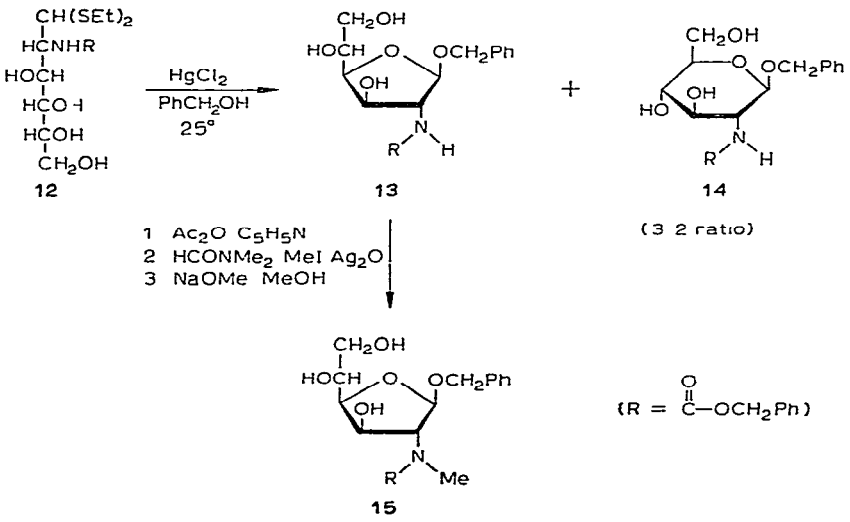
amino-α-D-mannopyranoside, which did not show carbonyl absorption in the infrared, was treated with benzyl chloroformate to yield benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-D-mannopyranoside (**10**)

Preparation of the N-*methyloxazolidinone* **6** *and benzyl* **2**-[(*benzyloxycarbonyl*)-*methylamino*]-α-D-*mannofuranoside* (**9**) — 2-[(Benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (**1**) was treated with cold benzyl alcohol containing mercuric chloride and mercuric oxide[10], and the product was chromatographed on silicic acid to give crystalline benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannofuranoside (**4**) in 29% yield As it had a specific rotation of +81°, the α-furanoside structure was assigned, and oxidation with lead tetraacetate in acetic acid

gave formaldehyde It was converted into its triacetate, which, in contrast to its pyranoside isomer, could be *N*-methylated by the Kuhn procedure Treatment of the product with methanolic sodium methoxide eliminated benzyl alcohol forming the oxazolidone **6** Cleavage of the latter with aqueous barium hydroxide yielded benzyl 2-deoxy-2-methylamino-α-D-mannofuranoside with formation of barium carbonate, and treatment of the sugar with benzyl chloroformate provided benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-D-mannofuranoside (**9**)

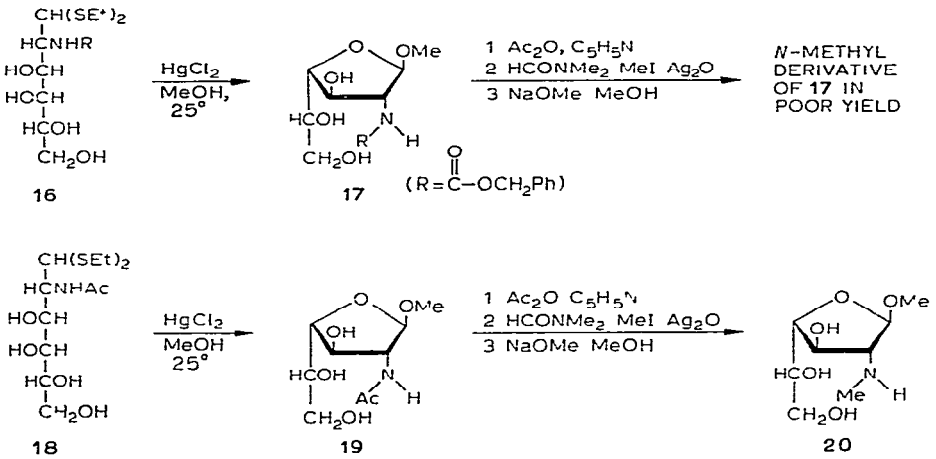
By reactions starting with 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal, and by a similar route to that already described, crystalline methyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannofuranoside and its syrupy mannopyranoside counterpart were prepared As the benzyl glycoside series proved more useful as intermediates in synthesis, further work on the methyl glycosides was not conducted

Preparation of benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-β-D-glucofuranoside (**15**) — 2-[(Benzyloxycarbonyl)]amino-2-deoxy-D-glucose diethyl dithioacetal[11] (**12**) was treated with mercuric chloride–benzyl alcohol in the presence of mercuric oxide giving a mixture of benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-glucofuranoside (**13**, 21%) and the corresponding β-D-glucopyranoside (**14**, 14%)[12], which was resolved chromatographically on silicic acid Treatment of **13** with lead tetraacetate in acetic acid resulted in the formation of formaldehyde The furanoside had a specific rotation of −36°, and gave an n m r spectrum in accord with its proposed structure It was converted in 47% yield into benzyl 2-[(benzyloxycarbonyl)-methylamino]-2-deoxy-β-D-glucofuranoside (**15**), by successive acetylation, Kuhn methylation, and deacetylation



Scheme 2 Reaction scheme for preparation of benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-β-D-glucofuranoside

