[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

The Acetone Derivatives of the Mercaptals of Some Monosaccharides. V. The 5,6-Monoacetone Derivative of *d*-Galactosedibenzylmercaptal and the 6-Methyl Derivative of *d*-Galactose

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In continuation of our revisionary work[2] on the structures of the acetone derivatives and the methylated acetone derivatives of certain hexose mercaptals, the structure of the monoacetone galactose mercaptal with m. p. 112.5° and $[\alpha]^{20}\text{D}$ 17.4° in chloroform solution was investigated. This substance was isolated[2] as one of the two components of the formerly[3] described "2,3-monoacetone galactosedibenzylmercaptal" with m. p. 102–103° and $[\alpha]^{18}\text{D}$ 8.8° in acetylene tetrachloride solution, the other component being what has been proved[2b] to be the 4,5-monoacetone galactosedibenzylmercaptal with m. p. 103° and $[\alpha]^{20}\text{D}$ 31.0° in chloroform solution. On the basis of the following experimental results it is now established definitely that this substance represents the 5,6-monoacetone galactosedibenzylmercaptal.

Negative reaction with triphenylmethyl chloride[4] in pyridine solution was the first indication that the hydroxyl group in position 6 was occupied. On removal of the benzyl mercaptan residues in ethyl alcoholic solution according to the method of Pacsu and Green[5] the monoacetone mercaptal yielded a sirupy product which represented the 5,6-monoacetone β-ethylgalactofuranoside. The structure of this compound was proved by analyses for the ethoxyl and isopropylidene groups and by the fact that on oxidation by periodic acid according to Jackson and Hudson[6] the substance required one mole equivalent of the oxidant and no formaldehyde was produced in the reaction. From the theoretically possible monoacetone β-ethylgalactofuranosides only the 5,6-monoacetone derivative would give such experimental results. Confirmatory evidence for the assigned structure was obtained from the results of methylation and subsequent hydrolysis of the methylated product. The former operation yielded a substance representing the 2,3-dimethyl 5,6-monoacetone β-ethylgalactofuranoside as indicated by the result of analysis for the alkoxyl groups. On hydrolysis, this substance gave rise to 2,3-dimethyl galactose first prepared by Robertson and Lamb[7] by a different method. The structure of this compound was confirmed by the result of the oxidation by periodic acid. In this experiment two mole equivalents were used up by a sample of the substance. A survey of the possible structures of dimethyl galactose indicated that the 2,3-, 2,6-, 3,4-, 3,6-, 4,5- and 4,6-dimethyl derivatives would require two mole equivalents of periodic acid. However, the last four of these isomers would give rise to dimethyl osazones, whereas the first two would yield monomethyl osazones, since the methoxyl in position 2 would be lost during the formation of an osazone. Experiments showed that the dimethyl galactose in question yielded the 3-monomethyl galactosazone first obtained by Robertson and Lamb,[7] and not the 6-monomethyl galactosazone of Freudenberg and Smeykal.[8] Finally, the crystalline anilide prepared from our dimethyl galactose proved to be identical with the 2,3-dimethyl galactose anilide of Robertson and Lamb. From these experimental results it follows that in the original starting material the acetone residue was attached to carbon atoms 5 and 6. Therefore, it is now well established that the "2,3-monoacetone galactosedibenzylmercaptal"[3] consists of a mixture of about equal quantities of 4,5- and 5,6-monoacetone galactosedibenzylmercaptal.

For the preparation of a monomethyl galactose Pacsu and Löb[3] used a sirupy diacetone galactosedibenzylmercaptal as the starting material. In this substance the acetone residues were assumed to occupy the positions 2,3 and 5,6. This assumption was based mainly on supposed dissimilarities between the properties of Freudenberg and Smeykal's 6-monomethyl galactose and those of what consequently was incorrectly designated as the 4-monomethyl galactose. In 1936 Munro

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[1] Research Assistant on Special Funds from the Rockefeller Foundation.

[2] (a) Pacsu, THIS JOURNAL, **58**, 2076 (1936); (b) Part IV, Pacsu, Trister and Green., *ibid.*, **61**, 2444 (1939).

[3] Part III, Pacsu and Löb, *Ber.*, **62**, 3104 (1929).

[4] Ref. 2b, note 12.

