371. *Descent of the Series of Methylated Sugars by the Weerman Reaction.*

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A study of the action of sodium hypochlorite on seven methylated sugar acid amides reveals the following facts. With a methylated amide as with an unmethylated amide, the ultimate product is the sugar lower in the series. The first stage involves the formation of an *iso*cyanate (not isolated), the subsequent transformation of which depends on the nature of the amide. The *iso*cyanate of an α-hydroxy-amide decomposes with the liberation of sodium *iso*cyanate. If, however, the α-position is methylated, no trace of sodium *iso*cyanate is formed. If the α-methoxy-amide has a suitably placed hydroxyl group (as in 2 : 3 : 4 : 6- and 2 : 3 : 5 : 6-tetramethyl gluconamide), cyclisation takes place of the *iso*cyanate from it and the isomeric cyclic urethane is isolated. Proof is given of the ring structure of these urethanes. Cold dilute alkali solution suffices to decompose the urethane with the formation of the lower sugar. Thus, the cyclic urethane from 2 : 3 : 4 : 6-tetramethyl gluconamide gives 2 : 3 : 5-*trimethyl* d-*arabofuranose*. Where there is no available hydroxyl group, as in *pentamethyl gluconamide*, no cyclic urethane is formed and the lower sugar, in this case, *tetramethyl* aldehydo-d-*arabinose*, is directly produced. Cyclisation is inhibited when the *iso*cyanate is derived from an α-hydroxy-amide. Thus, 3 : 5 : 6-*trimethyl gluconamide*, when treated with Weerman's reagent, gives 2 : 4 : 5-*trimethyl* aldehydo-d-*arabinose* without the intermediate formation of a cyclic urethane.

In an attempt to apply the Weerman degradation method to tetramethyl gluconamide, Irvine and Pryde (J., 1924, **125**, 1045) observed that the reaction followed an unusual course which did not lead by degradation to the expected trimethyl arabinose. There was isolated a nitrogen-containing product for which a cyclic urethane structure was suggested on the basis of its stability and high specific rotation. Later, Humphreys, Pryde, and Waters isolated analogous compounds from 2 : 3 : 5-trimethyl and 2 : 3 : 4-trimethyl *l*-arabinose and these too were regarded as cyclic urethanes (J., 1931, 1298).

In a study of the Weerman reaction applied to α-hydroxy- and α-methoxy-amides we have encountered the urethanes described above together with others and have been

able to furnish proof of their cyclic structure. In addition it has been possible to show that the cyclic urethane represents simply an intermediate stage in a Weerman degradation. It is found, therefore, that this reaction is now applicable to methylated and unmethylated sugar acid amides as a general means of descent in the sugar series.

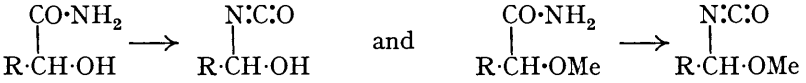
Seven amides were examined, namely, 2 : 3 : 4 : 6-tetramethyl gluconamide, 2 : 3 : 5 : 6-tetramethyl gluconamide, 2 : 3 : 6-trimethyl gluconamide, 3 : 5 : 6-*trimethyl gluconamide*, *pentamethyl gluconamide*, 2 : 3 : 4-trimethyl *l*-arabonamide and 2 : 3 : 5-trimethyl *l*-arabonamide. 3 : 5 : 6-Trimethyl gluconamide was prepared from crystalline 3 : 5 : 6-*trimethyl γ-gluconolactone*.

The urethane of Irvine and Pryde is obtained when 2 : 3 : 4 : 6-tetramethyl gluconamide (I) is treated in the cold with a solution of sodium hypochlorite prepared according to the directions of Weerman (*Annalen*, 1913, **401**, 1). This urethane (III) is decomposed, also in the cold, by contact with 1% sodium hydroxide solution, the product being 2 : 3 : 5-*trimethyl* d-*arabofuranose* (IV). By boiling with methyl-alcoholic hydrogen chloride, the sugar was converted into *trimethyl methyl*-d-*arabofuranoside*, the furanose structure of which was indicated by its ease of hydrolysis with 0·1N-acid, and by the following behaviour : Oxidation of the trimethyl sugar yielded trimethyl *d*-arabono-*γ*-lactone (m. p. 33°), the constants of which showed it to be identical with that prepared by Avery, Haworth, and Hirst (J., 1927, 2317). From the lactone, 2 : 3 : 5-*trimethyl* d-*arabonamide* (m. p. 137·5°) was prepared by the action of ammonia.