Preparation of methyl 2-deoxy-2-methylacetamido-β-D-galactofuranoside (**20**) *and other related galactofuranoside derivatives* — 2-[(Benzyloxycarbonyl)amino]-2-deoxy-D-galactose diethyl dithioacetal (**16**) was prepared from 2-amino-2-deoxy-D-galactose hydrochloride by successive treatments with ethanethiol–hydrochloric acid (saturated at 0°) and benzyl chloroformate The crystalline product gave the anticipated p m r spectrum and elemental analyses, but surprisingly had a m p and specific rotation differing from those of the crystalline compound assigned structure **16** by Whitehouse *et al* [11], who prepared it by the same procedure Their product was therefore not compound **16**



Scheme 3 Reaction scheme for preparation of methyl glycosides based on galactosamine and 2-deoxy-2-methylamino-D-galactose

Compound **16** was treated with benzyl alcohol–mercuric chloride–mercuric oxide overnight The product was not benzyl 2-[(benzyloxycarbonyl)amino]-D-galactofuranoside, as evidenced by its p m r spectrum In another synthesis, use of methanol in place of benzyl alcohol resulted in a more successful elimination, although it was evident that formation of the glycoside was much slower than in the mannofuranoside and galactofuranoside series The product, methyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactofuranoside (**17**), had a specific rotation of −39°, and treatment with lead tetraacetate resulted in formation of formaldehyde in accord with the proposed structure Its acetate was subjected to the Kuhn procedure but unfortunately *N*-methylation proceeded very slowly and simultaneous deacetylation and *O*-methylation took place

An attempt was made to prepare benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-galactofuranoside from 2-amino-2-deoxy-D-galactose diethyl dithioacetal hydrochloride by treatment with benzyl alcohol–mercuric chloride–mercuric oxide and reaction of the product with benzyl chloroformate The crystalline product, isolated by chromatography on silicic acid, was impure as its m p was indefinite and it was not free from sulfur

Methyl 2-acetamido-2-deoxy-β-D-galactofuranoside (**19**) was prepared in good yield from 2-acetamido-2-deoxy-D-galactose diethyl dithioacetal[13] (**18**) by the action of methanol–mercuric chloride–mercuric oxide Its specific rotation of −73°, p m r spectrum, and its liberation of formation of formaldehyde on periodate oxidation agreed with the proposed structure Successive acetylation, Kuhn methylation and deacetylation gave a product having $[\alpha]_D$ −89°, corresponding to methyl 2-deoxy-2-methylacetamido-β-D-galactofuranoside (**20**) Its p m r. spectrum was complex, many signals such as those of H-1, OMe, and NMe were broad doublets One explanation is that restrictive rotation of the C-2 to nitrogen bond occurs so that both rotamers[14] are detected

Replacement of methanol by benzyl alcohol–*N*,*N*-dimethylformamide in the foregoing reaction was carried out in an attempt to obtain benzyl 2-acetamido-2-deoxy-β-D-galactofuranoside An impure crystalline product was isolated in low yield, and it was not investigated further

Factors affecting N-*methylation with the Kuhn reagent* — The foregoing experiments on preparation of starting materials in synthesis of *O*-methyl 2-deoxy-2-methylamino-hexoses provide information on factors governing the Kuhn *N*-methylation of amides It is evident that *N*-methylation does not occur when comparatively bulky substituents are in the vicinity of the NH group Several comparisons demonstrate this The tri-*O*-acetyl derivative of methyl 2-acetamido-2-deoxy-β-D-galactofuranoside can be readily *N*-methylated, whereas its 2-(benzyloxycarbonyl)amino analogue can not In the mannose series, neither the 2-acetamido- nor 2-(benzyloxycarbonyl)amino derivatives of benzyl tri-*O*-acetyl-2-deoxy-α-D-mannopyranoside are susceptible to *N*-methylation, in contrast to the less sterically hindered benzyl tri-*O*-acetyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-glucopyranoside The same inert *N*-acetyl derivative can be compared in the same way with the susceptible 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranoside, in which the *O*-benzyl group is replaced by a smaller acetyl group It is also significant that, in contrast with compound **5**, the peracetates of the *N*-methoxycarbonyl derivative **7** and oxazolidinone **8**, both lacking the bulky *N*-benzyloxycarbonyl group, are readily *N*-methylated It follows therefore that data on the Kuhn methylation obtained from naturally occurring polysaccharides containing 2-acetamido-2-deoxy-hexose and particularly 2-acetamido-2-deoxy-mannose residues must be sterically evaluated in order to judge whether undermethylation of OH or NH groups is possible

EXPERIMENTAL

General — T l c was carried out with silica gel Merck 0 05–0 2 mm (70–325 mesh ASTM). Spots were revealed by spraying with 50% sulfuric acid and charring the products for 30 min at 120° Column chromatography was performed on Mallinckrodt silicic acid of 100 mesh

2-Amino-2-deoxy-D-mannose hydrochloride and 2-amino-2-deoxy-D-galactose hydrochloride were supplied by Sigma Chemical Company, St Louis, Mo U S A

and 2-amino-2-deoxy-D-glucose hydrochloride by Eastman Organic Chemicals, Rochester, New York, U S A

P m r spectra were recorded at 25° unless otherwise stated with a Varian 100-MHz n m r spectrometer Tetramethylsilane was used as external standard for compounds in D_2O, Me_2SO-d_6, or in mixtures of the two solvents (1 9 v/v), and as an internal standard for determinations in chloroform-*d* Chemical shifts are expressed on the τ scale

