[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Glycofuranosides and Thioglycofuranosides. VII. Crystalline Alkyl Furanosides and Dimethylacetal of *d*-Mannose

BY ALLEN SCATTERGOOD[1] AND EUGENE PACSU

The general method of Pacsu and Green[2] for the preparation of glycofuranosides from the sugar mercaptals was applied to mannosediethylmercaptal which was previously obtained[3] from sirupy mannose by Fischer and from crystalline mannose by Levene and Meyer.[4] It was found that this starting material could be prepared conveniently and in good yield directly from the readily available α-methyl-*d*-mannopyranoside[5] by the action of hydrochloric acid and ethyl mercaptan. As was reported in a preliminary communication,[2f] the reaction between mannosediethylmercaptal and mercuric chloride in methyl alcoholic solution under neutral conditions resulted in a 60% yield of pure α-methyl-*d*-mannofuranoside (m. p. 118°; $[\alpha]^{20}D$ 108.4° in water solution) previously prepared by Haworth and co-workers through the dicarbonate[6] and direct from mannose[7] and methyl alcoholic hydrogen chloride. Green and Pacsu used pyridine to remove the excess mercuric chloride necessary to carry this type of reaction to completion. During the course of this work it was found that metallic mercury was also suitable for this purpose, the reaction being $Hg^{++} + Hg \rightarrow Hg_2^{++}$. On acetylation by acetic anhydride and sodium acetate, α-methyl-*d*-mannofuranoside readily gave a crystalline tetraacetate (m. p. 61–62°; $[\alpha]^{20}D$ 108.8° in chloroform solution) which was identical with the compound obtained[7a] by Haworth and co-workers by the pyridine method of acetylation. The substance had a specific rotation[8] of 105.3° in *trans*-dichloroethylene and 120.3° in *cis*-dichloroethylene.

When the sirupy residue of the mother liquor of α-methyl-*d*-mannofuranoside was treated with a saturated aqueous solution of calcium chloride, crystallization of a non-reducing, negatively rotating substance started immediately. After recrystallization by the addition of isobutyl alcohol to its concentrated methyl alcoholic solution, the substance had a specific rotation of −58.5° in water solution. It represented a calcium chloride addition compound of β-methyl-*d*-mannofuranoside with the composition of $C_7H_{14}O_6 \cdot CaCl_2 \cdot 3H_2O$. Subsequent investigation revealed that the sirupy residue of the mother liquor of α-methyl-*d*-mannofuranoside prepared according to Haworth and co-workers[7] would also combine with calcium chloride to yield the same addition compound. Furthermore, it was also obtained directly from mannose and methyl alcoholic hydrogen chloride at room temperature in the presence of calcium chloride. Considering the difficulties involved in the preparation of crystalline mannose, it is probably best to prepare this calcium chloride compound from the mercaptal. Removal of the calcium chloride from the addition compound by silver oxalate resulted in the pure β-methyl-*d*-mannofuranoside, which was obtained from ethyl acetate solution in long needles. Irvine and Burt[9] first suggested the existence of this substance as they believed that the "γ-methylmannoside" which they obtained in the sirupy condition was a mixture of two forms. Recently Haworth and co-workers obtained[10] β-methyl-*d*-mannofuranoside by the carbonate method but were unable to secure it in the crystalline condition. Our purest preparation which had been recrystallized three times from ethyl acetate melted at 47° and had a specific rotation of −112.6° in water solution as against −107° observed first[2f] on a slightly reducing sample. From the rotation of the calcium chloride compound (−58.5°) a rotation of −108.2° is calculated for the optically active portion of

(1) This paper is based upon a thesis submitted by Allen Scattergood, Albert Plaut Fellow in Chemistry, former Research Assistant on Special Funds from the Rockefeller Foundation, to the Faculty of Princeton University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) (a) Pacsu and Green, THIS JOURNAL, **58**, 1823 (1936); (b) Green and Pacsu, *ibid.*, **59**, 1205 (1937); (c) Green and Pacsu, *ibid.*, **59**, 2569 (1937); (d) Green and Pacsu, *ibid.*, **60**, 2056 (1938); (e) Green and Pacsu, *ibid.*, **60**, 2288 (1938); (f) Pacsu and Scattergood, *ibid.*, **61**, 534 (1939); (g) Pacsu, *ibid.*, **61**, 1671 (1939).

(3) Fischer, *Ber.*, **27**, 678 (1894).

(4) Levene and Meyer, *J. Biol. Chem.*, **74**, 695 (1927).

(5) Hudson, "Organic Syntheses," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1927, p. 64.

(6) (a) Haworth and Porter, *J. Chem. Soc.*, 151 (1930); (b) *ibid.*, 649 (1930).

(7) (a) Haworth, Hirst and Webb, *ibid.*, 654 (1930); (b) Haworth, Hirst and Wood, *ibid.*, 2108 (1932).

(8) Unless otherwise stated, the rotations given in this paper are all for sodium light at 20°.

(9) Irvine and Burt, *J. Chem. Soc.*, **125**, 1343 (1924).

