CLXXII.—*Constitutional Studies in the Monocarboxylic Acids Derived from Sugars. Part V. Hexonic and Pentonic Acid Amides. The Action of Sodium Hypochlorite on the Isomeric Trimethyl Arabonamides.*

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TWO crystalline amides derived from lactones of tetramethylated hexonic acids have been previously described. Irvine and Pryde (J., 1924, **125**, 1045) recorded the preparation of tetramethyl gluconamide, formulated in the light of the then existing notions regarding the constitution of the parent tetramethyl glucose, as the 2 : 3 : 5 : 6-tetramethyl derivative. Later Pryde, Hirst, and Humphreys (J., 1925, **127**, 348) described the isolation of another crystalline compound of this type, namely, a tetramethyl galactonamide, which was provisionally considered as being derived from the corresponding butylene-oxidic (furanoid) lactone. The parent lactone in this case had been prepared from tetramethyl methylgalactoside, which had in turn been obtained from galactose by treatment with methyl sulphate and alkali, and therefore consisted of both pyranoid and furanoid forms, as the authors themselves pointed out (*vide* also Haworth, Ruell, and Westgarth, J., 1924, **125**, 2468).

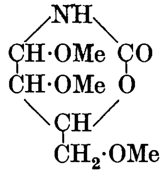
In view of the advances made in the last few years in elucidating sugar structure, it has now become possible to establish beyond all doubt the constitutions of these two amides, and the work has been extended to include the preparation of all four isomeric hexonamides related to the pyranoid and furanoid forms of tetramethyl glucose and of tetramethyl galactose, and also of the two corresponding amides related to trimethyl arabinose.

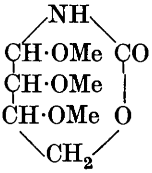
The amide described by Irvine and Pryde (*loc. cit.*) is a derivative of the stable form of glucose, and it is therefore obvious that it must now be regarded as 2 : 3 : 4 : 6-tetramethyl gluconamide and not, as originally formulated, as the 2 : 3 : 5 : 6-substituted compound. The latter *compound* has been prepared in the course of the present investigation and is found to differ materially from the former compound. Moreover it has been ascertained that the crystalline amide isolated by Pryde, Hirst, and Humphreys (*loc. cit.*) is related to the pyranoid form of tetramethyl galactose and is therefore a 2 : 3 : 4 : 6-substituted compound. The corresponding 2 : 3 : 5 : 6-substituted amide is also described in this communication, together with the isomeric 2 : 3 : 5- and 2 : 3 : 4-trimethyl arabonamides. All six amides are crystalline and are readily obtained in a pure state from the corresponding lactones by passing dry ammonia into their solutions in absolute alcohol. They all crystallise in needles and possess a faint characteristic odour. Those related to the pyranoid forms of the methylated hexoses and pentoses show a tendency to deliquesce and are difficult to recrystallise, whilst the corresponding amides obtained from the furanoid hexono- and pentono-lactones separate in crisp needles which can be recrystallised with ease. The accompanying table records the melting points and specific rotations of the six amides, and also the specific rotations of the parent lactones. In each case the 2 : 3 : 5-substituted derivatives have higher melting points than the corresponding members of the pyranoid series. It will also be seen that all six amides are dextrorotatory, whereas two of the lactones (those related to galactopyranose and arabopyranose) are lævorotatory. In considering the properties of the first-described amide of this type Irvine and Pryde (*loc. cit.*) favoured the aminolactone constitution, but this view does not gain support from the failure of two of the amides to exhibit the characteristic direction of rotation of the lactone. Furthermore all six amides, including the three related to the pyranoid lactones, show a rotation in water which remains constant for several days at least, whereas pyrano-lactones are characterised by a rapid change in rotation in this solvent.