Glycol cleavage reactions were conducted in 5-mm diameter n m r tubes, and production of formaldehyde detected with a Varian XL-100-15 n m r spectrometer with Fourier transform To a sample of sugar (2 mg) in D_2O (0 5 ml), sodium periodate (10 mg) was added and after 18 h formaldehyde was detected as a signal 344 Hz upfield from that of an internal standard of HCO_2D Sugars (2 mg) insoluble in D_2O were dissolved in CD_3CO_2D (0 5 ml) and lead tetraacetate (15 mg) was added After 2 days, formaldehyde could be detected as a signal 323 Hz downfield from the central signal of CHD_2CO_2D, present as an impurity in the solvent In both types of determination, the number of transients used was 100, the sweep width was 5000 Hz with a sweep offset of 45447 Hz from the deuterium lock, the acquisition time was 2 sec, and the pulse-width 50 μsec

*2-[(Benzyloxycarbonyl)amino]-2-deoxy-*D*-mannose diethyl dithioacetal* (**1**) — 2-Amino-2-deoxy-D-mannose hydrochloride (10 g) was shaken with hydrochloric acid (saturated at 0°, 80 ml) and ethanethiol (30 ml) for 18 h The mixture was neutralized by addition to ethanol (500 ml) containing lead carbonate, the solution was filtered and the filtrate evaporated to a syrup containing 2-amino-2-deoxy-D-mannose diethyl dithioacetal hydrochloride This was dissolved in water (100 ml), sodium hydrogen carbonate (10 g) and benzyl chloroformate (10 ml) were added, and the mixture was shaken for 18 h It was extracted with ethyl acetate and the extract was evaporated to a mobile syrup Fractionation on a column of silicic acid was carried out by using chloroform–Skellysolve B (1 1 v/v) as eluant followed by chloroform containing 2% of methanol The latter eluted compound **1** (12 8 g) having $[\alpha]_D^{25}$ +22° (*c* 0 8, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°), τ 2 17 (5 aromatic protons), 4 26 (*N*-benzyloxycarbonyl CH_2), complex at 8 21–8 40 (2Me groups)

Anal Calc for $C_{18}H_{29}O_6NS_2$ C, 51 52, H, 6 97, N, 3 34 Found C, 51 17, H, 6 80, N, 3 13

Benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α*-*D*-mannopyranoside* (**3**) — Mercuric chloride (8 g) in benzyl alcohol (25 ml) was added to benzyl alcohol (25 ml) containing compound **1** (4 59 g), both solutions being maintained at 60°. After 20 min at this temperature, the solution was cooled and acetone (200 ml) containing pyridine (3 ml) added The solution was filtered and evaporated, and t l c of the product [solvent, 9 1 (v/v) chloroform–ethanol] revealed two spots Chromatography on silicic acid [eluant, 49 1 (v/v) chloroform–methanol], provided the major faster-moving component (2 34 g) having $[\alpha]_D^{25}$ +50° (*c* 3 0, ethanol), which corresponded to compound **3** Its p m r spectrum was identical with that of a pure sample, but

its specific rotation was less than +64° (see below) thus showing it to be impure A mixed fraction (1 30 g) was also obtained

Compound **3** could be prepared free of the slower-moving material by the following 2-step process Mercuric chloride (35 g) was dissolved in acetone (200 ml) and cadmium carbonate (50 g) added Compound **1** (28 g) in acetone (200 ml) containing water (20 ml) was then added and the mixture shaken overnight Pyridine (15 ml) was added to remove excess mercuric chloride as its insoluble pyridine complex, and the solution was filtered One tenth of the product obtained on evaporation was fractionated on a cellulose column (eluant acetone) and syrupy 2-[(benzyloxycarbonyl)amino]-2-deoxy-α.β-D-mannose (**2**) was obtained having $[\alpha]_D^{25}$ −4° (*c* 1 0, ethanol) The p m r spectrum indicated that it consisted of 60% of the α- and 40% of the β-anomer of the pyranose form, p m r data (D_2O) τ 2 12 (5 aromatic protons), 4 40 (benzyl CH_2 and H-1 of α-form), 4 56, J 2 Hz H-1 of β-form)

Anal Calc for $C_{14}H_{19}NO_7$ C, 53 67, H, 6 11, N, 4 47 Found C, 53 23, H, 6 34, N, 4 16

The remaining material was converted into its benzyl glycoside by dissolving it in benzyl alcohol containing 2% of hydrogen chloride (100 ml) and heating for 30 min at 60° The solution was neutralized by addition to excess aqueous sodium hydrogen carbonate, and the product was extracted with ethyl acetate The extract was evaporated to a syrup that gave one black spot on t l c Column chromatography on silicic acid (foregoing conditions) provided a fraction containing the benzyl glycoside **3** (8 18 g) having $[\alpha]_D^{25}$ +45° (*c* 3 0, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 13 (10 aromatic protons), 4 52 (*N*-benzyloxycarbonyl CH_2), 4 79, *J* 1 5 Hz (H-1), τ 4 84, 4 96, 5 07, 5 18 (*O*-benzyl CH_2)

