60. *Some Derivatives of Methylated Glucosamine.*

By W. O. Cutler and S. Peat.

A study has been made of the relative stability towards acid of the α- and the β-form of each of the following: *N*-acetyl trimethyl methylglucosaminide, N-*acetyl trimethyl benzylglucosaminide*, N-*benzoyl trimethyl methylglucosaminide*, and N-*benzoyl trimethyl benzylglucosaminide*. With each pair there is observed an irreversible transformation of the β-form into the α-form under the influence of acid alcohol and possible explanations of the superior stability of the α-forms are discussed.

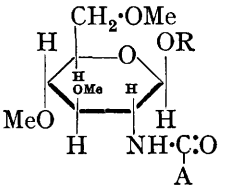
The preparation of the α- and the β-form of *trimethyl methylglucosidyl-2-trimethyl-ammonium iodide* is described and comment is made on the extreme stability of these quaternary ammonium iodides towards alkaline reagents and towards acid methyl alcohol. From the α-isomeride, *trimethyl 2-dimethylamino-α-methylglucoside* was prepared by distillation. This tertiary amine also was stable towards alkali.

Comment was made by Cutler, Haworth, and Peat (J., 1937, 1981) on the unusual stability towards acid alcohol of the α-form of *N*-acetyl trimethyl methylglucosaminide. When either the α- or the β-form of a methylglycoside is heated with methyl-alchoholic hydrogen chloride, there is established an equilibrium mixture of the two forms, but *N*-acetyl trimethyl β-methylglucosaminide is converted by the same reagent completely into the α-form and the conversion is irreversible.

The question has been further investigated in regard to a series of *N*-acyl glucosaminides. In addition to *N*-acetyl trimethyl β-methylglucosaminide (I*a*; R = A = Me) we have prepared and examined the β-forms of N-*acetyl trimethyl benzylglucosaminide* (I*b*; A = Me, R = CH_2Ph), N-*benzoyl trimethyl benzylglucosaminide* (I*c*; A = Ph, R = CH_2Ph), and N-*benzoyl trimethyl methylglucosaminide* (I*d*; A = Ph, R = Me) and have found that each is converted in acid alcohol into the corresponding α-isomeride and that the change is irreversible.

The superior stability of the α-forms might suggest that the irreversible β ⟶ α change is structural rather than configurational in character. Since it is only with glucosaminides

in which the amino-group is acylated that the irreversible β ⟶ α transformation is observed, it would seem that, if the change is not simply a change of configuration on C_1, it implies the chemical interaction of the glucosidic group with the *N*-acyl group. The most likely course for such interaction to take would be in the formation of an ortho-acid linkage. As it is now possible to represent derivatives of glucosamine by configurational formulæ (see preceding paper), the alternative modes of expressing the β ⟶ α change are (I) ⟶ (II) (configurational) and (I) ⟶ (III) (structural). That the β-forms can only be represented as true glucosides (I) follows from their mode of formation, whereby the glucosidic substituent is introduced into the molecule before the amino-group is acylated. The migration of the glucosidic radical, R, implied by the conversion of (I) into (III) is not improbable, for we have demonstrated that during the β ⟶ α change, the radical R becomes detached (at least momentarily) from the molecule. Thus, in effecting the irreversible transformation of *N*-benzoyl trimethyl β-benzylglucosaminide (I*c*) into the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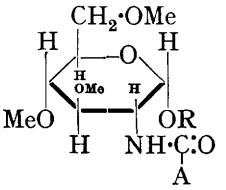
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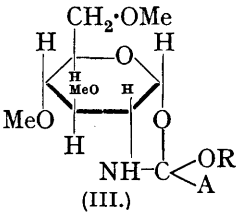
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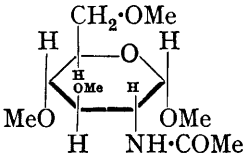

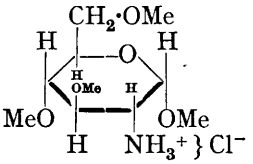
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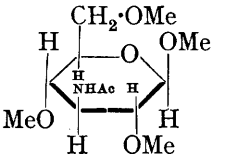
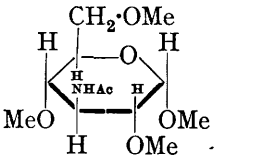



(VII.)