(10) Haworth, Porter and Waine, *Rec. trav. chim.*, **57**, 541 (1938).

this substance by multiplying by the formula weight ratio of 359/194. In a special experiment we found that addition of the calculated amount of calcium chloride to the aqueous solution of the pure furanoside changed the observed rotation from −6.65 to −6.40°. Further amounts of calcium chloride added to the solution did not appreciably change the rotation of the solution. This experiment clearly indicated that calcium chloride has a perturbing effect upon the rotation of the glycoside with which it is combined and that it is unsafe to calculate the rotation of a sugar or sugar derivative from the rotation of its calcium chloride compound by multiplying by the formula weight ratio.

By application of the furanoside synthesis to mannosediethylmercaptal in ethyl, normal propyl, and isopropyl alcohols, respectively, the corresponding α-alkyl mannofuranosides were obtained in the crystalline state. Table I contains the more important constants of the furanosides prepared in the course of the present work.

TABLE I

ALKYL MANNOFURANOSIDES WITH THEIR MELTING POINTS, OBSERVED AND CALCULATED ROTATIONS AND A''_x VALUES

d-Manno-furanosides	Mol. wt.	M. p., °C.	$[\alpha]^{20}D$ in water	[M]	A''_x [M] − $B_{\alpha\beta}$[a]	$[\alpha]_D$ calcd. from (A_x[b] + $B_{\alpha\beta}$[a] + F[c])
α-Methyl	194	118	108.4	21,030	21,455	...
β-Methyl	194	47	−112.8	−21,880	−21,455	...
α-Ethyl	208	90	105.0	21,840	22,265	105.4
α-*n*-Propyl	222	89	96.0	21,310	21,735	100.2
α-*i*-Propyl	222	82–84	96.7	21,470	21,895	100.8

[a] $B_{\alpha\beta}$ = −425, one-half the sum of the molecular rotation of α- and β-methyl-*d*-mannofuranoside. [b] A_x designates the following "normal" values for the aldoses: A_{OMe} = 18,700; A_{OEt} = 19,600; A_{OPr} = 19,925; $A_{Oi\text{-}Pr}$ = 20,060. [c] F = 2755 obtained from $A'_{OMe} - A_{OMe}$.

When the pentaacetate of mannosediethylmercaptal was submitted to the action of mercuric chloride in absolute methyl alcohol under neutral conditions, mannosedimethylacetal pentaacetate was formed. On deacetylation, this substance gave rise to crystalline mannosedimethylacetal with m. p. 101° and $[\alpha]^{20}D$ 0.6° in water solution. The dimethylacetal was stable in neutral and alkaline media but it suffered gradual hydrolysis at room temperature in a 0.05% hydrochloric acid solution. The specific rotation in the latter medium changed in forty-eight hours from the initial value of 0.6° to −34°. This change was probably due to the formation of a mixture of the α- and β-methylmannofuranoside from the dimethylacetal and the reaction followed a first order course with the velocity constant of 10^4k = 240. After the point of maximum levorotation had been reached, the rotation changed slowly to the final value of +12.8°, the approximate final rotation of *d*-mannose. This second change apparently represented the hydrolysis of the furanosides to methyl alcohol and mannose and it proceeded about one-twentieth as rapidly ($10^4 k$ = 11.8) as the first stage of the hydrolysis reaction.

Mannopyranose and its derivatives have been known for a long time to present a notable exception to the validity of van't Hoff's hypothesis of optical superposition as applied by Hudson to the sugars and certain of their derivatives. By the preparation of the crystalline β-methylmannofuranoside, it has now become possible to test Hudson's isorotation rules in the mannofuranose series also. It is seen in Table I that half of the rotational difference of the two mannofuranosides, A''_{OMe} = 21,455, is considerably larger than the "normal" value, A_{OMe} = 18,700, for the methylglycosides of the aldoses. It appears, therefore, that the isorotation rules do not hold for the furanoid derivatives of mannose just as they are not applicable directly to mannose and its pyranoid derivatives where the value of the same coefficient is A'_{OMe} = 14,225. In a recent communication[11] it has been shown that by introduction of a new term (F) in the simple equations used for the calculation of the rotations, correct values are obtained for *d*-mannose and *l*-sorbose and its pyranoid derivatives from the "normal" A_x and a_x coefficients for the aldoses and ketoses, respectively. The numerical value of F is calculated by subtraction of the value of any "normal" A_x coefficient from that of the corresponding "abnormal" coefficient. It represents a constant characteristic of a particular sugar and its derivatives in a certain solvent. Thus, F = −4475 was calculated from $A'_{OMe} - A_{OMe}$ (14,225 − 18,700) for *d*-mannopyranose and all its glycosidic derivatives in water solution. It is to be expected that by introduction of a similar constant for the mannofuranose series the calculated and observed rotations of the glycosidic derivaatives will show satisfactory agreement. The pertinent data in Table I reveal that this, indeed, is the case. The value of the new term, F = 2755, represents the difference between the "abnormal" and the "normal" coefficients of

(11) Pacsu, THIS JOURNAL, **61**, 2669 (1939).