The compound was purified as follows The benzyl glycoside (**3**, 8 18 g), was acetylated with acetic anhydride (20 ml)–pyridine (20 ml) overnight at room temperature The reagent was decomposed by addition of ice–water, and the product was extracted with chloroform, which was evaporated to a syrup Crystallization from ethyl acetate–Skellysolve B provided benzyl 3,4,6-tri-*O*-acetyl-2-[(benzyloxycarbonyl) amino]-2-deoxy-α-D-mannopyranoside (**5**, 6 80 g) having m p 111–112°, $[\alpha]_D^{25}$ +43° (*c* 0 3, chloroform), p m r data ($CDCl_3$) τ 2 68, 2 70, 2 77 (10 aromatic protons, NH), 4 91 (*N*-benzyloxycarbonyl CH_2), 5 00, *J* 3 2 Hz (H-1), 5 21, 5 33, 5 43, 5 55 (*O*-benzyl CH_2), 7 97, 7 99, 8 01 (3 acetates)

Anal Calc for $C_{27}H_{31}NO_{10}$ C, 61 24, H, 5 90, N, 2 70 Found C, 61 01, H, 5 83, N, 2 51

From the mother liquors was recovered 0 80 g of acetate, and deacetylation by 0 1M sodium methoxide in methanol provided the benzyl glycoside **3** having $[\alpha]_D^{25}$ +64° (*c* 3 0, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 19 (10 aromatic protons), 4 52 (*N*-benzyloxycarbonyl CH_2), 4 81, *J* 1 2 Hz (H-1), 4 81, 4 93, 5 07, 5 19 (*O*-benzyl CH_2)

Anal Calc for $C_{21}H_{25}NO_7$ C, 62 52, H, 6 25, N, 3 47 Found C, 62 11, H, 6 03, N, 3 22

Benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannofuranoside (**4**). — Mer-

curic chloride (7 1 g) was dissolved in benzyl alcohol (60 ml) and mercuric oxide (6 4 g) added To this mixture 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (**1**, 5 8 g) in benzyl alcohol (60 ml) was added and the mixture shaken overnight The reaction mixture was diluted with acetone, the solution filtered and pyridine (3 ml) added to the filtrate to remove mercuric chloride as its insoluble pyridine complex The solution was filtered and evaporated, in the presence of barium carbonate, to a syrup that gave a single black spot on t l c column chromatography on silicic acid, with chloroform–methanol (49 1 v/v) as eluant, provided a fraction that contained at least two compounds, according to the H-1 region of the p m r spectrum Crystallization from ethyl acetate–Skellysolve B gave the benzyl glycoside **4** (1 64 g) having m p 138°, $[\alpha]_D^{25}$ +81° (*c* 0 3, ethanol), p m r data (dimethyl sulfoxide-d_6) τ 2 50, *J* 9 Hz (NH), (dimethyl sulfoxide–d_6–deuterium oxide at 70°) 2 30, 2 25 (10 aromatic protons), 4 47 (*N*-benzyloxycarbonyl CH_2), 4 50 *J* approx 5 Hz (H-1), τ 4 82, 4 93, 5 01, 5 13 (*O*-benzyl CH_2)

Anal Calc for $C_{21}H_{25}NO_7$ C, 62 52, H, 6 25, N, 3 47 Found C, 62 26, H, 6 12, N, 3 36

The triacetate of **4**, obtained from ethanol, had m p 152°, $[\alpha]_D^{25}$ +103° (*c* 0 9, chloroform), p m r data (chloroform-*d*), τ 2 73 (10 aromatic protons, 4 95 (*N*-benzyloxycarbonyl CH_2), 8 00, 8 01, 8 04 (3 Ac groups)

Anal Calc for $C_{27}H_{31}NO_{10}$ C, 61 24, H, 5 90, N, 2 70 Found C, 61 04, H, 5 77 N, 2 45

N-*Methyloxazolidinone* **11** — As benzyl 3,4,6-tri-*O*-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannopyranoside (**5**) could not be *N*-methylated by the Kuhn procedure in order to provide an intermediate for the preparation of compound **10** or the *N*-methyloxazolidinone **11**, and alternative synthesis was devised

The acetate **5** (2 0 g) was treated for 3 h with refluxing 0 1M methanolic sodium methoxide (50 ml) The solution was neutralized with acetic acid and evaporated to a residue that was partitioned between ethyl acetate and water Evaporation of the ethyl acetate layer, provided a mixture, shown by t l c (solvent chloroform–ethanol, 9 1 v/v), to consist of two materials Column chromatography on silicic acid of 5% of the product (eluant chloroform–methanol, 49 1 v/v) provided in the first fraction the 2,3-oxazolidinone derivative (**8**) of benzyl 2-amino-2-deoxy-α-D-mannopyranoside, p m r data (dimethyl sulfoxide-d_6), τ 1 90 (NH), (dimethyl sulfoxide-d_6–D_2O at 70°), 2 15 (5 aromatic protons), 4 57, *J* 0 Hz (H-1), 4 73, 4 84, 4 97, 5 09 (*O*-benzyl CH_2)

Anal Calc for $C_{14}H_{17}NO_6$ C, 56 94, H, 5 80, N 4 74 Found C, 56 50, H, 5 67, N, 4 51

The second fraction had a p m r spectrum corresponding to benzyl 2-[(carboxymethyl)amino]-2-deoxy-α-D-mannopyranoside (**7**), p m r data (dimethyl sulfoxide-d_6), τ 2 93 (NH), (dimethyl sulfoxide-d_6–D_2O at 70°), τ 2 13 (5 aromatic protons), 4 69, *J* 0 Hz (H-1), 4 75, 4 87, 4 97, 5 09 (*O*-benzyl CH_2), 5 90 (OMe)