[5] Pacsu and Green, THIS JOURNAL, **58**, 1823 (1936), *et seq.*

[6] Jackson and Hudson, *ibid.*, **59**, 994 (1937), *et seq.*

[7] Robertson and Lamb, *J. Chem. Soc.*, 1321 (1934).

[8] Freudenberg and Smeykal, *Ber.*, **59**, 100 (1926).

and Percival[9] repeated the preparation of the supposed 4-methyl galactose and found that it was identical with the 6-methyl galactose of Freudenberg and Smeykal. In our present reinvestigation of this problem we have arrived at the same conclusion. We have found no significant difference between the physical constants of our preparation as well as its osazone and phenylhydrazone and those of the 6-monomethyl galactose and its corresponding derivatives. Moreover, we have obtained confirmatory evidence for the structure of this compound from the result of the application of the periodic acid oxidation method of Jackson and Hudson.[6] Our experiments showed that the monomethyl galactose in question required four equivalents of periodic acid for oxidation and no formaldehyde was produced in the reaction. A survey of the possible structures of monomethyl galactose indicated that only the 6-monomethyl derivative would require four equivalents of periodic acid, all the other isomers requiring only three equivalents of the reagent.

It also should be noted that the preparation of the monomethyl galactose was accomplished by the use of a method somewhat different from that previously employed by Pacsu and Löb and subsequently adapted by Munro and Percival. In this new procedure methylation of the diacetone galactosedibenzylmercaptal was advantageously carried out by the process of Pacsu and Trister[10] with the result that the product was completely methylated as indicated by the nearly theoretical methoxyl content of the monomethyl galactose obtained from it. Incomplete methylation of the diacetone mercaptal frequently occurred when dimethyl sulfate was used and subsequent removal of the acetone residues from the product by hydrolysis gave rise to monomethyl galactosedibenzylmercaptal contaminated with galactosedibenzylmercaptal. Separation of such a mixture by fractional crystallization from chloroform is rendered difficult by the fact that the galactosedibenzylmercaptal becomes considerably soluble in chloroform in the presence of the monomethyl derivative. The consistently low methoxyl contents of the respective products of Munro and Percival may be attributed to incomplete methylation of the starting material. For the removal of the mercaptan residues from the monomethyl galactosedibenzylmercaptal we have employed the general procedure of Pacsu and Green[5] for the preparation of furanosides. Since the resulting monomethyl methylgalactofuranoside could not be secured in crystalline form, there seems to be no special reason why the procedure originally developed[8] should not be followed.

Finally it should be pointed out that the formation of the crystalline 6-monomethyl galactosedibenzylmercaptal from the sirupy diacetone mercaptal in itself cannot be regarded as proof of the purity of the latter substance. The low yield (18–33%) of the monomethyl mercaptal together with the existence of two crystalline monoacetone mercaptals would seem to make such a conclusion unwarranted. If the sirupy diacetone mercaptal took its origin from the two monoacetone derivatives, then the former substance would represent a mixture of a 2,3-4,5- and a 2,3-5,6-diacetone mercaptal. From the latter component, on methylation and subsequent hydrolysis, 4-monomethyl galactosedibenzylmercaptal should be obtained. However, the evident absence of this compound in the reaction product would seem to indicate that either the two monoacetone isomers were not involved as intermediates in the formation of the diacetone mercaptal or, if they were, migration of the isopropylidene group occurred in the 5,6-monoacetone derivative. The final solution of this problem would require thorough studies on the behavior of the monoacetone mercaptals toward the acetone–sulfuric acid reagent.

The investigation is being continued.

Experimental

Conversion of 5,6-Monoacetone Galactosedibenzylmercaptal into 5,6-Monoacetone β-Ethylgalactofuranoside.—Fifteen grams of the monoacetone mercaptal with m. p. 112.5° and $[\alpha]^{20}D$ 17.4 in chloroform solution[2] was dissolved in 200 cc. of absolute ethyl alcohol and the solution was treated at room temperature with 15 g. of yellow mercuric oxide and 18 g. of mercuric chloride according to the procedure of Pacsu and Green.[5] After six hours of continuous stirring a negative test for unchanged mercaptal was obtained. The reaction mixture was then worked up in the usual manner. Because of the sensitivity of the isopropylidene group to acid the residual sirup obtained after the pyridine treatment was extracted with very dilute alkali (phenolphthalein indicator) instead of water. After filtration with activated carbon the solution was concentrated *in vacuo* to a clear, viscous liquid; yield, 6.8 g. The substance was devoid of action toward Fehling solution. The high negative rotation, $[\alpha]^{22}D$ −70.0° in water solution (*c*, 1.625) indicated that the glycoside belonged to the β-series.