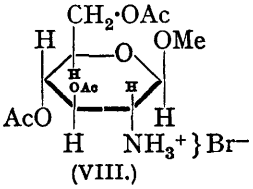
α-isomeride, the reagent used is a 2% solution of hydrogen chloride in benzyl alcohol. When, however, methyl alcohol is used instead of benzyl alcohol as solvent, an exchange of benzyl and methyl radicals takes place and the product is not the α-benzyl derivative but *N*-benzoyl trimethyl α-methylglucosaminide. Furthermore, from the fact that no such exchange of radicals occurs when the α-form of *N*-benzoyl trimethyl benzylglucosaminide is boiled with methyl-alcoholic hydrogen chloride, it follows that no tendency exists at all for the glucosidic radical, R, to separate when in the " α " position or for the β ⟶ α change to be reversed under the action of anhydrous acid.

There is thus nothing inherently unreasonable in the description of the α-forms of *N*-acylglucosaminides as derivatives of ortho-acids (III). Nevertheless many facts are not in harmony with this conception. For example, the *N*-acyl α-glucosaminides do not show the properties characteristic of true ortho-acetates (cf. Haworth, Hirst, and Miller, J., 1929, 2469; Bott, Haworth, and Hirst, J., 1930, 1395), which are hydrolysed by aqueous acid with a velocity greatly exceeding the velocity of hydrolysis of a normal acetylated methylglycoside. In the amino-glucoside series the reverse is true. Whereas *N*-acetyl trimethyl α-methylglucosaminide is not substantially affected by boiling 0·01 N-hydrochloric acid, the β-isomeride (which is a true glucoside) is slowly hydrolysed with the partial loss of both the glycosidic methyl and the *N*-acetyl group. This point is not stressed, for there is an obvious alternative explanation of the difference in stability of *N*-acetyl α-methylglucosaminide and the ortho-acetate of methylmannoside, namely that it is the presence of the NH-group in the ring system of the former substance (III) which is responsible for the enhanced resistance to acid hydrolysis.

Again, if *N*-acetyl trimethyl α-methylglucosaminide has the structure (III*a*), it is unlikely that the acetyl group would be detached by hydrolysis whilst leaving the glycosidic methyl intact. Yet this result is obtained by digestion of the glucosaminide with 7% methyl-alcoholic hydrogen chloride, the product being trimethyl α-methylglucosaminide hydrochloride (V). It is considered improbable that the glycosidic methyl is simultaneously removed and then replaced during this reaction, for the reason that it is impossible to form a methylglucosaminide by the action of methyl-alcoholic hydrogen chloride on either glucosamine or 3 : 4 : 6-trimethyl glucosamine. The reverse change, the regeneration of *N*-acetyl trimethyl α-methylglucosaminide by the acetylation of (V), is also unlikely if the first-named substance has the constitution (III*a*). Nevertheless, this reaction proceeds with the greatest ease (Cutler, Haworth, and Peat, *loc. cit.*).

Perhaps the most potent argument against the hypothesis of an ortho-acid structure in the α-forms is based on analogy with the behaviour of the equivalent derivatives of 3-amino-glucose (cf. Peat and Wiggins, J., 1938, 1810). The β-form of trimethyl 3-acetamido-methylglucoside (VI) is converted by methyl-alcoholic hydrogen chloride (1%) into the α-form (VII) and polarimetric observation of a solution of the pure α-isomeride in boiling acid alcohol shows that the transformation cannot be reversed. The analogy is complete and it is obvious that interaction between the *N*-acetyl group and the methyl-glycosidic group in (VII) is impossible on stereochemical grounds.

The discussion set out here has been concerned with *N*-acylated glucosaminides. The nitrogen atom in these substances does not bear a charge and it is of some interest to find that the usual β ⟶ α change does not take place in quaternary ammonium salts where the nitrogen atom bears a positive charge. We encountered substances of this type during an attempt to effect the de-amination of glucosamine by the method of Irvine and Hynd (J., 1912, **101**, 1128). These authors experienced great difficulty in the methylation of the amino-group when β-methylglucosaminide was treated with methyl iodide and silver oxide in methyl-alcoholic solution. We have found that the methylation can be achieved with ease by the action of methyl iodide and silver oxide on triacetyl β-methylglucosaminide hydrobromide (VIII). Not only are methyl groups introduced into the amino-group, but the *O*-acetyl groups are replaced also by methyl groups and the product is *trimethyl β-methylglucosidyl-2-trimethylammonium iodide* (IX).