Anal Calc for $C_{15}H_{21}NO_7$ C, 55 04, H, 6 47, N, 4 28 Found C, 54 59, H, 6 22, N, 3 98

Comparison of the H-1 signals in the p m r spectrum of the unresolved mixture shows it contained 50% of oxazolidinone **8** and 50% of the *N*-methoxycarbonyl derivative **7**

A mixture of compounds **7** and **8** obtained from the acetate **5** was treated overnight in a 1 1 mixture of acetic anhydride and pyridine (10 ml) Excess reagent was decomposed with ice–water and the acetate was isolated by extraction with chloroform It was *N*-methylated by shaking overnight in a solution of *N*,*N*-dimethylformamide (10 ml) and methyl iodide (10 ml) containing silver oxide (2 0 g) The mixture was diluted with chloroform, which was filtered and evaporated to a syrup Deacetylation was effected with 0 1M methanolic sodium methoxide (30 ml) for 30 min The solution was neutralized (acetic acid), evaporated, and the resulting residue partitioned between ethyl acetate and water. The ethyl acetate layer was evaporated to a syrup, which was chromatographed on a column of silicic acid (eluant chloroform–methanol, 49 1 v/v) The resulting *N*-methyloxazolidinone (**11**, 0 78 g) had $[\alpha]_D^{25}$ +52° (*c* 1 0, ethanol) and showed infrared absorption at 1750 cm^{-1}, p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 12 (5 aromatic protons), 4 38 *J* 1 Hz (H-1), 4 68, 4 78, 4 88, 5 00 (*O*-benzyl CH_2), 6 73 (NMe)

Anal Calc for $C_{15}H_{19}NO_6$ C, 58 24, H, 6 19, N, 4 53 Found C, 57 93, H, 5 90, N, 4 11

N-*Methyloxazolidinone* **6** — Benzyl 3,5,6-tri-*O*-acetyl-2-[(benzyloxycarbonyl)-amino]-2-deoxy-α-D-mannofuranoside (triacetate of **4**) (0 35 g) was converted by Kuhn methylation followed by deacetylation (methodology, see previous procedure) into the oxazolidone **6** It crystallized (0 12 g) from ethyl acetate–Skellysolve B and had m p 107°, $[\alpha]_D^{25}$ +37° (*c* 0 3, ethanol) and absorbed at 1750 cm^{-1} in the i r , p m r data (dimethyl sulfoxide-d_6–D_2O at 70°). τ 2 19 (5 aromatic protons) 4 31, *J* 0 Hz (H-1), 4 81, 4 93, 4 98, 5 08 (*O*-benzyl CH_2), 6 69 (NMe)

Anal Calc for $C_{15}H_{19}NO_6$ C, 58 24, H, 6 19, N, 4 53 Found C, 57 90, H, 6 21, N, 4 46

*Benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-*D*-mannopyranoside* (**10**) — To the *N*-methyloxazolidinone derivative (**11**, 344 mg), barium hydroxide (0 5 g) in water (40 ml) was added and the reaction mixture was heated for 18 h at 100° During this period, a precipitate of barium carbonate formed Excess alkali was removed with carbon dioxide and the solution was evaporated to a residue, which was extracted with ethanol The resulting benzyl 2-deoxy-2-methylamino-α-D-mannopyranoside (322 mg) did not absorb in the carbonyl region of the infrared and had $[\alpha]_D^{25}$ +53° (*c* 0 4, ethanol), p m r. data (dimethyl sulfoxide-d_6) τ 2 28 (5 aromatic protons), 4 79, *J* 2 Hz (H-1), 4 86, 4 98, 5 13, 5 25 (*O*-benzyl CH_2)

Anal Calc for $C_{14}H_{31}NO_5$ C, 59 35, H, 7 47, N, 4 94 Found. C, 59 01, H, 7 22, N, 4 77.

The product (0 30 g) was shaken in a solution of sodium hydrogen carbonate (0 3 g) in water (5 liters) with benzyl chloroformate (0 3 ml) After 18 h the solution was extracted with ethyl acetate which was evaporated to a syrup. Following exhaustive removal of volatile material the resulting compound **10** (0 27 g) crystallized from

ethyl acetate–Skellysolve B The product had m p 159°, $[\alpha]_D^{25}$ +87° (*c* 0 3, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 20 (10 aromatic protons), 4 46 (*N*-benzyloxycarbonyl CH_2), 4 63, *J* 2 2 Hz (H-1), 4 80, 4 91, 5 02, 5 14 (*O*-benzyl CH_2), 6 57 (NMe)

Anal Calc for $C_{22}H_{27}NO_7$ C, 63 30, H, 6 52, N, 3 36 Found C, 63 37, H, 6 43, N, 3 48

*Benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-*D*-mannofuranoside* (**9**) — Following a procedure similar to that just described for the conversion of compound **11** into compound **10**, benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-α-D-mannofuranoside (**9**, 0 13 g) was prepared from the *N*-methyoxazolidinone derivative **6** (0 15 g) The product, which crystallized from ethyl acetate–Skellysolve B, had m p 114°, $[\alpha]_D^{25}$ +110° (*c* 0.3, ethanol), p m r data (dimethyl sulfoxide-d_6-D_2O at 70°) τ 2 17, 2 21 (10 aromatic protons), 4 10, *J* 4 0 Hz (H-1), 4 40 (*N*-benzyloxycarbonyl CH_2), 4 78, 4 88, 4 95, 5 07 (*O*-benzyl CH_2), 6 61 (NMe)