By an analogous procedure, a *cyclic urethane* (m. p. 110°) (VII) was prepared from 2 : 3 : 5 : 6-tetramethyl gluconamide (V), and this urethane also was degraded by dilute alkali solution with the formation of a trimethyl arabinose. The latter is interesting in that the disposition of the methoxyl groups is such that neither a pyranose nor a furanose ring is possible. The only cyclic structure that might be assumed is a propylene oxide form, but this is unlikely and we prefer to regard the substance as being essentially 2 : 4 : 5-*trimethyl* aldehydo-d-*arabinose* (XI), a view that is supported by its properties. It reduces Fehling's solution in the cold, decolourises permanganate and restores the colour to Schiff's reagent. Some evidence was obtained of the formation of a methylarabinoside when the sugar was boiled with methyl-alcoholic hydrogen chloride, but the conversion was by no means complete.

The same trimethyl *aldehydo*-arabinose was obtained when 3 : 5 : 6-trimethyl gluconamide (IX) was treated with hypochlorite solution. From this α-hydroxy-amide an intermediate cyclic urethane could not be isolated and similarly pentamethyl gluconamide yielded no urethane but was degraded directly to *tetramethyl* aldehydo-*arabinose*.

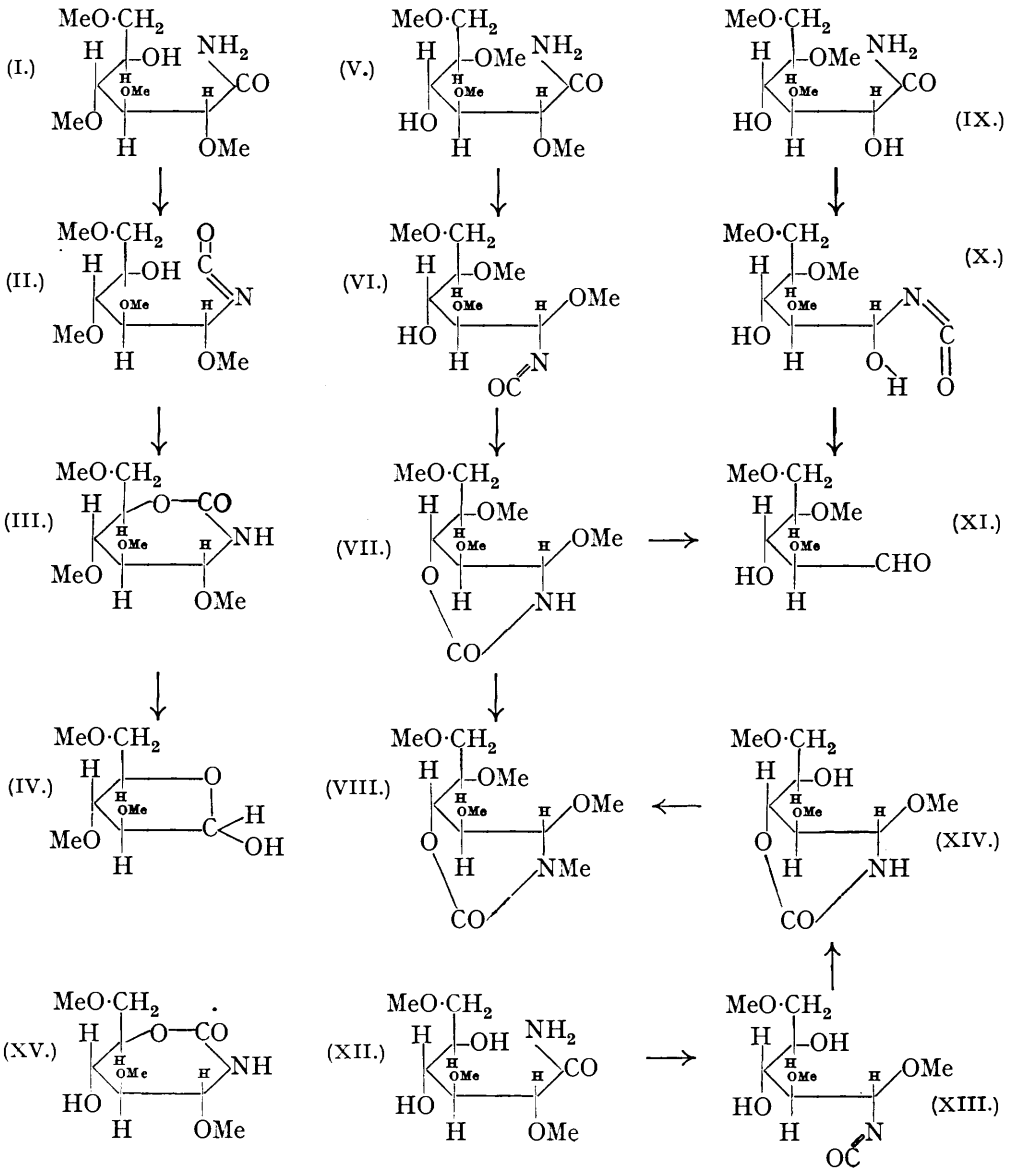
The probable course of a Weerman degradation has been set out by Ault, Haworth, and Hirst (J., 1934, 1722), the first stage being the formation of an open-chain *iso*cyanate thus :