$A''_{OMe} = 21{,}455$ and $A_{OMe} = 18{,}700$, respectively, and it remains practically constant for the different alkyl mannofuranosides.

As to the physical significance of F, it has been suggested[11] that this constant probably represents the numerical value of the contribution of a hitherto unrecognized optical factor, the ring conformation, to the total rotation of the molecule. In the furanose series, where the ring is almost certainly planar, large deviations from the isorotation rules should not be found if ring conformation were the only disturbing factor. However, it is quite certain that the B coefficient of the sugars and their derivatives consists of at least four optical factors without considering a possible solvent effect. These factors are the number (N) of the different atoms, the conformation (C) of the ring, the configuration (C_f) of the hydrogen atoms and hydroxyl groups around the asymmetric centers, and the orientation (O) about the C–O bonds of all the hydroxyl groups. The last factor is probably due to the formation of hydrogen bonds. Obviously these factors must have nearly constant values for both the α- and β-isomers of those pyranoid or furanoid sugars and sugar derivatives which obey the rules of isorotation in first approximation, since in such instances only will the difference between the B parts of the isomers be zero, and, consequently, the value of A_x be a constant quantity. On the other hand, in instances where the isorotation rules are not valid, the value of at least one of the factors must be different for the α- and β-forms, since the difference, in such cases, between the B parts of the α,β-isomers will not be zero and, consequently, the value of A_x will be modified by this difference. Of the four factors under consideration, factor N represents a constant characteristic of certain groups of sugars, such as pentoses, aldohexoses, ketohexoses, etc., and it must have the same value for both the ring and the α,β-isomers of any member within these groups. Similarly, the factor C_f should have a constant value characteristic of the individual members of the different groups of sugars and should not change either for the ring isomers or for the α,β-isomers of a particular sugar. With regard to factor C, any simple sugar molecule containing a strainless six-membered ring should, according to Haworth,[12] be theoretically capable of existing in two *trans* and six *cis* forms constituted on the Sachse principle. However, Pacsu[11] recently reported that attempts to build up these forms from the Fisher–Hirschfelder atom models resulted in the discovery that only one *cis* and one *trans* form could be constructed. The diameters of these atom models are the so-called collision diameters obtained from the kinetic theory or from a rule of Pauling that the collision diameter is equal to 3.2 times the covalent radius. Figures 1 to 8 represent the skeleton models of a pyranose molecule constructed from these atom models in the eight conformations advocated by Haworth.

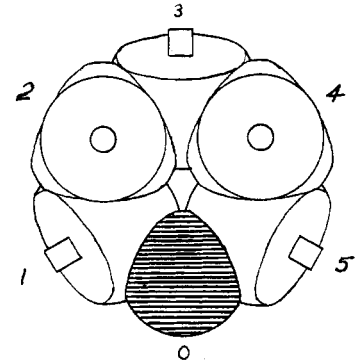

Fig. 1.—*trans*-Form, O above plane of paper, C_3 below plane of paper. A —CH_2OH group projecting outward on C_5 (*d*-form) would not interfere with groups attached to neighboring carbon atoms. This conformation is possible for the *d*-aldohexoses but not for the *l*-forms, which would have the —CH_2OH group on the lower valence of C_5 where it would block groups on the lower valences of C_1 and C_3. This does not mean that the *d*- and *l*-forms of an aldohexopyranose will not be mirror images. It simply indicates that the mirror image of the *d*-form will be derived from a different figure (Fig. 2).

It becomes evident by handling these models that *d*-hexopyranose molecules with conformations represented by Figs. 2, 4, 5, 6, 7, and 8 cannot be constructed because more or less obstruction occurs between certain atoms or atomic groups such as the hydrogen atom and the hydroxyl group of one or more ring carbon atoms and the —CH_2OH group which would be on carbon atom 5 of an aldohexose molecule. On the other hand, molecules with either of the two conformations represented by Figs. 1 and 3 can be constructed readily without obstructions occurring between any of the addenda of the ring. Since theoretical considerations[13] indicate that a *cis* form would be unstable and would pass over to the *trans* form because of large repulsion both in the ring and among the

(12) Haworth, "The Constitution of Sugars," Edward Arnold and Co., London, 1929, p. 91.

(13) Gorin, Kauzmann and Walter, *J. Chem. Phys.*, **7**, 327 (1939).

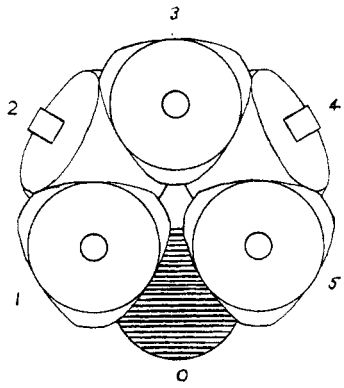

Fig. 2.—*trans*-Form, O below plane of paper, C_3 above plane of paper. Bottom view of Fig. 1. A $-CH_2OH$ group projecting upward on C_5 (*d*-form) partially covers the upper valences of C_1 and C_3. Even with hydrogen atoms on the two latter positions, there would be some interference. This conformation is possible for the *l*-aldohexoses but not for the *d*-forms. The *d*-form of a given aldohexose would be derived from Fig. 1 while the *l*-form, its mirror image, would be derived from Fig. 2.

subsidiary groups, there remains only one *trans* form (Fig. 1) from which all the *d*-hexopyranose molecules and their derivatives must be derived. In such a case factor C will have the same value for the α- and β-form of any pyranoid sugar or sugar derivative. Finally, factor O for the α-form (O_α) of any sugar may differ considerably from the same factor for the β-isomer (O_β) and, therefore, will not cancel out in the calculation of the numerical value of A_x. This appears to be the case in mannose, rhamnose, sorbose, etc., and their pyranoid derivatives where large deviations from the isorotation rules have been observed.