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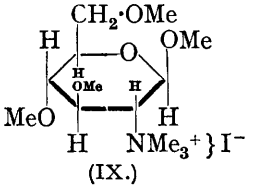

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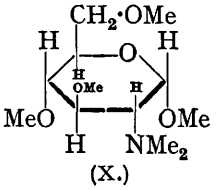

(X.)

The quaternary iodide (IX) is not converted by methyl-alcoholic hydrogen iodide into the α-isomeride, but is recovered unchanged after boiling with this reagent. *Trimethyl α-methylglucosidyl-2-trimethylammonium iodide* is prepared by the methylation, with Purdie's reagents, of trimethyl α-methylglucosaminide. The α-form shows the same stability towards acid alcohol as is shown by the β-form. Extreme stability is also exhibited by these quaternary ammonium iodides towards alkali, for each form is recovered unchanged after prolonged boiling with either saturated barium hydroxide solution or aqueous sodium hydroxide. By distillation in a high vacuum, however, the iodide (α-form) is dissociated into *trimethyl 2-dimethylamino-methylglucoside* (X) and methyl iodide. The tertiary amine (X), like the iodides, is unaffected by strong alkali, its behaviour in this respect being remarkably different from that of the 2-dimethylamino-methylglucoside of Irvine and Hynd (*loc. cit.*).

Experimental.

Tetrabenzoyl β-Methylglucosaminide.—Triacetyl β-methylglucosaminide hydrobromide (1·0 g.), dissolved in 10% sodium hydroxide solution (40 c.c.), was shaken with benzoyl chloride (4 c.c.) for 12 hours (it was necessary to cool the mixture during the first ½ hour). The insoluble product

was washed with water and dissolved in chloroform and the solution, after extraction with water, was dried over magnesium sulphate and evaporated. After two recrystallisations from ethyl alcohol, *tetrabenzoyl β-methylglucosaminide* was obtained in colourless needles, m. p. 182° (yield 75%). It showed $[\alpha]_D^{19°}$ + 18·7° in chloroform (*c*, 0·32) (Found : C, 68·8; H, 5·2. $C_{35}H_{31}O_9N$ requires C, 69·0; H, 5·1%). This substance was unsuitable for methylation owing to the stability of the benzoyl ester groups towards alkali.

N-*Benzoyl Triacetyl β-Methylglucosaminide*.—Triacetyl β-methylglucosaminide hydrobromide (0·57 g.) in water (15 c.c.) was shaken at room temperature for 14 hours with benzoyl chloride (0·2 c.c.) and silver carbonate (0·4 g.). The mixture was shaken with chloroform, filtered, and the chloroform solution washed with water (4 times). Evaporation of the chloroform solution gave N-*benzoyl triacetyl β-methylglucosaminide*, which was crystallised from ethyl alcohol. Yield, 0·61 g. The product was insoluble in water, ether, and carbon tetrachloride. It was easily soluble in chloroform and acetone. It had m. p. 222° and $[\alpha]_D^{22°}$ + 29·6° in chloroform (*c*. 0·54) (Found : C, 56·8; H, 5·6; N, 3·3; *O*-acetyl, 30·9. $C_{20}H_{25}O_9N$ requires C, 56·8; H, 5·9; N, 3·3; *O*-acetyl, 30·6%).

N-*Benzoyl Trimethyl β-Methylglucosaminide*.—This was prepared by the methylation of the triacetate in acetone solution with methyl sulphate and 30% sodium hydroxide solution. It separated from ethyl alcohol in long needles, m. p. 198°, $[\alpha]_D^{19°}$ + 29·6° in chloroform (*c*, 0·30) (Found : C, 60·2; H, 7·5; N, 4·5; OMe, 36·4. $C_{17}H_{25}O_6N$ requires C, 60·3; H, 7·4; N, 4·2; OMe, 36·6%). The substance was insoluble in water or ether and easily soluble in alcohol, acetone, chloroform, and pyridine. It was recovered unchanged after boiling for 16 hours with 10% aqueous-alcoholic sodium hydroxide. When boiled for 10 hours with 2% methyl-alcoholic hydrogen chloride, it was quantitatively converted into the α-isomeride (m. p. 162°). The *N*-benzoyl derivative was distinguished from the *N*-acetyl analogue in that the benzoyl group was not removed by boiling with 7% methyl-alcoholic hydrogen chloride.