The subsequent course of the reaction depends on whether the α-hydroxyl group is substituted or not. The action of alkali in the two cases is represented as follows :

The formation of sodium *iso*cyanate thus provides an excellent test for the presence of α-hydroxy-amides. The validity of the test has been disputed, however, by Micheel, who alleges (*Ber.*, 1934, **67**, 841) that sodium *iso*cyanate may be obtained in small yield from certain α-methoxy-amides. The results of our investigation fully support the contention of Ault, Haworth, and Hirst. Of the seven sugar acid amides examined, only one yielded sodium *iso*cyanate (detected as hydrazodicarbonamide) when treated with hypochlorite. This was 3 : 5 : 6-trimethyl gluconamide, the only α-hydroxy-amide of the series. The

other amides, which were all α-methoxy-amides, did not yield any sodium *iso*cyanate. It should be mentioned, however, that precautions were taken to ensure that traces of α-hydroxy-amides were not present. It is obvious that there is interaction between the *iso*cyanate residue and the adjacent hydroxyl group, but conjecture as to the nature of such interaction is not at present susceptible of experimental test. This mutual influence makes itself felt in another respect. We have failed to isolate a nitrogen-containing derivative (either cyclic or open chain) as an intermediate stage in the degradation of 3 : 5 : 6-trimethyl gluconamide, although the α-methoxy-amides examined (with the exception of pentamethyl gluconamide) give crystalline derivatives with the compositions of *iso*cyanates. It is significant that in each case where a stable derivative of this type is obtained there is available in the molecule a suitably placed hydroxyl group for the formation, by intramolecular addition, of an internal carbamic ester (or cyclic urethane) [cf. (II) and (III); (VI) and (VII); etc.]. Pentamethyl gluconamide, which has no



available hydroxyl group, does not yield a stable intermediate *iso*cyanate. There are thus strong reasons for the belief that the *iso*cyanate formed in the Weerman degradation is stabilised by conversion, when that change is possible, into the isomeric cyclic urethane, and the following facts confirm the view.