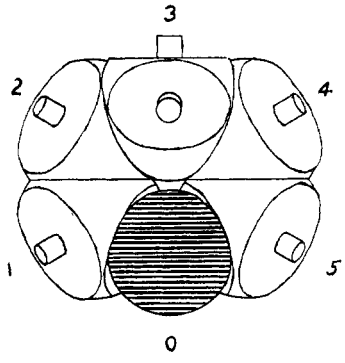

Fig. 3.—Symmetrical *cis*-form, O and C_3 above plane of paper. A $-CH_2OH$ group projecting outward on C_5 (*d*-form) would not interfere with groups of neighboring carbon atoms. This conformation is possible for the *d*-aldohexoses but not for the *l*-forms, which would have the $-CH_2OH$ group on the lower valence of C_5 where it would partially cover the lower valences of C_1 and C_4.

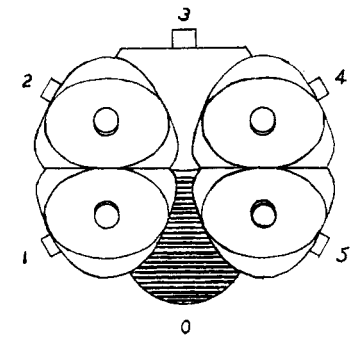

Fig. 4.—Symmetrical *cis*-form, O and C_3 below plane of paper. Bottom view of Fig. 3. A $-CH_2OH$ group projecting upward on C_5 (*d*-form) partially covers the upper valences of C_1 and C_4. This conformation is possible for the *l*-aldohexoses but not for the *d*-forms.

In the mannopyranose series $F = -4475$ represents, therefore, the numerical value of half of such difference $[(O'_\alpha - O'_\beta)/2]$. Since factor C is necessarily constant for all the furanosides (planar ring) any large deviation from the rules in this series must also be ascribed to the difference in the rotation values of the O factors for the α- and β-isomers. Obviously this is the case in the alkyl mannofuranosides where $F = 2725$ represents the numerical value of half of such difference $[(O''_\alpha - O''_\beta)/2]$. In both the pyranose and furanose series, therefore, the physical significance of F appears to be confined to the disturbing optical effect of the different orientation of the hydroxyl groups in the α- and β-isomers of certain sugars. As pointed out previously,[11] the occurrence of such disturbances at present cannot be predicted, neither can the effect be measured by physical or chemical methods. In many

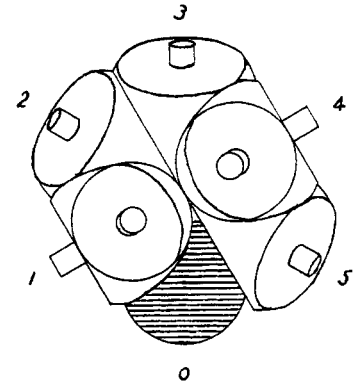

Fig. 5.—Asymmetrical *cis*-form, C_1 and C_4 above plane of paper. In both the *d*- and *l*-forms there would be interference between OH groups and H atoms on the upper valences of C_1 and C_4. Neither form can exist in this conformation.

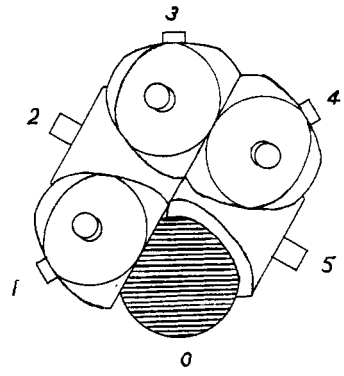

Fig. 6.—Asymmetrical *cis*-form, C_2 and C_5 below plane of paper. Bottom view of Fig. 5. In both the *d*- and *l*-forms there would be no interference on the top face of the molecule. However, on the bottom face of C_2 and C_5 there would always be interference. Neither form can exist in this conformation.

instances the optical effect of the orientation appears to be negligible (glucose-arabinose series) but for certain sugars (mannose, sorbose, etc.) it must be eliminated from the calculations by the introduction of term *F*, a characteristic constant for each of these sugars.