N-*Benzoyl trimethyl α-methylglucosaminide* was prepared in 95% yield by the action of benzoyl chloride on a solution of trimethyl α-methylglucosaminide hydrochloride in 20% aqueous sodium hydroxide. It had m. p. 162° and $[\alpha]_D^{18°}$ + 122·8° in chloroform (*c*, 0·648) (Found : C, 60·5; H, 7·5; N, 4·2; OMe, 37·0%). The substance was stable to alkali and to 7% methyl-alcoholic hydrogen chloride. On boiling with the latter reagent no change in rotation occurred, showing that, as with the *N*-acetyl analogues, the change β-form ⟶ α-form is irreversible.

Triacetyl α-Benzylglucosaminide Hydrobromide.—Acetobromoglucosamine (5 g.) was dissolved in benzyl alcohol (100 c.c.) containing 1% of anhydrous pyridine. After 12 hours, the solvent was removed by distillation at 80—85° (bath temp.)/0·03 mm. The residue, after extraction with cold ethyl acetate, was recrystallised from methyl alcohol–ether–petrol. The substance decomposed at 237—240° and showed $[\alpha]_D^{14°}$ + 24·2° in chloroform (*c*, 0·99) (Found : C, 47·7; H, 5·5; N, 2·7. Calc. for $C_{19}H_{26}O_8NBr$: C, 47·9; H, 5·6; N, 2·9%). It was soluble in water.

Tetra-acetyl β-benzylglucosaminide was prepared by the acetylation of triacetyl β-benzylglucosaminide hydrobromide with acetic anhydride and silver acetate in dry methyl alcohol at room temperature. The product had m. p. 163° and $[\alpha]_D^{14°}$ − 38·3° in chloroform (*c*, 0·63). It was only slightly soluble in water (Found : C, 58·4; H, 5·7; N, 3·3; *O*-acetyl, 29·4. $C_{21}H_{27}O_9N$ requires C, 57·8; H, 6·1; N, 3·2; *O*-acetyl, 29·5%).

N-*Acetyl trimethyl β-benzylglucosaminide* was prepared from the tetra-acetate by treatment with methyl sulphate and 40% sodium hydroxide solution at 50° in the presence of carbon tetrachloride. Yield, 0·3 g. from 0·5 g. The compound had m. p. 174° and $[\alpha]_D^{14°}$ − 36·2° in chloroform (*c*, 0·44) (Found : C, 60·8; H, 7·5; N, 3·8; OMe, 25·8. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·6; N, 3·9; OMe, 26·3%). It was slightly soluble in water and was recovered unchanged after boiling with 10% aqueous-alcoholic sodium hydroxide.

Conversion into the α-isomeride. *N*-Acetyl trimethyl β-benzylglucosaminide (0·15 g.) was heated at 75° with benzyl alcohol (25 c.c.) containing 2% of dry hydrogen chloride, the reaction being followed polarimetrically : $[\alpha]_D$ − 29·6° (initial reading); + 57·5° (25 mins.); + 82·3° (50 mins.); + 102·1° (160 mins.); + 106·5° (3½ hrs.); + 111·8° (5 hrs); + 118·2° (constant value, 7 hrs.). The solution was now diluted with chloroform and neutralised with lead carbonate, and the solvents removed in a high vacuum. N-*Acetyl trimethyl α-benzylglucosaminide*, m. p. 138°, was isolated in 75% yield (Found : OMe, 26·1%). The conversion was complete, no trace of the β-isomeride being detected.

N-*Benzoyl triacetyl β-benzylglucosaminide* was obtained in 97% yield when triacetyl β-benzylglucosaminide hydrobromide (2 g.) was treated in water (100 c.c.) with benzoyl chloride (0·3 g.) and silver carbonate (0·6 g.). It had m. p. 216° and $[\alpha]_D^{19°}$ − 6·4° in chloroform (*c*, 1·24) (Found :

C, 62·2; H, 5·8; N, 2·8; *O*-acetyl, 26·0. $C_{26}H_{29}O_9N$ requires C, 62·5; H, 5·8; N, 2·7; *O*-acetyl, 26·3%). The substance was soluble in acetone and chloroform, insoluble in water and carbon tetrachloride.