The urethane (VII) from 2 : 3 : 5 : 6-tetramethyl gluconamide when methylated with methyl iodide yielded a product (m. p. 99°) (VIII) containing one additional methyl group. This additional methyl group was attached to the nitrogen atom, for, on hydrolysis of the methylation product with alkali, methylamine was evolved. Consideration of the formulæ (VI) and (VII) clearly shows that the attachment of the methyl group to nitrogen can take place only if the urethane has the cyclic structure (VII). Furthermore, two methyl groups are introduced when the urethane (XIV) from 2 : 3 : 6-trimethyl gluconamide (XII) is methylated, and one of these is attached to nitrogen. The product is, in fact, identical (mixed m. p. determination) with (VIII). Two cyclic structures (XIV and XV) are possible for the urethane from 2 : 3 : 6-trimethyl gluconamide and the formation of (VIII) from it by methylation proves that (XIV) is the true representation. Presumably, the six-membered urethane ring-structure is a more stable arrangement than the seven-membered ring present in (III). Nevertheless, the latter is sufficiently stable to resist rupture by methylating agents, for the methylation of (III) results in the attachment of methyl to the nitrogen only. The product is a syrup.

It is to be observed that 3 : 5 : 6-trimethyl gluconamide (IX) has a hydroxyl group on C_4 available for ring formation. That no cyclic urethane is obtainable from it is to be ascribed to the modifying influence of the hydroxyl group at C_2 on the *iso*cyanate residue (cf. X), an influence which has been commented upon earlier in this communication.

Experimental.

The standard sodium hypochlorite solution was prepared according to the directions of Weerman (*loc. cit.*) and contained 58·2 g. of NaOCl per litre.

The methylated sugar acid amides used in these experiments included the following:

2 : 3 : 5 : 6-Tetramethyl *d*-gluconamide (m. p. 91°) prepared by the action of methyl-alcoholic ammonia on tetramethyl γ-gluconolactone (m. p. 26°).

2 : 3 : 4 : 6-Tetramethyl *d*-gluconamide (m. p. 68°; $[\alpha]_D^{20°}$ + 52·0° in water) prepared by solution of tetramethyl δ-gluconolactone in liquid ammonia (cf. Glattfield and MacMillan, *J. Amer. Chem. Soc.*, 1934, **56**, 2481).

2 : 3 : 6-Trimethyl *d*-gluconamide was obtained as a syrup by the solution of syrupy 2 : 3 : 6-trimethyl gluconolactone in liquid ammonia. In the course of this preparation, 2 : 3 : 6-trimethyl δ-gluconolactone was obtained in crystalline form, m. p. 84° and $[\alpha]_D^{16°}$ + 99·3° → + 42·3° in water (*c*, 0·95; constant value attained in 24 hours).

3 : 5 : 6-*Trimethyl* d-*gluconamide*. 3 : 5 : 6-Trimethyl glucofuranose (25 g.) (Anderson, Charlton, and Haworth, J., 1929, 1329) was oxidised by treatment with bromine water at room temperature. The product, isolated in the usual way, distilled at 135°/0·003 mm. and then crystallised completely (yield, 18·6 g.). 3 : 5 : 6-*Trimethyl γ-gluconolactone* showed m. p. 44—45°, $n_D^{18°}$ 1·4600 (superfused solid), and $[\alpha]_D^{20°}$ + 51·8°, changing to a constant value, + 14·1°, in 860 hours (water, *c*, 1·06) (Found: C, 49·1; H, 7·5; OMe, 42·5. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%). The lactone (18 g.) was dissolved in liquid ammonia (300 c.c.) in a Dewar flask. After being kept for 6 hours, the solution was poured into a basin, and the ammonia allowed to evaporate. In this way 3 : 5 : 6-*trimethyl gluconamide* was obtained which, after recrystallisation from alcohol, had m. p. 144°, $[\alpha]_D^{20°}$ + 34·0° in water (*c*, 1·176); yield, 18 g. (Found: C, 45·7; H, 8·1; N, 6·0; OMe, 39·0. $C_9H_{19}O_6N$ requires C, 45·6; H, 8·0; N, 5·9; OMe, 39·2%).

Pentamethyl d-*gluconamide*. Methyl pentamethyl gluconate (cf. Pryde, J., 1924, **125**, 520) on treatment with methyl-alcoholic ammonia gave *pentamethyl gluconamide*, which crystallised after distillation at 140°/0·002 mm. Recrystallised from ether–light petroleum, the amide showed m. p. 66° and $[\alpha]_D^{18°}$ + 51·1° in water (*c*, 0·61) (Found: C, 49·9; H, 8·9; N, 5·4; OMe, 58·2. $C_{11}H_{23}O_6N$ requires C, 49·8; H, 8·7; N, 5·3; OMe, 58·5%).