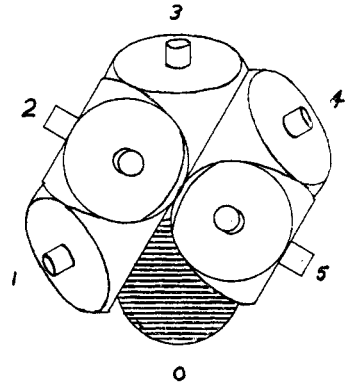

Fig. 7.—Asymmetrical *cis*-form, C_2 and C_5 above plane of paper. Mirror image of Fig. 5. A $-CH_2OH$ group projecting upward on C_5 (*d*-form) partially covers the upper valence of C_2. Even for the *l*-form, with H atoms on the upper valences of C_2 and C_5, there is interference. Neither form can exist in this conformation.

Experimental Part

Preparation of Mannosediethylmercaptal from α-Methyl-*d*-mannopyranoside.—One hundred cc. of ethyl mercaptan was added to 100 g. of crude α-methylmannopyranoside[5] in 100 cc. of concd. hydrochloric acid and the mixture was shaken for twenty hours at room temperature. At the end of this time the reaction product was treated with ice-cold water (150 cc.) and the crystals which soon formed were filtered and washed with small quantities of ice water. The crude product was purified by crystallization from water containing enough ammonia

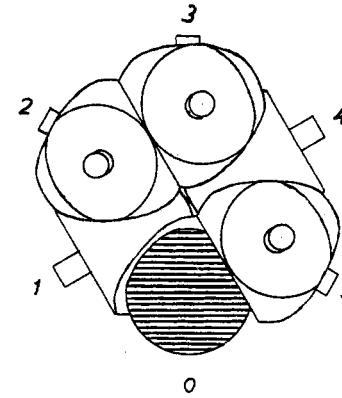

Fig. 8.—Asymmetrical *cis*-form, C_1 and C_4 below plane of paper. Bottom view of Fig. 7, mirror image of Fig. 6. A $-CH_2OH$ group projecting upward on C_6 (*d*-form) partially covers the upper valence of C_3. There would also be interference for both the *d*- and *l*-forms on the bottom valences of C_1 and C_4. Neither form can exist in this conformation.

to make the solution alkaline and decolorized by the use of activated carbon; yield, 54%; m. p. 131–133°.

Preparation of α-Methylmannofuranoside and its Tetraacetate.—A warm solution of 109 g. of mercuric chloride (0.4 mole) in 500 cc. of absolute methyl alcohol was added slowly to a suspension of 87 g. of yellow mercuric oxide in a solution of 57.6 g. of mannosediethylmercaptal (0.2 mole) in 500 cc. of absolute methyl alcohol. During the addition the mixture was either shaken mechanically or stirred. After the addition had been completed, the mixture was stirred or shaken for three hours. A test for the completion of the reaction was usually made after this time by heating the clear filtrate of a sample of the mixture with water. The reaction was complete if no precipitate of mercaptoethyl mercuric chloride would form. The insoluble mercury compounds were then filtered off and washed with methyl alcohol. The filtrate and washings contain mercuric chloride, which must be removed. This can be accomplished either by the use of pyridine according to Pacsu and Green[2] or by means of metallic mercury. In the latter procedure the united liquids were shaken with 7 cc. of mercury until the solution was free of chloride ion. This usually required four days of continuous shaking. After this time the mixture was filtered and the solution was evaporated *in vacuo* to a sirup which often crystallized spontaneously. If this was not the case then the sirup was dissolved in two or three times its volume of normal propyl alcohol and the solution was inoculated with seed crystals secured by evaporation of a methyl alcoholic solution of a small sample of the sirup in a stream of air. In either case the crystals were washed with cold normal propyl alcohol until the rotation of the washings became positive. Evaporation of the filtrate and washings *in vacuo* or in a stream of air gave a sirup which deposited more crystals on addition of an equal volume of normal propyl alcohol. After a thorough chilling the crystals were filtered and washed with ice-cold normal propyl alcohol in 10-cc. portions until the washings became positively rotating. The total yield of

the crude product was 25 g. or 64%. The strongly negative rotating filtrate and washings were saved for the preparation of the β-isomer. Haworth and co-workers[7a] used a mixture of methyl alcohol and ether to crystallize α-methylmannofuranoside. Six crystallizations were reported necessary with this combination of solvents. In the present work, normal propyl alcohol was found to be a better solvent, as pure material was obtained after two recrystallizations. The substance was dissolved in ten times its weight of normal propyl alcohol at 75°. The hot solution was filtered through a steam-jacketed funnel and the filtrate was kept in the icebox overnight. After the second recrystallization the substance had m. p. 118° and $[\alpha]^{20}D$ 108.4° in water solution, in agreement with the data of Haworth, Hirst and Wood.[7b]

Anal. Calcd. for $C_7H_{14}O_6$: OCH_3, 15.97. Found: OCH_3, 15.92.

For acetylation, 1 g. of α-methylmannofuranoside was boiled for two minutes with 5 cc. of acetic anhydride containing 0.25 g. of anhydrous sodium acetate. After the solution had been worked up in the usual manner, the product crystallized spontaneously from its chloroform solution upon evaporation in a stream of air. After recrystallization from aqueous alcohol it had m. p. 61–62° and $[\alpha]^{20}D$ 108.8° in chloroform (*c*, 1.23), 105.3° in *trans*-dichloroethylene (*c*, 1.56) and 120.3° in *cis*-dichloroethylene (*c*, 1.18). Haworth, Hirst and Webb[7a] prepared this substance by acetylation of the furanoside in pyridine at 0°. By the above procedure the acetate was secured in the crystalline condition without the difficulty which Haworth and co-workers encountered.