N-*Benzoyl trimethyl* β-*benzylglucosaminide* was prepared in the usual way by the methylation of the triacetate with methyl sulphate and sodium hydroxide in acetone solution. It showed m. p. 180° and $[\alpha]_D^{17°}$ — 21·75° in chloroform (*c*, 0·23) (Found : C, 66·1; H, 7·3; N, 3·7; OMe, 22·8. $C_{23}H_{29}O_6N$ requires C, 66·3; H, 7·4; N, 3·4; OMe, 22·3%). It was insoluble in water and was recovered unchanged after boiling with alkali. Conversion into the α-isomeride was quantitatively effected by warming at 75° with 2% benzyl-alcoholic hydrogen chloride. The reaction was followed polarimetrically : $[\alpha]_{5461}$ — 39·8° (initial value); + 24·1° (10 mins.); + 113·2° (60 mins.); + 134·5° (140 mins., constant value). N-*Benzoyl trimethyl* α-*benzylglucosaminide* crystallised from alcohol in needles, m. p. 184°; $[\alpha]_D^{22°}$ + 123·2° in chloroform (*c*, 0·50) (Found : C, 66·3; H, 7·0; N, 3·5; OMe, 22·8%).

The Action of Methyl-alcoholic Hydrogen Chloride on the Benzylglucosaminides.—(a) *N*-Benzoyl trimethyl α-benzylglucosaminide (29 mg.) was boiled with 2% methyl-alcoholic hydrogen chloride (30 c.c.) for 24 hours. No polarimetric change occurred ($[\alpha]_D$ + 164°) and unchanged α-form (25 mg.) was recovered from the solution.

(b) *N*-Benzoyl trimethyl β-benzylglucosaminide (0·10 g.) was boiled with 2% methyl-alcoholic hydrogen chloride (30 c.c.), and the following polarimetric changes observed : $[\alpha]_D$ — 26·9° (initial value); 0·0° (20 mins.); + 45·1° (1½ hrs.); + 62·7° (2·1 hrs.); + 92·5° (4 hrs.); + 102·3° (5 hrs.); + 113·5° (7½ hrs., constant value). The solution was neutralised with lead carbonate; the product, isolated in the usual manner, was *N*-benzoyl trimethyl α-methylglucosaminide m. p. 161° (alone or in admixture with an authentic specimen). Yield, 98 mg.

(c) *N*-Acetyl trimethyl β-benzylglucosaminide (0·21 g.) was boiled with 2% methyl-alcoholic hydrogen chloride (30 c.c.) : $[\alpha]_D$ — 34·4° (initial value); 0·0° (25 mins.); + 44·8° (1¼ hrs.); + 77·5° (2·1 hrs.); + 106·2° (4 hrs.); + 112·1° (5 hrs.); + 117·6° (7½ hrs., constant value). The product was a mixture of *N*-acetyl trimethyl α-methylglucosaminide (m. p. and mixed m. p. 150°) (yield, 152 mg.) and trimethyl α-methylglucosaminide hydrochloride, m. p. 237° (yield, 38 mg.).

The Action of 0·01N-*Hydrochloric Acid on the Glucosaminides.*—(a) *N*-Acetyl trimethyl β-methylglucosaminide (68 mg.) was heated on a boiling water-bath with 0·01N-hydrochloric acid (10 c.c.). The reaction was followed polarimetrically : $[\alpha]_D$ — 25·6° (initial reading); — 21·0° (2 hrs.); — 14·0° (6·3 hrs.); — 8·4° (10·5 hrs.); — 3·2° (16 hrs.); + 5·4° (24½ hrs.); + 13·1° (35 hrs.); + 14·1° (40 hrs.). The solution now reduced Fehling's solution and an estimation of iodine value showed that the glycosidic methyl had been removed. The very small value obtained in a van Slyke estimation of amino-nitrogen indicated that the *N*-acetyl group was still intact. After warming with alkali, the solution gave a positive Ehrlich reaction.

(b) *N*-Acetyl trimethyl α-methylglucosaminide under the same conditions with 0·1% hydrochloric acid showed $[\alpha]_D$ + 103° (initial reading); + 106° (2½ hrs.); + 112° (9 hrs.); + 115° (18 hrs.). The reaction was thus very slight, the increase in rotation being due probably to concentration of the solution. Fehling reduction, iodine value, and van Slyke estimation showed that very little hydrolysis of either the glycosidic methoxyl or *N*-acetyl had occurred. The Ehrlich test was negative.

(c) *N*-Benzoyl trimethyl β-methylglucosaminide (98·8 mg.) in acetone (5 c.c.) and 0·02N-hydrochloric acid (5 c.c.) were heated on a boiling water-bath. The volume was kept constant by the addition of acetone : $[\alpha]_D$ + 6·1° (initial value); + 10·1° (4½ hrs.); + 14·2° (8½ hrs.); + 24·3° (20 hrs.); + 29·3° (28 hrs.); + 33·4° (39 hrs.); + 43·5° (50 hrs.); + 44·5° (60 hrs.); + 45·6° (80 hrs.). The solution (after removal of acetone) reduced Fehling's solution and, after being warmed with alkali, gave a positive Ehrlich reaction.