2 : 3 : 4-Trimethyl *l*-arabonamide [m. p. 96°; $[\alpha]_D^{19°}$ + 25·2° in water (*c*, 1·814)] and 2 : 3 : 5-trimethyl *l*-arabonamide [m. p. 137—138°; $[\alpha]_D^{20°}$ + 19·0° in methyl alcohol (*c*, 2·78)] were prepared as described by Humphreys, Pryde, and Waters (*loc. cit.*).

The Action of Sodium Hypochlorite under Standard Conditions on Methylated Amides.—The

conditions employed were the same for all amides examined and need be described for one only. 2 : 3 : 5 : 6-Tetramethyl gluconamide (2 g.) in water (10 c.c.) was mixed at 0° with the standard hypochlorite solution (10·2 c.c.) and kept at 0° for 2 days. Thereafter the small excess of hypochlorite was removed by the addition of dilute sodium thiosulphate solution until acidified starch–iodide paper was no longer coloured. To the solution were then added sodium acetate (2 g.) and semicarbazide hydrochloride (0·7 g.); a slight evolution of carbon dioxide occurred. No hydrazodicarbonamide was formed even after 2 days. Moreover, free semicarbazide was still present, for the addition of benzaldehyde immediately gave a crystalline deposit of the semicarbazone.

No sodium *iso*cyanate could therefore have been formed from 2 : 3 : 5 : 6-tetramethyl gluconamide. Similarly treated, the 2 : 3 : 4 : 6-tetramethyl, 2 : 3 : 6-trimethyl, and pentamethyl gluconamides failed to give hydrazodicarbonamide, as did also the 2 : 3 : 4-trimethyl and 2 : 3 : 5-trimethyl arabonamides. On the other hand, the only α-hydroxy-amide examined, namely, 3 : 5 : 6-trimethyl gluconamide (0·4 g.), gave in a short time 0·11 g. of hydrazodicarbonamide (m. p. 250°) (yield, 55% of the theoretical).

Preparation of Cyclic Urethanes.—(a) *From* 2 : 3 : 5 : 6-*tetramethyl gluconamide.* The amide (5·2 g.), dissolved in water (26 c.c.) and cooled to 0°, was slowly mixed with an excess of standard hypochlorite solution (30 c.c.). After 15 minutes the solution was acidified with dilute hydrochloric acid and warmed (35°). Some carbon dioxide and chlorine were evolved. The solution was neutralised with calcium carbonate, filtered, and evaporated in a vacuum. The dry residue was extracted with boiling alcohol and the extract after evaporation was again extracted with acetone. Evaporation of the acetone extract left the *cyclic urethane*, which crystallised from boiling ether in long white needles, m. p. 110°; $[\alpha]_D^{14\cdot5°}$ + 99·3° in water (*c*, 0·56). The yield of recrystallised material was 0·85 g. (Found: C, 48·5; H, 7·7; N, 5·7; OMe, 50·4. $C_{10}H_{19}O_6N$ requires C, 48·2; H, 7·6; N, 5·6; OMe, 49·8%).

(b) *From* 2 : 3 : 4 : 6-*tetramethyl gluconamide.* Following the procedure of Irvine and Pryde (*loc. cit.*), the amide (17·8 g.) was converted into the cyclic urethane, which formed rectangular prisms from acetone; m. p. 165—166°; $[\alpha]_D^{18°}$ + 167·8° in water (*c*, 1·49); yield, 10·2 g. (Found: C, 48·4; H, 7·6; N, 5·3; OMe, 49·2%). The urethane distilled without decomposition at bath temp. 170°/0·01 mm.

(c) *From* 2 : 3 : 6-*trimethyl gluconamide.* By the method described under (a), the syrupy trimethyl gluconamide (5 g.) was converted into the *cyclic urethane* (1·74 g.), which, after recrystallisation from acetone, had m. p. 157° and $[\alpha]_D^{17°}$ + 103° in water (*c*, 0·66) (Found: C, 46·5; H, 7·0; N, 5·6; OMe, 39·4. $C_9H_{17}O_6N$ requires C, 45·9; H, 7·2; N, 6·0; OMe, 39·6%).