Preparation of the Calcium Chloride Compound of β-Methylmannofuranoside.—From the combined filtrate and washings of the α-methylmannofuranoside a strongly negatively rotating sirup was obtained by evaporation of the solution *in vacuo*. A saturated aqueous solution of 8 g. of calcium chloride was added to the sirup. Crystallization of the calcium chloride mannoside compound started within a few minutes, and was initiated by stirring. During the crystallization an equal volume of normal propyl alcohol was stirred in so that the mixture would not set to a solid. The crystalline slush was chilled in ice for several hours and then filtered with suction. The crystals were washed with cold absolute ethyl alcohol, in which they were insoluble. The substance was dried *in vacuo* over calcium chloride; yield, 8 g. or 13%. From the mother liquor, after the removal of the excess calcium chloride by means of silver oxalate, several small quantities of α-methylmannofuranoside were obtained. A careful search failed to reveal the presence of any mannosedimethylacetal.

The crude calcium chloride compound was dissolved in a minimum quantity (about 20 cc.) of cold methyl alcohol. The formation of the solution is a slow process and an excess of methyl alcohol is to be avoided. Isobutyl alcohol was then added to the solution, a few cc. at a time, until a total of 60 cc. had been added at room temperature. Crystallization started at this point and 20 cc. of isobutyl alcohol was added during the crystallization, making a total of 80 cc. The crystals were kept in the icebox overnight and then filtered and washed with isobutyl alcohol; yield, practically quantitative; $[\alpha]^{20}D$ −58.5° in water solution (*c*, 1.711). A similar process of recrystallization by the use of water instead of methyl alcohol and normal propyl alcohol instead of isobutyl alcohol was employed to prepare a sample of the substance for analysis, since the methyl alcohol method gave high values to the methoxyl content.

Anal. Calcd. for $C_7H_{14}O_6 \cdot CaCl_2 \cdot 3H_2O$: Ca, 11.16; Cl, 19.74; H_2O, 15.04; OCH_3, 8.64. Found: Ca, 11.08; Cl, 19.70; H_2O, 15.13; OCH_3, 8.70.

The compound was very soluble in water and methyl alcohol and almost insoluble in ethyl alcohol and higher alcohols. It was devoid of action toward Fehling solution. In testing the compound with Fehling solution it was found that an excess of the alkaline tartrate portion of the reagent would keep the calcium in solution as a complex ion during the test. The substance was hydrolyzed in 0.575 *N* hydrochloric acid at 19° in two days to give mannose with $[\alpha]D$ 14.0°.

The same substance was obtained from the mother liquor of the α-methylmannofuranoside prepared according to Haworth and co-workers.[7a] After several crops of the α-compound were removed, a sirup was obtained which was strongly negatively rotating. This was treated with an equal volume of a saturated aqueous solution of calcium chloride and the crystalline compound formed was filtered with some ethyl alcohol; yield, 0.5 g. from 10 g. of mannose.

The calcium chloride compound of β-methylmannofuranoside was also prepared direct from mannose in the following way. To 360 cc. of methyl alcohol containing 1% of dry hydrogen chloride, there was added 11 g. of calcium chloride (0.1 mole) and 18 g. of *d*-mannose (0.1 mole). The mixture was shaken on the machine until the mannose had all dissolved. After twenty hours of standing at room temperature the solution showed its lowest negative rotation. The acid was then neutralized by shaking the solution with silver carbonate. After filtration the solution was evaporated *in vacuo* to a sirup which was dissolved in 125 cc. of warm normal propyl alcohol. On inoculation with a crystal of the calcium chloride compound the product crystallized at 0°; yield 6 g. or 17%; $[\alpha]^{20}D$ −58.0° in water solution.

Preparation of β-Methylmannofuranoside from its Calcium Chloride Compound.—A solution of 3.6 g. of the calcium chloride compound in 50 cc. of water was shaken for thirty minutes with an equivalent quantity of silver oxalate, which was prepared by mixing 21 cc. each of normal solutions of potassium oxalate and silver nitrate and washing the resulting precipitate thoroughly by decantation. The reaction mixture was filtered, the filtrate was rendered alkaline by a few drops of ammonia, then evaporated *in vacuo* to a sirup which was repeatedly treated with alcohol, each time the solvent being evaporated *in vacuo* to ensure the removal of water. Seed crystals were secured by extraction of a small portion of the sirup with 25 cc. of hot ethyl acetate and slow evaporation of the solution in a vacuum desiccator. The main portion of the sirup was then extracted with warm ethyl acetate in several portions, which were kept in separate flasks. Each ethyl acetate extract deposited a small quantity of sirup at room temperature. The solutions were decanted into clean flasks and inoculated with crystals. The crystallization of the substance was slow and the flasks were al-

lowed to remain at 0° for several days. The furanoside was deposited in the form of buttons made up of fine needles. The crystals (1 g.) were filtered and shaken at room temperature with 25-cc. portions of ethyl acetate until all but a trace had dissolved. The combined solutions were kept in the icebox for three days. Well developed crystals of the β-furanoside were obtained; yield, 70%; m. p. 46–47°; $[\alpha]^{20}D$ −112.6° in water solution (*c*, 2.952). Further recrystallization did not change the rotation or the melting point.