Anal. Calcd. for $C_{11}H_{20}O_6$: OC_2H_5, 18.1. Found: OC_2H_5, 18.9.

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[9] Munro and Percival, *J. Chem. Soc.*, 640 (1936).

[10] Pacsu and Trister, THIS JOURNAL, **61**, 2442 (1939).

The presence of one isopropylidene group was shown by a micro acetone estimation according to the method of Bell and Harrison[11] (Calcd.: $(CH_3)_2C$, 16.9. Found: $(CH_3)_2C$, 13.0).

For the oxidation experiment a sample of the monoacetone ethylgalactofuranoside was treated with three moles of a periodic acid solution which had been neutralized previously with sodium hydroxide. Aliquot parts of the reaction mixture were then titrated for the excess of periodate with standard arsenite solution and it was found that 0.75, 0.95 and 1.1 moles of periodic acid were used up for the oxidation of the glycoside after thirty minutes, one hour and two hours, respectively. Negative reaction with dimedone was the indication that formaldehyde was absent in the reaction mixture. These results proved that one mole of periodic acid was required for the oxidation of the compound, which fact was considered as evidence that the analyzed product was the 5,6-monoacetone ethylgalactofuranoside.

2,3-Dimethyl 5,6-Monoacetone β-Ethylgalactofuranoside and its Hydrolysis into the 2,3-Dimethyl Galactose.—The 5,6-monoacetone β-ethylgalactofuranoside (6.8 g.) was dissolved in 25 cc. of methyl iodide and the solution was treated with 20 g. of silver oxide according to the method of Purdie and Irvine.[12] The methylated product was isolated in the usual manner and then it was methylated a second time with the same quantities of reagents. After purification 5.7 g. of a non-reducing pale yellow liquid representing the 2,3-dimethyl 5,6-monoacetone β-ethylgalactofuranoside was obtained.

Anal. Calcd. for $C_{13}H_{24}O_6$: alkoxyl, 38.7. Found: alkoxyl, 37.3.

A sample of the product, on addition of periodic acid neutralized with alkali, remained unchanged even after several hours of standing at room temperature as indicated by the result of the titration for the excess of periodate with standard arsenite solution.

For the preparation of 2,3-dimethyl galactose 3.3 g. of the substance was dissolved in 50 cc. of 0.05 *N* hydrochloric acid and the solution was heated at 90° until constant rotation was obtained (−64.8° after one hour; +62.9° after fifteen hours, const.). The clear solution was worked up in the usual manner and the residue was purified by treatment with a 1:1 mixture of methyl alcohol and ether; yield, 2 g. of a clear, viscous liquid representing the 2,3-dimethyl galactose. The substance had $[\alpha]^{22}_D$ 64.7° in water solution (*c*, 2.1), which value changed after ninety minutes to 80.9°, and $[\alpha]^{20}_D$ 17.2° in chloroform solution (*c*, 1.62). Robertson and Lamb[7] give $[\alpha]^{16}_D$ 11.3° in chloroform solution (*c*, 1.15) and OCH_3, 27.8.

Anal. Calcd. for $C_8H_{16}O_6$: OCH_3, 29.8. Found: OCH_3, 29.4.

For the oxidation experiment 5 cc. of a 0.1 *M* solution of the substance was treated with 15 cc. of a 0.1 *M* periodic acid solution. After one hour and two hours, 5-cc. samples of the reaction mixture were titrated for the excess of periodic acid with a standard arsenite solution and it was found that, respectively, 1.90 and 2.00 moles of periodic acid were used up for the oxidation of the dimethyl galactose.

On the treatment with phenylhydrazine and acetic acid the substance gave rise to the 3-monomethyl galactosazone of Robertson and Lamb[7]; m. p. 176–179° and $[\alpha]^{17}_D$ 63.5° in pyridine solution (*c*, 0.425). Mutarotation could not be observed because the solution became dark on standing. Robertson and Lamb give m. p. 176–179° and OCH_3, 7.9.