Amide.	M. p.	$[\alpha]_D$.	$[\alpha]_D$ of parent lactone (initial value in water).
2 : 3 : 4 : 6-Tetramethyl gluconamide ...	68°	+ 60·4° (in acetone)	+ 99°
2 : 3 : 5 : 6-Tetramethyl gluconamide ...	91	+ 39·2 (in water)	+ 62·5
2 : 3 : 4 : 6-Tetramethyl galactonamide	120	+ 37·9 (in acetone)	+ 166·5
2 : 3 : 5 : 6-Tetramethyl galactonamide	155	+ 6·5 (in water)	− 29
2 : 3 : 4-Trimethyl arabonamide	96	+ 25·7 (in water)	+ 179·5
2 : 3 : 5-Trimethyl arabonamide	132	+ 15·8 (in water)	− 44·4

Irvine and Pryde (*loc. cit.*), using the method of Weerman (*Rec. trav. chim.*, 1917, **36**, 16; 1918, **37**, 16), found that the action of alkaline hypochlorite on tetramethyl gluconamide yielded a crystalline derivative having the composition $C_{10}H_{49}O_6N$, which is that of the intermediate *iso*cyanate compound. This was formulated as a six-membered cyclic urethane. It is clear from the foregoing observations that this urethane must now be regarded as a seven-membered ring compound. It is now found that the reaction involving the formation of such intermediate *iso*cyanate compounds is a general one, although the yields obtained from the various amides vary considerably. In the present communication there are described the two *iso*cyanate derivatives obtained from the isomeric trimethyl arabonamides. These may be formulated as follows :

(I.)





(II.)

Although in this instance the parent amides do not exhibit a marked difference in optical rotation, the corresponding cyclic *urethanes* do. Thus, that derived from the 2 : 3 : 5(furanoid)-trimethyl arabonamide (I) shows in water a rotation of $[\alpha]_D + 5{\cdot}0°$, which in the presence of dilute hydrochloric acid changes in a few hours to $[\alpha]_D - 118°$. The isomeric urethane from the 2 : 3 : 4 (pyranoid)-trimethyl arabonamide (II) has in water a rotation of $[\alpha]_D + 42°$, which changes in the presence of dilute acid to $[\alpha]_D + 1°$. The latter compound was obtained in much smaller yield than its isomeride, an observation which is in accord with the probable greater stability of a six-membered as compared with a seven-membered ring system of this type. In the case of the former urethane it is tentatively suggested that the marked change of rotation in the presence of dilute acid may be related to a keto-enol tautomerism. Thus, after the urethane had been subjected to the action of 1% hydrogen chloride in methyl alcohol at room temperature, there was obtained a crystalline derivative giving analytical figures identical with those of the original compound, but possessing a different melting point (63—65°, as compared with 76°) and a marked lævorotation ($[\alpha]_D$ — 178°, as compared with the original low dextrorotation, $[\alpha]_D$ + 5°). In the presence of 1% sodium hydroxide the high lævorotation fell to $[\alpha]_D$ — 30·8° in the course of 24 hours, and indications of considerable degradation were obtained. On the other hand, treatment of the original urethane ($[\alpha]_D$ + 5·0°) with alkali gave some indication of the formation of a dimethyl tetrose. This possibility is being further investigated.

EXPERIMENTAL.

2 : 3 : 4 : 6-*Tetramethyl Gluconamide.*—The lactone used for the preparation of this amide was obtained by the simultaneous hydrolysis and oxidation of tetramethyl methylglucopyranoside with aqueous hydrobromic acid and bromine, and had $n_D^{18°}$ 1·4556 and $[\alpha]_D$ + 97·4° (3 mins. after solution in water), falling to an equilibrium value of $[\alpha]_D$ + 37·1° (c = 1·47). The lactone, dissolved in absolute alcohol, was treated with dry ammonia; the syrup obtained after evaporation of the solvent slowly crystallised. Considerable difficulty was experienced in recrystallising the amide, but a sample was eventually obtained having m. p. 68° with preliminary softening, and $[\alpha]_D$ + 60·4° in acetone. These constants are in agreement with those previously noted by Irvine and Pryde (*loc. cit.*) but ascribed by them to the 2 : 3 : 5 : 6-tetramethyl compound.