(d) *N*-Acetyl trimethyl β-benzylglucosaminide with 0·01*N*-hydrochloric acid, carried out at the same time as (a) : $[\alpha]_D$ — 30·5° (initial value); — 27·1° (2 hrs.); — 20·3° (6·3 hrs.); — 13·6° (10·5 hrs.); + 3·4° (16 hrs.); + 13·6° (24·5 hrs.); + 20·3° (35 hrs.); + 22·1° (40 hrs.). The solution now reduced Fehling's solution and, after warming with alkali, gave a positive Ehrlich reaction.

(e) *N*-Benzoyl trimethyl β-benzylglucosaminide (93 mg.), as under (c) : $[\alpha]_D$ — 34·4° (initial reading); — 23·7° (6 hrs.); — 7·5° (20 hrs.); + 3·4° (30 hrs.); + 10·8° (40 hrs.); + 18·2° (48 hrs.); + 25·8° (60 hrs.); + 26·9° (80 hrs.). The product was reducing to Fehling's solution and gave a positive Ehrlich reaction after treatment with alkali.

Methylation of Trimethyl α-*Methylglucosaminide.*—The methylated glucosamine (0·6 g.) was dissolved in methyl iodide (10 c.c.), and dry silver oxide (4 g.) slowly added. A vigorous

reaction ensued and cooling was necessary. Thereafter the solution was boiled for 12 hours. The methyl iodide was distilled, and the residue extracted with chloroform. Evaporation of the chloroform gave a syrup, which was dissolved in hot water, and the solution extracted repeatedly with chloroform. The aqueous solution was taken to dryness; the residue (0·77 g.), which crystallised on trituration with petrol, was recrystallised from chloroform–ether–petrol. The product was *trimethyl α-methylglucosidyl-2-trimethylammonium iodide*. The m. p. was not definite (softening at 45°), $[\alpha]_D^{19°}$ + 119·1° in chloroform (*c*, 0·57) (Found: C, 39·0; H, 6·9; N, 2·9; *O*- and *N*-methyl, 25·8; ionised I, 31·3. $C_{13}H_{28}O_5NI$ requires C, 38·6; H, 6·9; N, 3·4; *O*- and *N*-methyl, 25·9; ionised I, 31·4%). The salt was soluble in water but insoluble in ether, hydrocarbons and carbon tetrachloride. It was recovered unchanged after boiling for 14 hours with either a saturated solution of barium hydroxide or a 10% solution of potassium hydroxide. On distillation of the iodide at 160° (bath temp.)/0·03 mm., dissociation occurred; the mobile oil which distilled ($n_D^{20°}$ 1·4530) had the composition of *trimethyl dimethylaminomethylglucoside* (X) (Found: *O*- and *N*-methyl, 32·6. $C_{12}H_{25}O_5N$ requires *O*- and *N*-methyl 34·2%). It was non-reducing and contained no iodine. The tertiary amine (X) was recovered unchanged after boiling for 12 hours with either saturated barium hydroxide solution or 10% sodium hydroxide solution.

Direct Methylation of Triacetyl β-Methylglucosaminide Hydrobromide.—Digestion of this triacetate with methyl iodide and dry silver oxide was attended by de-acetylation and simultaneous methylation, the product being *trimethyl β-methylglucosidyl-2-trimethylammonium iodide*, m. p. 145°; $[\alpha]_D^{20°}$ − 12·9° in chloroform (*c*, 0·70) (Found: *O*- and *N*-methyl, 25·8; ionised I, 31·2%). The usual transformation of the β-form into the α-form in acid alcohol did not take place with the quaternary ammonium iodide. The β-isomeride was recovered unchanged after boiling with 1% methyl-alcoholic hydrogen iodide.

Action of Methyl-alcoholic Hydrogen Chloride on Trimethyl 3-Acetamido-α-methylglucoside.—The material (see Peat and Wiggins, *loc. cit.*) (0·10 g.) was boiled for 4 hours with 1% methyl-alcoholic hydrogen chloride. No rotation change occurred ($[\alpha]_D$ + 162°) and the α-glucoside was recovered unchanged, m. p. and mixed m. p. 156°. Yield, 70 mg.

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