Anal Calc for $C_{22}H_{27}NO_7$ C, 63 30, H, 6 52, N, 3 36 Found C, 63 08, H, 6 42, N, 3 53

*Methyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-*D*-mannopyranoside* — By a method analogous to that used for the preparation of the benzyl glycoside **3** in which benzyl alcohol–mercuric chloride was used, 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (**1**, 0 75 g) was converted by the action of methanol–mercuric chloride into a mixture It gave, on t l c (solvent chloroform–ethanol, 9 1 v/v) a main spot and a faster-moving, minor spot Column chromatography on silicic acid (eluant. chloroform–methanol, 49 1 v/v) gave the required methyl glycoside as the main component (0 45 g) having $[\alpha]_D^{25}$ +22° (*c* 2 0, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 20 (5 aromatic protons), 4 52 (*N*-benzyloxycarbonyl CH_2), 5 02, *J* 1 4 Hz (H-1), 6 27 (OMe)

Anal Calc for $C_{15}H_{21}NO_7$ C, 55 04, H, 6 47, N, 4 28 Found C, 54 77, H, 6 41; N, 3 96

*Methyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-*D*-mannofuranoside* — This material was prepared from 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal (1 53 g) by a method analogous to that used in preparation of the benzyl analogue **4** T l c of the crude product (solvent as previously used) gave a main spot and a trace of faster-moving material Column chromatography on silicic acid (preceding eluant) provided a fraction (0 49 g) that crystallized from ethyl acetate–Skellysolve B The crystals (0 25 g) gave rise to two H-1 signals in the n m r. spectrum, but a pure methyl glycoside (0 12 g), m p 137°, $[\alpha]_D^{25}$ +73° (*c* 1 0, ethanol) could be obtained on a further recrystallization from ethyl acetate, p m r data (dimethyl sulfoxide-d_6–D_2O at 70°)· τ 2 20 (5 aromatic protons), 4 50 (*N*-benzyloxycarbonyl CH_2), 4 74, *J* 5 Hz (H-1), 6 28 (OMe)

Anal Calc for $C_{15}H_{21}NO_7$ C, 55 04, H, 6 47, N, 4 28 Found C, 55 16, H, 6 56, N, 4 01

*2-Acetamido-2-deoxy-*D*-mannose diethyl dithioacetal* — 2-Amino-2-deoxy-D-mannose hydrochloride (5 0 g) was converted into its diethyl dithioacetal hydrochloride

as described earlier, and converted into a mixture containing 2-acetamido-2-deoxy-D-mannose diethyl dithioacetal by the following method described for the D-galactose isomer The product gave by t l c (solvent chloroform–methanol, 4 1 v/v) two spots, the faster major one being the required material Crystallization from ethanol–ethylacetate gave 2-acetamido-2-deoxy-D-mannose diethyl dithioacetal (3 5 g), m p 145°, $[\alpha]_D^{25}$ −15° (*c* 0 3, ethanol), p m r data (dimethyl sulfoxide-d_6) τ 2 25, *J* 10 Hz (NH), 6 88, 6 95, 7 03, 7 10 (2 CH_2 groups), 7 72 (NAc), 8 30, 8 34, 8 37, 8 41, 8 45, 8 49 (2 Me groups)

Anal Calc for $C_{12}H_{25}NO_5S_2$ C, 44 01; H, 7 70, N, 4 28, S, 19 58 Found C, 43 83, H, 7 81; N, 4 01, S, 19 30

Benzyl 2-acetamido-3,4,6-tri-O-*acetyl-2-deoxy-α*-D-*mannopyranoside* — 2-Acetamido-2-deoxy-D-mannose diethyl dithioacetal (3 5 g) was treated with benzyl alcohol–mercuric chloride, as already described for the preparation of benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-mannopyranoside from 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-mannose diethyl dithioacetal, and converted into a mixture containing benzyl 2-acetamido-2-deoxy-α-D-mannopyranoside This was acetylated with acetic anhydride–pyridine to give a mixture of acetates, which was chromatographed on a column of silicic acid (eluant chloroform The second fraction contained the required syrupy tri-*O*-acetyl derivative (1 43 g) having $[\alpha]_D^{25}$ +43° (*c* 2 3, chloroform), p m r data ($CDCl_3$) τ 2 71 (5 aromatic protons), 3 89, *J* 10 Hz (NH), 5 20, *J* 1 6 Hz (H-1), 5 27, 5 38, 5 44, 5 56 (*O*-benzyl CH_2), 7 91, 7 98, 8 00, 8 04 (4 Ac groups)

Anal Calc for $C_{21}H_{27}NO_9$ C, 57 66, H, 6 22, N, 3 20 Found C, 57 21, H, 6 05, H, 3 01

Attempted N-*methylation of benzyl 2-acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-α*-D-*mannopyranoside* — The tri-*O*-acetyl derivative (700 mg) was treated overnight with the Kuhn reagent and the product deacetylated with methanolic sodium methoxide An aqueous solution of the deacetylated material was deionized with mixed-bed resins to give a syrup (0 32 g) having $[\alpha]_D^{25}$ +44° (*c* 1 4, ethanol) and the p m r spectrum corresponding to benzyl 2-acetamido-2-deoxy-α-D-mannopyranoside and not its *N*-methyl derivative; p m r data (D_2O) τ 2 20 (5 aromatic protons), 4 73, *J* 1 5 Hz (H-1), 4 84, 4 95, 5 05, 5 16 (*O*-benzyl CH_2), 7 54 (NAc)

Benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-*glucofuranoside* (**13**) — Crude 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride was prepared from 2-amino-2-deoxy-D-glucose hydrochloride by the method of Whitehouse *et al* [11] It was then converted into 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-glucose diethyl dithioacetal (**12**), which was purified by column chromatography on silicic acid (eluant chloroform–methanol, 49 1 v/v), and crystallized from ethyl acetate–Skellysolve B Its m p and specific rotation corresponded to those of known material

2-[(Benzyloxycarbonyl)amino]-2-deoxy-D-glucose diethyl dithioacetal (**12**, 3 55 g) was converted into **13** by the method already described for the mannofuranoside analogues The crude product gave on t l c (solvent chloroform–methanol, 9 1 v/v) 2 spots having R_F 0 3 and 0 6 Column chromatography on silicic acid (eluant chloroform–methanol, 49 1 v/v) gave 0 72 g of the faster-moving material Crystalliza-

tion from ethyl acetate gave compound **13** (0 54 g), m p 128°, $[\alpha]_D^{25}$ −36° (*c* 0 6, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 61, 2 64 (10 aromatic protons), 4 88 (*N*-benzyloxycarbonyl CH_2), 4 98, *J* 2 Hz (H-1), 5 08, 5 30, 5 41, 5 53 (*O*-benzyl CH_2)

Anal Calc for $C_{21}H_{25}NO_7$ C, 62 52, H, 6 25, N, 3 47 Found C, 62 34, H, 6 13, N, 3 24

Further elution of the column (eluant chloroform–methanol, 19 1 v/v) gave benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-glucopyranoside (**14**, 0 50 g) which crystallized from ethyl acetate (yield 0 30 g) and had m p 182–184°, $[\alpha]_D^{25}$ −42° (*c* 0 3, pyridine) Gross and Zimmerman[12] reported m p 190–191°, $[\alpha]_D$ −47° (pyridine) Its p m r spectrum was identical with that of authentic material, p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 66, 2 70 (10 aromatic protons), 4 98 (*N*-benzyloxycarbonyl CH_2), 5 58, *J* 8 2 Hz (H-1), 5 12, 5 24, 5.41, 5 53 (*O*-benzyl CH_2)

Anal Calc for $C_{21}H_{25}NO_7$ N, 3 47 Found N, 3 27

In another preparation, crystalline β-furanoside (2 0 g) and β-pyranoside (1 07 g) was obtained from 5 3 g of starting material (**12**)

Benzyl 2-[(benzyloxycarbonyl)methylamino]-2-deoxy-β-D-glucofuranoside (**15**) — Compound **13** (1 10 g) was converted into its tri-*O*-acetyl derivative (1 57 g) by treatment with pyridine–acetic anhydride The resulting syrup was *N*-methylated by the Kuhn procedure and deacetylated with sodium methoxide in methanol The procedure was identical with that used in the conversion of compounds (**7**+**8**) into the *N*-methyl oxazolidinone **11** The product (0 54 g) crystallized from ethyl acetate–Skellysolve B, and following column chromatography on silicic acid (eluant chloroform–methanol, 49 1 v/v) a further 0 23 g of crystals could be obtained from the mother liquors Compound **15** had m p 79°, $[\alpha]_D^{25}$ −55° (*c* 0 7, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 67, 2 71 (10 aromatic protons), 4 91 (*N*-benzyloxycarbonyl CH_2), 4 97, *J* 4 Hz (H-1), τ 5 25, 5 36, 5 45, 5 57 (*O*-benzyl CH_2), 6 15 (NMe)

Anal Calc for $C_{22}H_{27}NO_7$ C, 63 30, H, 6 52, N, 3 36 Found C, 63 65, H, 6 57, N, 3 26

2-[(Benzyloxycarbonyl)amino]-2-deoxy-D-galactose diethyl dithioacetal (**16**) — This compound was prepared from 2-amino-2-deoxy-D-galactose hydrochloride (10 g) via its diethyl dithioacetal hydrochloride by the method of Whitehouse *et al*[11] The product was purified by column chromatography on silicic acid (eluant chloroform–methanol, 49 1 v/v) and crystallized from ethyl acetate–Skellysolve B The crystals (6 9 g) had m p 110–111°, $[\alpha]_D^{25}$ −22° (*c* 0 6, ethanol), and $[\alpha]_D^{25}$ −22° (chloroform) [Whitehouse *et al*[11] reported m p 59–61° and $[\alpha]_D^{25}$ +33° (*c* 0 3, chloroform)], p m r data (dimethyl sulfoxide-d_6)· τ 2 68 (5 aromatic protons, NH), 4 80, 4 92, 4 97, 5 10 (*N*-benzyloxycarbonyl CH_2), 8 76, 8 78, 8 85, 8 90, 8 93 (2 Me groups)

Anal Calc for $C_{18}H_{29}O_6NS_2$ C, 51 52, H, 6 97, N, 3 34, S, 15 29 Found C, 51 64, H, 6 90, N, 3 20, S, 15 03

Because of the difference of the specific rotation and melting point, the compound isolated by Whitehouse *et al* is considered not to be compound **16**

Methyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactofuranoside (**17**) — Compound **16** (0 88 g) was converted into compound **17** by the action of mercuric chloride and methanol in the presence of mercuric oxide (see conversion of compound **1** into **4**) After 2 h the reaction was incomplete, but was complete after 20 h A little pyridine was added and the solution evaporated The residue was partitioned between ethyl acetate and water, and the aqueous layer was evaporated Crystallization of the residue (0 42 g) from ethyl acetate–Skellysolve B gave the methyl glycoside **17** (0 28 g), m p 106°, $[\alpha]_D^{25}$ −39° (*c* 0 4, ethanol), p m r data (dimethyl sulfoxide-d_6–D_2O at 70°) τ 2 64 (5 aromatic protons), 4 96 (*N*-benzyloxycarbonyl CH_2), 5 35, *J* 3 Hz (H-1), 6 75 (OMe)

Anal Calc for $C_{15}H_{21}NO_7$ C, 55 04; H, 6 47, N, 4 28 Found C, 54 74, H, 6 65, N, 4 10

In a similar reaction with benzyl alcohol in place of methanol, two products were obtained on t l c which could be partially separated by column chromatography on silicic acid The main fraction did not have the required structure as its p m r spectrum displayed two large upfield signals in the CH_2 and CH_3 regions

Methyl 2-acetamido-2-deoxy-β-D-galactofuranoside (**19**) — 2-Amino-2-deoxy-D-galactose hydrochloride (5 0 g) was converted into its crude diethyl dithioacetal, which was acetylated with acetic anhydride–pyridine at room temperature The resulting acetate was deactylated with sodium methoxide in methanol, the solution neutralized with acetic acid, and evaporated The residue was dissolved in water, and treated with Amberlite IR-120 (H^+ form) Following filtration, the solution was evaporated to a residue that crystallized from ethyl acetate to give 2-acetamido-2-deoxy-D-galactose diethyl dithioacetal (**18**, 4 35 g), m p 160°, $[\alpha]_D^{25}$ −28° (*c* 0 4, ethanol) Wolfrom and Onodera[13] reported m p 163–165° and $[\alpha]_D^{30}$ −32° (ethanol) P m r data (dimethyl sulfoxide-d_6) τ 2 02, *J* 8 Hz (NH), 7 72 (NAc) complex at 8 34 to 8 52 (2 Me groups)

The diethyl dithioacetal (**18**, 1 0 g) was converted into the methyl glycoside by the action of mercuric chloride in methanol overnight in the presence of mercuric oxide The mixture was filtered and the filtrate evaporated to a small volume Water and ethyl acetate were added, and after shaking the water layer was deionized and evaporated to a syrup that crystallized Recrystallization from ethanol afforded compound **19** (**19**, 0 41 g), m p 171°, $[\alpha]_D^{25}$ −73° (*c* 0 3, water), p m r data (D_2O) τ 4 64, *J* 2 Hz (H-1), 6 16 (OMe), 7 52 (Ac)

Anal Calc for $C_9H_{17}NO_6$ C, 45 95; H, 7 28, N, 5 96 Found. C, 45 47, H, 7 01, N, 5 59

Acetylation of **19** (0 20 g) followed by Kuhn methylation, deacetylation, and treatment in aqueous mixed-ben resins provided methyl 2-deoxy-2-methylacetamido-β-D-galactofuranoside (**20**, 0 13 g) having $[\alpha]_D^{25}$ −81° (*c* 0 2, water) It gave a single spot on a paper chromatogram (solvent butanol–ethanol–water, 40.11.19 v/v/v, spray ammoniacal silver nitrate) moving slightly faster than the non-*N*-methylated derivative, p m r. data (D_2O at 70°) τ 4 25, 4 63 (H-1), 6 05, 6 08 (OMe), 6 40, 6 56 (NMe), 7 28 (Ac)

Anal Calc for $C_{10}H_{19}NO_6$ C, 48 18, H, 7 68, N, 5 62 Found C, 47 73; H, 7 54, N, 5 31

*Attempted preparation of benzyl 2-acetamido-2-deoxy-*D*-galactofuranoside* — Preparation of the benzyl glycoside from the diethyl dithioacetal was carried out in benzyl alcohol–*N*,*N*-dimethylformamide A small amount of product was obtained after two recrystallizations from ethyl acetate–methanol, but as its m p was not sharp (152–157°) it was not further investigated

*Attempted preparation of benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-*D*-galactofuranoside* — The diethyl dithioacetal was prepared from 2-amino-2-deoxy-D-galactose hydrochloride (1 0 g) and demercaptalated overnight in benzyl alcohol containing mercuric chloride and mercuric oxide maintained at room temperature by the general method already described The product was dispersed between water and ethyl acetate and the water layer was treated with benzyl chloroformate The product was fractionated on a column of silicic acid (eluant chloroform–methanol, 49 1 v/v) The syrupy product (0 67 g) crystallized from ethyl acetate–Skellysolve B and had m p 173–179°, $[\alpha]^{25}$ −25° (*c* 0 3, ethanol); p m r data (dimethyl sulfoxide-d_6–D_2O at 50°) two sets of benzyl CH_2 signals observed, one a singlet, the other a quadruplet (τ 4 88 and 4 37, *J* 12 Hz) Based on 10 protons for the aromatic proton signal at τ 2 57, the H-1 signal at τ 5 06 ($J = 3$ 4 Hz) represented 0 7 protons The other H-1 signal was partly obscured by the *N*-benzyloxycarbonyl CH_2 signal at τ 4 88 The crystals contained 0 30% of S The data therefore suggest a mixture ,

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