2 : 3 : 5 : 6-*Tetramethyl Gluconamide.*—Tetramethyl methylglucofuranoside having $n_D^{15°}$ 1·4440 was hydrolysed and oxidised as described above for the pyranoside compound. The lactone finally obtained was a colourless syrup having $n_D^{15·5°}$ 1·4486 and $[\alpha]_D$ + 63·2° (5 mins. after solution in water), changing to $[\alpha]_D$ + 40·85° (constant after 24 days). Drew, Goodyear, and Haworth (J., 1927, 1237), and Haworth, Hirst, and Miller (*ibid.*, p. 2436) give the constants of 2 : 3 : 5 : 6-tetramethyl gluconolactone as $n_D^{14°}$ 1·4501 and $[\alpha]_D^{20°}$ + 62·5° (0 hr.), changing to $[\alpha]_D$ + 32·9° (501 hrs.). The *amide* was prepared from the lactone by the method already referred to and was readily obtained in long needles. Recrystallised from acetone it melted at 91° and showed $[\alpha]_D^{24°}$ + 39·2° (c = 1·06 in water), which value remained unchanged for several days (Found :

C, 47·8; H, 8·3; N, 5·75; OMe, 49·0. $C_{10}H_{21}O_6N$ requires C, 47·8; H, 8·4; N, 5·6; OMe, 49·4%).

2 : 3 : 4 : 6-*Tetramethyl Galactonamide.* Tetramethyl methylgalactopyranoside was obtained by the standard methods, and the preparation used for conversion into the lactone had an equilibrium value in acid methyl alcohol of $[\alpha]_D^{22°}$ + 96·5°. By hydrolysis and oxidation the lactone was obtained from the galactopyranoside and after distillation showed $[\alpha]_D$ + 144·8° (2 mins.), changing to $[\alpha]_D$ + 25·2° (constant for 17 hrs.), and $n_D^{18°}$ 1·4581. The amide was obtained by the customary method and proved, like the corresponding gluconamide, to be rather difficult to recrystallise. A crystalline specimen was eventually obtained having $[\alpha]_D$ + 37·9° (c = 1·4 in acetone) and m. p. 120°. Pryde, Hirst, and Humphreys (*loc. cit.*) have already recorded the preparation of this amide but were unable at the time to differentiate between the two possible isomerides derived respectively from the amylene-oxidic and butylene-oxidic lactones. It is now apparent from the data which they recorded that they were handling the 2 : 3 : 4 : 6-tetramethyl amide.

2 : 3 : 5 : 6-*Tetramethyl Galactonamide.*—For the preparation of this lactone tetramethyl methylgalactofuranoside was used. The latter showed $n_D^{18°}$ 1·4414 and $[\alpha]_D$ − 50·5°. Haworth, Ruell, and Westgarth (*loc. cit.*) have recorded for this compound $n_D^{20°}$ 1·4405 and $[\alpha]_D$ − 45·2°. The lactone obtained from the fully methylated galactofuranoside showed $n_D^{17°}$ 1·4492 and $[\alpha]_D$ − 28·5° (2 mins.), changing to a constant value of $[\alpha]_D$ − 25·9°. These figures agree with those already recorded by Pryde (J., 1923, **123**, 1808) and by Haworth, Ruell, and Westgarth (*loc. cit.*). The *amide* prepared from the lactone was recrystallised with ease. It had m. p. 153° (slight decomp.), and showed $[\alpha]_D$ + 6·53° (c = 1·17) in water, and $[\alpha]_D$ + 5·76° (c = 1·46) in acetone (Found: C, 47·8; H, 8·6; N, 5·7; OMe, 49·3. $C_{10}H_{21}O_6N$ requires C, 47·8; H, 8·4; N, 5·6; OMe, 49·4%).

2 : 3 : 4-*Trimethyl Arabonamide.*—This *amide* was prepared from the lactone previously described by Pryde and Humphreys (J., 1927, 559), and had m. p. 96° and $[\alpha]_D$ + 35·5° (c = 1·13) in alcohol, and $[\alpha]_D$ + 25·7° (c = 0·82) in water. The latter value was unchanged 48 hours later (Found: C, 46·3; H, 8·3; N, 6·9; OMe, 44·0. $C_8H_{17}O_5N$ requires C, 46·4; H, 8·2; N, 6·8; OMe, 44·9%).

2 : 3 : 5-*Trimethyl Arabonamide.*—The lactone from which this amide was prepared has also been described by Pryde and Humphreys (*loc. cit.*). The *amide* crystallised much more readily than its isomeride described above. It had m. p. 132° and $[\alpha]_D$ + 19·3° (c = 0·82) in alcohol, and $[\alpha]_D$ + 15·8° (c = 0·75) in water.

The latter value was unchanged 48 hours later (Found : C, 46·3; H, 8·35; N, 6·85; OMe, 44·2. $C_8H_{17}O_5N$ requires C, 46·4; H, 8·2; N, 6·8; OMe, 44·9%).