Anal. Calcd. for $C_{19}H_{24}O_4N_4$: OCH_3, 8.3. Found: OCH_3, 8.1.

The anilide of 2,3-dimethyl galactose was prepared as described by Robertson and Lamb.[7] The crystals melted at 128–129°. Robertson and Lamb gave m. p. 130–131° and OCH_3, 20.9.

Anal. Calcd. for $C_{14}H_{21}O_5N$: OCH_3, 21.9. Found: OCH_3, 21.6.

6-Monomethyl Galactosedibenzylmercaptal.—The starting material, galactosedibenzylmercaptal with m. p. 143–144°, was prepared according to Pacsu and Ticharich.[13] Fifty grams of this substance was dissolved in 500 cc. of acetone to which 15 cc. of concd. sulfuric acid previously had been added at 0°. The solution was kept at room temperature for twenty hours, then it was neutralized with solid sodium carbonate under stirring, filtered and the filtrate concentrated *in vacuo* to a sirup. This was dissolved in chloroform, the solution was dried with anhydrous sodium sulfate, then concentrated *in vacuo* to a sirupy residue which was extracted several times with cold petroleum ether (b. p. 60–70°) by shaking on the machine. The united petroleum ether extracts were dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to an orange-yellow colored sirup; yield, 46 g. This substance representing the diacetone galactose dibenzylmercaptal was methylated according to Pacsu and Trister[10] by conversion into the sodium salt and subsequent treatment with methyl iodide. It is advisable to subject the product so obtained to a second methylation; yield, practically quantitative. For the removal of the isopropylidene groups from the methylated diacetone derivative, the lemon-yellow colored sirup was dissolved in 400 cc. of 80% ethyl alcohol containing 15 cc. of concd. hydrochloric acid. The solution was then heated under reflux for twenty minutes, cooled, neutralized with 6 *N* sodium hydroxide solution, diluted with an equal volume of water and kept at 0° overnight. The voluminous precipitate, the 6-monomethyl galactosedibenzylmercaptal, was filtered off and recrystallized from ethyl alcohol; yield, 15 g. It had m. p. 130° and $[\alpha]^{18}_D$ −27.1° in pyridine solution (*c*, 2.49). These values are in good agreement with those reported by Pacsu and Löb[3] for their supposed 4-monomethyl galactosedibenzylmercaptal.

Anal. Calcd. for $C_{21}H_{28}O_5S_2$: OCH_3, 7.3. Found: OCH_3, 7.1.

6-Monomethyl β-Methylgalactofuranoside and its Hydrolysis into 6-Monomethyl Galactose.—Nine grams of the 6-monomethyl mercaptal was dissolved in 200 cc. of absolute methyl alcohol and the solution was treated at 60° with 9 g. of yellow mercuric oxide and 11 g. of mercuric chloride according to the procedure of Pacsu and Green.[5] After six hours of continuous stirring the solution was worked up in the usual manner; yield, 4.2 g. of a pale yellow liquid representing the 6-monomethyl methyl-

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(11) Bell and Harrison, *J. Chem. Soc.*, 350 (1939).

(12) Purdie and Irvine, *ibid.*, **83**, 1021 (1903).

(13) Pacsu and Ticharich, *Ber.*, **62**, 3008 (1929).

galactofuranoside. The low rotation, $[\alpha]^{20}_{D}$ −78.7° in water solution (c, 3.25), indicated that the substance consisted mainly of the β-isomer.

Anal. Calcd. for $C_8H_{16}O_6$: OCH_3, 29.8. Found: OCH_3, 26.9.

For hydrolysis the furanoside was dissolved in 150 cc. of 0.05 *N* hydrochloric acid and the solution was heated under reflux for four hours in a boiling water-bath. During this time the initial rotation of −78.7° changed into the constant value of +74.5°. The solution was then worked up in the usual manner and the monomethyl galactose was crystallized from absolute ethyl alcohol; m. p. 113–114° and $[\alpha]^{18}_{D}$ 137.2° in water solution (c, 3.09), which value after six hours changed to the constant rotation of 77.0°.