Re-formation of the Calcium Chloride Compound from β-Methylmannofuranoside.—A solution of 0.1476 g. of β-methylmannofuranoside in 5 cc. of water gave an observed rotation of −6.65° in a 2-dm. tube. This corresponds to a specific rotation of −112.6°. To 3 cc. of this solution there was added 84 mg. of calcium chloride, a small excess over the calculated quantity to form the addition compound. The rotation of this solution was −6.40° which corresponds to a specific rotation of −108.4°. Thus the specific rotation of the furanoside is lowered 4.2° by the addition of calcium chloride. From the specific rotation of the crystalline calcium chloride addition compound (−58.5°) a rotation of −108.2° is calculated for the optically active portion of this substance by multiplying by the formula weight ratio 359/194. Further quantities of calcium chloride added to this solution did not appreciably change the rotation. Evaporation of this solution resulted in the formation of a crystalline substance which on recrystallization from methyl alcohol and isobutyl alcohol had $[\alpha]^{20}D$ −58.5° in water solution. This experiment indicates that the same calcium chloride compound may be re-formed from crystalline β-methylmannofuranoside.

Preparation of α-Alkylmannofuranosides.—A hot solution of 22.8 g. of mannosediethylmercaptal in the desired alcohol was made (200 cc. of ethyl alcohol, 400 cc. of either *n*- or *i*-propyl alcohol). To the cooled solution, 34 g. of yellow mercuric oxide[2b] was added. A warm solution of 43.6 g. of mercuric chloride in 200 cc. of ethyl alcohol, in 325 cc. of normal propyl alcohol or in 280 cc. of isopropyl alcohol was added under vigorous stirring to the mercaptal solution at room temperature. The mixture was shaken or stirred for the required period (three hours for isopropyl alcohol, six hours for ethyl alcohol and overnight for normal propyl alcohol) until a test showed that the reaction was complete. The reaction mixture was filtered and the filtrate and washings were treated by either of the procedures given for the preparation of α-methylmannofuranoside. The sirups obtained crystallized spontaneously. The products were recrystallized from ethyl acetate and showed the constants given in Table I.

Anal. Calcd. for $C_6H_{11}O_5(OR)$: OR, 21.6 (R, C_2H_5), 26.6 (R, C_3H_7). Found: OR, 21.2 (R, C_2H_5), 26.1 (R, *n*-C_3H_7), 25.4 (R, *i*-C_3H_7).

Preparation of Mannosedimethylacetal.—The starting material, mannosediethylmercaptal pentaacetate, was prepared by acetylation of the mercaptal with hot acetic anhydride containing anhydrous sodium acetate. It was identical with the substance previously prepared by Pirie,[14] who acetylated the mercaptal in pyridine. The demercaptalation of the acetate was carried out in an apparatus fitted with a separatory funnel, a reflux condenser and a mercury-sealed mechanical stirrer. A solution of 12 g. of the acetate in 120 cc. of methyl alcohol was gently refluxed and stirred for five hours with 6 g. of yellow mercuric oxide and a solution of 22.5 g. of mercuric chloride in 45 cc. of warm methyl alcohol. After this time, the mixture was stirred at room temperature overnight, then filtered and the filtrate and washings evaporated *in vacuo* to dryness. The chloroform extract of the residue contained, beside the mannosedimethylacetal pentaacetate, a small quantity of mercuric chloride. It was found in this investigation that metallic copper was an ideal reagent for removal of mercury in non-aqueous solvent. Moist bright copper turnings were added to the chloroform solution and the mixture was shaken until a sample no longer amalgamated a fresh copper turning. The reaction mixture was filtered and the combined filtrate and chloroform washings were evaporated *in vacuo* to a sirup. For deacetylation by the procedure of Zemplén and Pacsu[15] this sirup was dissolved in 50 cc. of absolute methyl alcohol and 2 cc. of 0.1 *N* sodium methylate in methyl alcohol was added to the solution. The mixture was kept at room temperature overnight, then the filtered solution was evaporated *in vacuo* to a sirup which crystallized spontaneously. The crude mannosedimethylacetal was then dissolved in a small volume of absolute ethyl alcohol and crystallized by the addition of isopropyl ether at 0°. The substance was then recrystallized twice from hot ethyl acetate; m. p. 101°; $[\alpha]^{20}D$ 0.6° in water solution (*c*, 6.86).

Anal. Calcd. for $C_6H_{12}O_5(OCH_3)_2$: OCH_3, 27.4. Found: OCH_3, 27.6.