The Action of Alkaline Hypochlorite on the Isomeric Trimethyl Arabonamides.—(1) *On* 2 : 3 : 4-*trimethyl arabonamide.* 10 G. of the amide dissolved in 50 c.c. of water were treated with alkaline hypochlorite, prepared according to the method of Weerman (*loc. cit.*), the procedure adopted being essentially that of Irvine and Pryde (*loc. cit.*). There was finally obtained in small yield a colourless crystalline product. Analysis showed it to be the intermediate iso*cyanate* or internal *urethane* (II) having m. p. 142° and $[\alpha]_D + 42°$ ($c = 0·87$ in water). The rotation remained constant during 48 hours, but in the presence of 2% aqueous hydrochloric acid at room temperature the rotation fell in the course of 12 hours to a constant value of $[\alpha]_D + 1°$ (Found : C, 46·6; H, 7·25; N, 6·85; OMe, 44·5. $C_8H_{15}O_5N$ requires C, 46·8; H, 7·3; N, 6·8; OMe, 45·3%).

(2) *On* 2 : 3 : 5-*trimethyl arabonamide.* In this instance the action of alkaline hypochlorite on 10 g. of the amide yielded 2·5 g. of a colourless crystalline product (2-*keto*-4 : 5 : ω-*trimethoxy*-6-*methyltetrahydro*-1 : 3-*oxazine*, I, which will be referred to as compound A), isomeric with that described above (Found : C, 47·0; H, 7·3; N, 6·9; OMe, 44·8%). It had m. p. 76° and $[\alpha]_D + 5·0°$ ($c = 1·05$ in water). In the presence of 2% hydrochloric acid the rotation changed within 24 hours to a constant value of $[\alpha]_D - 118·8°$.

The Action of Acid Methyl Alcohol on the Trimethoxy-urethane (I).—The crystalline urethane (compound A) was subjected at room temperature to the action of methyl alcohol containing 1% of hydrogen chloride. After 5 hours the specific rotation attained the constant value $[\alpha]_D - 117·6°$ ($c = 2·9$). From the neutralised solution a syrup was obtained which gradually crystallised. The crystals were separated on porous tile and after digestion with ether they were obtained as fine white needles having m. p. 63—65°, and $[\alpha]_D - 178°$ ($c = 0·7$ in water) (Found : C, 46·7; H, 7·2; N, 6·9; OMe, 45·3. $C_8H_{15}O_5N$ requires C, 46·8; H, 7·3; N, 6·8; OMe, 45·3%). The product (*compound* B) is therefore identical in composition with the original urethane (A), but differs from it considerably in melting point and widely in optical rotation.

The trimethoxy-urethane (compound A) in 1% acid methyl alcohol was heated in a sealed tube at 80° for 30 minutes. The solution, after neutralisation, showed $[\alpha]_D - 113·3°$ ($c = 3·9$). From this solution there was isolated a crystalline product having m. p. 45—47° and $[\alpha]_D - 108°$ ($c = 0·84$ in water). This substance gave analytical figures identical with those above (Found : C, 46·5; H, 7·1; N, 6·9; OMe, 43·4%). It is regarded as being a mixture of the two compounds A and B already described. Similar crystalline mixtures were obtained in other experiments.

The Action of Alkali on the Trimethoxy-urethanes.—When the compound B was subjected to the action of 1% aqueous sodium hydroxide, the rotation fell in the course of 24 hours from $[\alpha]_D$ − 178° to − 30·8° ($c = 0{\cdot}87$). From the neutralised solution there was isolated a nitrogen-free syrup having a methoxyl content of 13·4%. It is evident that extensive degradation had occurred. Compound A was subjected to a similar treatment with 1% aqueous alkali. In this instance the initially low dextrorotation changed to a lævorotation of $[\alpha]_D$ − 98·7°. From the neutralised solution there was obtained an ether-soluble syrup containing but slight traces of nitrogen and having $[\alpha]_D$ − 41° ($c = 0{\cdot}75$ in water) (Found : C, 48·6; H, 8·3; OMe, 39·2. $C_6H_{12}O_4$ requires C, 48·65; H, 8·1; OMe, 41·9%). It therefore seems probable that in this instance a dimethyl tetrose had been formed by alkaline degradation of the trimethoxy-urethane.

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