Anal. Calcd. for $C_7H_{14}O_6$: OCH_3, 16.0. Found: OCH_3, 15.6.

For the oxidation experiment 5 cc. of a 0.05 *M* solution of the monomethyl galactose was treated with 25 cc. of a 0.05 *M* periodic acid solution. After thirty minutes, one hour, eighty minutes and twenty hours, 5-cc. samples of the solution were titrated for the excess periodic acid with standard arsenite solution. It was found that 2.2, 3.7, 3.96 and 3.98 moles of periodic acid, respectively, were required for the oxidation of the monomethyl galactose. From the five possible isomers only the 6-monomethyl galactose would use up four equivalents of periodic acid.

For the 6-monomethyl galactose Freudenberg and Smeykal[8] gave m. p. 128° and $[\alpha]^{20}_{578}$ 114.0° in water solution (77.0° after three hours, const.), whereas Munro and Percival[9] recorded m. p. 118° and 122–123° for two different preparations with the respective rotations of $[\alpha]^{20}_{D}$ 120.0° (70.0° after six hours, const.) and 112.0° (66.0° after six hours, const.) in water solution. Pacsu and Löb's[3] values for the supposed 4-monomethyl galactose are m. p. 118° and $[\alpha]^{18}_{D}$ 117.0° (67.8° after three hours, const.) in the same solvent.

The phenylhydrazone of our 6-monomethyl galactose was prepared according to Freudenberg and Smeykal.[8] After recrystallization from methyl alcohol the substance had m. p. 117.5° and $[\alpha]^{26}_{D}$ 22.4° in pyridine solution (c, 2.25), which value after twenty-four hours changed to the constant rotation of 13.6°.

Anal. Calcd. for $C_{13}H_{20}O_5N_2$: OCH_3, 10.95. Found: OCH_3, 10.75.

Freudenberg and Smeykal gave m. p. 182–183° and $[\alpha]^{17}_{578}$ 14.5° in pyridine solution but they did not observe mutarotation, whereas Munro and Percival[9] reported m. p. 179° and changes from $[\alpha]^{20}_{D}$ 24.4° to 14.1° and from 23.5 to 14.8° in the same solvent for two different preparations.

The osazone of the monomethyl galactose was prepared and it was recrystallized from methyl alcohol. It had m. p. 200° and $[\alpha]^{26}_{D}$ 141.0° in pyridine solution (c, 1.045), which value after twenty-four hours changed to the constant rotation of 91.8°.

Anal. Calcd. for $C_{19}H_{24}O_4N_4$: OCH_3, 8.33. Found: OCH_3, 8.21.

Freudenberg and Smeykal[8] gave for 6-monomethyl galactosazone m. p. 204–206° and $[\alpha]^{71}_{578}$ 135.0° in pyridine solution. Munro and Percival[9] found for two different preparations m. p. 200° and 200–201°, and $[\alpha]^{20}_{D}$ 144.0° and 141.0°, respectively, in the same solvent. Pacsu and Löb[3] gave for the supposed 4-monomethyl galactosazone m. p. 194–195° and $[\alpha]^{18}_{D}$ 130.7° in pyridine solution. Mutarotation had not been observed by any of these authors.

Summary

1. The chemical structure of the monoacetone galactosedibenzylmercaptal with m. p. 112.5° and $[\alpha]^{20}_{D}$ 17.4 isolated from the "2,3-monoacetone galactosedibenzylmercaptal" of Pacsu and Löb was investigated and it was found that the isopropylidene group occupied the positions 5 and 6.

2. This was concluded from the results of a series of transformations involving the following steps: 5,6-monoacetone galactosedibenzylmercaptal ⟶ 5,6-monoacetone β-ethylgalactofuranoside ⟶ 2,3-dimethyl 5,6-monoacetone β-ethylgalactofuranoside ⟶ 2,3-dimethyl galactose ⟶ 3-monomethyl galactosazone.

3. The supposed 4-methyl galactose of Pacsu and Löb was prepared from the diacetone galactosedibenzylmercaptal by a new procedure and its identity with the 6-monomethyl galactose of Freudenberg and Smeykal was confirmed in agreement with the results of Munro and Percival.

4. Independent evidence for the structures assigned to the final products and some of the intermediates was obtained from the results of the application of the periodic acid oxidation method of Jackson and Hudson.

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