(d) *From* 2 : 3 : 4-*trimethyl* l-*arabonamide.* The cyclic urethane prepared by the method of Humphreys, Pryde, and Waters (*loc. cit.*) had m. p. 141—142° and $[\alpha]_D^{18°}$ + 40·8° in water (*c*, 1·05).

(e) *From* 2 : 3 : 5-*trimethyl* l-*arabonamide.* The cyclic urethane obtained (m. p. 75°) corresponded to the product prepared by Humphreys, Pryde, and Waters (*loc. cit.*).

Action of Hypochlorite Solution on Pentamethyl Gluconamide.—The material (1·0 g.) was treated at 0° in aqueous solution (12 c.c.) with the standard hypochlorite solution (4·9 c.c.). After 48 hours, the solution was acidified with hydrochloric acid, neutralised with barium carbonate, and evaporated to dryness. The residue, a syrup (0·7 g.), was completely soluble in ether. After distillation at bath temp. 85°/0·01 mm. it had $n_D^{17°}$ 1·4340 and $[\alpha]_D^{17·5°}$ + 16·6° in water (*c*, 2·89; no mutarotation). The substance is *tetramethyl* aldehydo-d-*arabinose*. It reduces Fehling's solution in the cold, decolourises cold permanganate solution, and instantly restores the colour to Schiff's reagent (Found: OMe, 59·6. $C_9H_{18}O_5$ requires OMe, 60·1%). The conditions of treatment of the amide with the hypochlorite solution were varied in subsequent experiments, but in no case was any intermediate *iso*cyanate or urethane detected. Furthermore, no substituted carbamic ester could be isolated when the reaction was conducted in either methyl- or ethyl-alcoholic solution, the sole product being again tetramethyl *aldehydo*-arabinose (cf. Ault, Haworth, and Hirst, *loc. cit.*).

Action of Hypochlorite Solution on 3 : 5 : 6-*Trimethyl Gluconamide.*—The α-hydroxy-amide (1·6 g.) was treated in aqueous solution (28 c.c.) with standard hypochlorite solution (8·5 c.c.) at 0°. After 2 hours, the solution was diluted with water to 40 c.c., acidified with hydrochloric acid, and then immediately neutralised with barium carbonate and evaporated to dryness. Hot chloroform extraction of the residue yielded 2 : 4 : 5-*trimethyl* d-*arabinose* as a thin syrup showing $n_D^{22°}$ 1·4609 and $[\alpha]_D^{17°}$ + 18·4° in water (*c*, 3·53) (Found: OMe, 47·4. $C_8H_{16}O_5$ requires OMe, 48·0%). The product (1·15 g.) behaved as an *aldehydo*-sugar in that it reduced Fehling's solution in the cold, decolourised permanganate solution, and immediately restored the colour

to Schiff's reagent. The trimethyl sugar distilled without decomposition at bath temp. 125—130°/0·02 mm.

The trimethyl arabinose (0·56 g.) was boiled with 2% methyl-alcoholic hydrogen chloride (30 c.c.) for 12 hours. The product, isolated in the usual way, was a syrup (0·49 g.) distilling at bath temp. 100°/0·002 mm. and showing n_D 1·4434. It reduced Fehling's solution on boiling and decolourised permanganate in the cold (Found: OMe, 58·1. Trimethyl pentose requires OMe, 48·0; trimethyl methylpentoside, OMe, 60·1%).