The acetal is non-reducing but is easily hydrolyzed by dilute aqueous acids. A study of the rate of hydrolysis was made and the data are reported in Table II.

TABLE II

HYDROLYSIS OF A SOLUTION OF 0.074 G. OF MANNOSEDIMETHYLACETAL IN 2 ML. OF 0.05% HYDROCHLORIC ACID AT 23° IN A 2-DM. TUBE.

Time, hours	Specific rotation	*k* (first order)
0	0.6	
0.1	.6	
.4	.2	
.8	− .4	
1	− .85	0.018
2	− 2.4	.019
3	− 5.0	.025
4	− 6.8	.026
5	− 9.1	.028
6	−10.4	.028
48	−34.0	Mean 0.024
48	−34.0	..
60	−33.0	0.00078
72	−31.4	.00103
240	− 7.3	.00153
317	− 4.0	.00140
560	+12.8	Mean 0.00118

It will be noticed that the solution of the acetal became negatively rotating as the reaction proceeded. This is

(14) Pirie, *Biochem. J.*, **30**, 374 (1936).

(15) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

interpreted as evidence of the formation of a β-glycoside. Since the acetal eventually became hydrolyzed to mannose as shown by the final rotation, it was concluded that the intermediate must have been β-methylmannofuranoside or a mixture of this substance and its α-form. The formation of these intermediates from the acetal proceeded about twenty times faster than the hydrolysis of these intermediates into mannose and methyl alcohol.

Acknowledgment is made to Mr. Richard C. Johnson, a student at the Union Junior College, Roselle, New Jersey, for making the drawings of the models.

Summary

1. By application of the general method of Pacsu and Green to mannosediethylmercaptal prepared directly from α-methylmannopyranoside, crystalline β-methyl, α-ethyl, α-*n*-propyl and α-isopropyl mannofuranosides have been obtained. The β-methylmannofuranoside has been isolated from its crystalline calcium chloride addition compound, $C_6H_{11}O_5OCH_3 \cdot CaCl_2 \cdot 3H_2O$, which was obtained from the mother liquor of the α-methylmannofuranoside. The same calcium chloride compound also has been obtained directly from the reaction products of mannose and methyl alcoholic hydrogen chloride and from the mother liquor of α-methylmannofuranoside prepared according to Haworth and co-workers.

2. It has been found that calcium chloride has a perturbing effect upon the rotation of the β-methylmannofuranoside with which it is combined and therefore it is unsafe to calculate the rotation of a sugar or a sugar derivative from the rotation of its calcium chloride compound by multiplying by a formula weight ratio.

3. Crystalline mannosedimethylacetal has been prepared and its hydrolysis has been studied.

4. It has been shown that Hudson's rules of isorotation hold closely in the mannofuranose series provided that a factor F is introduced in the equations. The numerical value of F has been determined to be 2725 for the furanoid derivatives of mannose in water solution.

5. It has been suggested that the factor F probably represents the disturbing optical effect of the different orientation of the hydroxyl groups in the α- and β-isomers of certain sugars and their pyranoid or furanoid derivatives.

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[CONTRIBUTION NO. 185 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Disubstituted Aminoacetones Containing Two Unlike Substituents[1]

BY J. WM. MAGEE[2] WITH HENRY R. HENZE

Continuing our attempts to prepare compounds possessing satisfactory activity as soporifics, we reported[3] recently our synthesis of ten disubstituted aminoacetones which subsequently were converted into disubstituted aminohydantoins. The ketones thus employed were all of the simple type $CH_3COCH_2NR_2$ in which the two substituents are identical and are either alkyl or allyl. We have now been interested in obtaining examples of the less well-known type CH_3COCH_2NRR', in which the two substituents are different, since these compounds present greater opportunity for variation in the combination of the groups most usually present in useful sedatives.

We have completed the synthesis of ten disubstituted aminoacetones, six of which had not been reported previously, by interaction of bromoacetone and the appropriate mixed secondary amine.[3] Most of the amines employed were produced in almost quantitative yield by catalytic reduction of the appropriate Schiff base by high pressure hydrogenation in the presence of Raney nickel catalyst.

(1) From the Ph.D. dissertation of J. Wm. Magee, June, 1938.

(2) Present address, Federal Bureau of Investigation, United States Department of Justice, Washington, D. C.

(3) Magee with Henze, THIS JOURNAL, **60**, 2148 (1938).

Experimental

Preparation of the Mixed Secondary Amines.—The monomethylaniline and monoethylaniline were redistilled immediately before use. Cyclohexylmethylamine was obtained by heating one mole of methylaniline for eight hours at 200° in the presence of Raney nickel catalyst and an initial hydrogen pressure of 3500 lb. (233 atm.). The product was of such purity as to permit use immediately upon filtration from the catalyst. In the other instances, one mole of benzaldehyde, or a derivative, was warmed on a steam cone with one mole of a primary amine for fifteen minutes. After cooling to room temperature and separating the water formed from the unsaturated base, the latter was reduced in thirty minutes at 75° under initial hydrogen pressure of 2000 lb. (133 atm.). Here, too, the mixed amines were obtained in excellent yield and in a state of practical purity.