Action of Alkali on the Cyclic Urethanes.—(a) *On the cyclic urethane from* 2 : 3 : 4 : 6-*tetramethyl gluconamide.* A solution of the urethane (2·0 g.) in 1% sodium hydroxide solution (200 c.c.) was kept at room temperature until no further change in rotation occurred (23 hours; $[\alpha]_D^{20°}$ + 157° → + 25°). The solution was then neutralised by the addition of a slight excess of hydrochloric acid, followed by barium carbonate. The residue left on evaporation was extracted with ether, which dissolved the trimethyl pentose. This (1·35 g.) was a colourless oil which reduced Fehling's solution and showed $n_D^{20°}$ 1·4490 and $[\alpha]_D^{14°}$ + 40·0° in methyl alcohol (*c*, 2·9) (Found: OMe, 46·8%). Subsequent reactions showed this substance to be 2 : 3 : 5-*trimethyl* d-*arabofuranose*. (The *l*-isomeride has $[\alpha]_D$ — 39·5° in water. See Baker and Haworth, J., 1925, **127**, 365.) The sugar was converted by boiling with 2% methyl-alcoholic hydrogen chloride into *trimethyl methyl*-d-*arabofuranoside*, a non-reducing syrup which distilled at bath temp. 135°/15 mm. and showed $n_D^{19°}$ 1·4350 and $[\alpha]_D^{15°}$ + 80·4° in water (*c*, 1·12) (Found: OMe, 59·6. $C_9H_{18}O_5$ requires OMe, 60·1%). The furanose structure was confirmed by its oxidation to the lactone and by the ease of hydrolysis of the methylpentoside, the hydrolysis being completed in 5 hours with 0·1N-hydrochloric acid at 100°.

Oxidation of the trimethyl arabinose with bromine gave trimethyl *d*-arabono-γ-lactone, m. p. 33° and $[\alpha]_D$ + 45·1° (in water), changing to + 25·3° in 480 hours (cf. Avery, Haworth, and Hirst, *loc. cit.*). By treatment of the lactone with methyl-alcoholic ammonia, 2 : 3 : 5-*trimethyl* d-*arabonamide* (m. p. 137·5°; $[\alpha]_D^{18°}$ — 14·6° in water, *c*, 0·89) was prepared (Found: C, 46·1; H, 7·0; OMe, 44·5. $C_8H_{17}O_5N$ requires C, 46·4; H, 6·8; OMe, 44·9%).

(b) *On the cyclic urethane from* 2 : 3 : 5 : 6-*tetramethyl gluconamide.* The urethane, when treated with 1% sodium hydroxide solution in the cold, gave 2 : 4 : 5-trimethyl *d*-arabinose, $n_D^{18°}$ 1·4641 (Found: OMe, 46·8%). The product restored the colour to Schiff's reagent.

Methylation of the Cyclic Urethane from 2 : 3 : 6-*Trimethyl Gluconamide.*—The urethane (0·38 g.), dissolved in dry methanol (1 c.c.), was heated at 45° for 12 hours with methyl iodide (15 c.c.) and silver oxide (10 g.). After filtration, the solution was again boiled with methyl iodide and silver oxide for 12 hours. Concentration of the filtered solution yielded a crystalline *compound* (0·15 g.), m. p. 99°, $[\alpha]_D^{17°}$ + 65·8° in water (*c*, 1·35). To this compound, the formula (VIII) is assigned (Found: C, 50·0; H, 7·6; N, 5·3; OMe, 46·6. $C_{11}H_{21}O_6N$ requires C, 50·2; H, 7·9; N, 5·3; OMe, 47·1%). The presence of *N*-methyl in the compound was shown in the following manner. The substance was distilled with 5% sodium hydroxide solution and to the distillate was added Nessler's reagent. A bright yellow precipitate indicated the presence of methylamine. Ammonia gives a brick-red precipitate under these conditions and such a precipitate was obtained when the urethanes from 2 : 3 : 4 : 6- and 2 : 3 : 5 : 6-tetramethyl gluconamide were similarly treated.

The urethane from 2 : 3 : 5 : 6-tetramethyl gluconamide (0·22 g.) was methylated by the procedure described and yielded a compound (0·18 g.), m. p. 99° (alone or in admixture with the methylated urethane obtained from 2 : 3 : 6-trimethyl gluconamide). The product of methylation of the urethane from 2 : 3 : 4 : 6-tetramethyl gluconamide was not crystalline. It had $[\alpha]_D$ + 38·1° in water (*c*, 0·78) and yielded methylamine on boiling with alkali solution.

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