RING–CHAIN ISOMERISM IN THE ACETATES OF GALACTOSE OXIME

BY M. L. WOLFROM, ALVA THOMPSON AND L. W. GEORGES

Isomerism of the ring–chain type has been studied[1] in two hexaacetates of glucose oxime and we now wish to report an extension of this study to the galactose series. Mild acetylation of the oxime of aldehydo-galactose pentaacetate yielded a hexaacetate (m. p. 145–146°; $[\alpha]_D + 23°$, CHCl₃) which was distinctly different and was thus isomeric with that (m. p. 129–130°; $[\alpha]_D + 33°$, CHCl₃) obtained by acetylation of galactose oxime under the conditions used by Behrend[2] for the acetylation of mutarotatory substances without change of structure. These two hexaacetates are represented by the formulas

HC=NOAc	H\C/N(Ac)OAc
(CHOAc)₄	(CHOAc)₃ O
CH₂OAc	CH——
Aldehydo-galactose	CH₂OAc
oxime hexaacetate	α-Galactose oxime
I	hexaacetate
	II
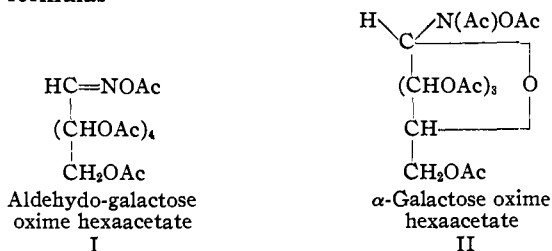
The structure of compound I above is determined from its method of synthesis from aldehydo-galactose pentaacetate.[3] The ring structure of compound II is determined by its non-identity with compound I. The only other alternative is that these acetates are isomers of the *syn–anti* type. This may be excluded by the fact that the two substances are not directly interconvertible and also by the fact that this type of isomerism is not at all established in aliphatic aldoximes. The ring assignment (1,5) of formula II is arbitrary but the exact size of the ring is not pertinent in this work. Since galactose oxime (un-acetylated) exhibits mutarotation in the levo direction, the designation α is given to its acetate in accordance with the classification of Hudson.[4] In this respect the oxime of galactose differs from that of glucose, which mutarotates in the opposite sense.

The above work may also be used as proof of the existence of a ring structure in α-galactose oxime. This substance is thus similar to the

[1] M. L. Wolfrom and Alva Thompson, THIS JOURNAL, 53, 622 (1931). In this communication we reported the synthesis of mannononitrile pentaacetate. This was also reported practically simultaneously by V. Deulofew, *J. Chem. Soc.*, 2602 (1930).

[2] R. Behrend and P. Roth, *Ann.*, 331, 359 (1904); R. Behrend, *ibid.*, 353, 109 (1907).

[3] M. L. Wolfrom, THIS JOURNAL, 52, 2464 (1930).

[4] C. S. Hudson, *ibid.*, 31, 66 (1909).

ammonia condensation product of galactose which has been assigned a ring structure by Levene[5] on the basis of its reactivity with nitrous acid. It differs from the hydrazones of galactose, which have been shown to be open chain or true hydrazones.[6] The same sugar may thus show a varying type of nitrogen condensation product.

Aldehydo-galactose pentaacetate was condensed with hydroxylamine in aqueous solution, in which this acetate exists as the aldehydrol. The resultant product was a monohydrate. Chloral hydrate likewise gives a hydrated oxime which has been formulated as $CCl_3CH(OH)NHOH$. In the case of the galactose compound the water was readily removed to produce the crystalline anhydrous substance. The practical identity of the molecular rotations in chloroform of the hydrated (13,500) and the anhydrous (13,800) galactose compounds is proof that the mole of water is not constitutional (primary valence) but is held by secondary valence forces. This may represent the first clear differentiation between a constitutional and non-constitutional hydrate and was made possible by the optical activity of the substances and by the solubility of the hydrate in a non-aqueous medium. A constitutional hydrate is exemplified by the aldehydrol of aldehydo-galactose pentaacetate ($[\alpha]_D + 23°$, $CHCl_3$) which has a rotation widely different from its anhydrous form ($[\alpha]_D -25°$, $CHCl_3$). A hydrated sugar acetate not containing a free carbonyl group is unusual, but recently Haworth and Hickinbottom[7] have reported a monohydrate of a partially acetylated non-reducing sugar, neotrehalose heptaacetate.

The one known form of galactose oxime was prepared by Rischbieth[8] and was the first crystalline sugar oxime obtained. Its mutarotation in water was noted by Jacobi,[9] but his constants have been considerably revised in this work. It is interesting to note that the aldehydo-galactose oxime acetates reverted to the ring form on alkaline de-acetylation.

All substances reported herein were obtained in pure crystalline form.

Experimental

Mutarotation of α-Galactose Oxime.—α-Galactose oxime was prepared according to the directions of Wohl[10] and was recrystallized from hot water. After one recrystallization the melting point of 176–178° (with decomposition) was obtained. This was unchanged by further recrystallization. In water solution at 25° the rotation shown was $[\alpha]_D +84°$ (extrapolated initial value) $\longrightarrow +14.5°$ (final) (c, 1.014; α +0.58° (final); 4-dm. tube). The melting point and final rotation values obtained are in good agreement with the literature. Rischbieth[8] obtained the melting point 175–176° and Jacobi[9]

5 P. A. Levene, J. Biol. Chem., 24, 59 (1916).

6 M. L. Wolfrom and Clarence C. Christman, THIS JOURNAL, 53, 3413 (1931).

7 W. N. Haworth and W. J. Hickinbottom, J. Chem. Soc., 2847 (1931).

8 P. Rischbieth, Ber., 20, 2673 (1887).

9 H. Jacobi, ibid., 24, 696 (1891).

10 A. Wohl, ibid., 30, 3103 (1897).

recorded the rotation in water as $[\alpha]_D$ +20.7° (ten minutes) changing to $[\alpha]_D$ +14.7° (final) for a concentration of 5% by volume. We found a much higher value for the initial rotation although the mutarotation was in the same direction. From the solution concentration recorded by Jacobi, it seems probable that initial heating was performed to effect solution before taking the first reading.

α-Galactose Oxime Hexaacetate.—Five grams of α-galactose oxime was treated with 30 cc. of pyridine and 20 cc. of acetic anhydride. After standing overnight, the solution was poured into ice water, whereupon the acetate crystallized immediately; yield, 6.5 g. After two recrystallizations performed by dissolving in a rather large volume of warm ethanol, cooling to room temperature, and adding water to incipient opalescence, the melting point was 130°, unchanged by further recrystallization. The rotation in U. S. P.[11] chloroform of the recrystallized material was $[\alpha]_D^{25}$ +32.1° (c, 3.02, α +0.97°, 1-dm. tube). Further recrystallization gave the value $[\alpha]_D^{23}$ +33.7° (c, 3.470, α +1.17°, 1-dm. tube) in the same solvent. This value was unchanged over an eighteen-hour period. The substance crystallized in six-sided plates. It was very soluble in chloroform, methyl alcohol, acetone and benzene; soluble in ether and ethyl alcohol; sparingly soluble in petroleum ether and water on heating.

The same product was obtained by acetylating below room temperature, but in lower yield due to the insolubility of α-galactose oxime in the acetylating mixture. A mixture of 18 cc. of pyridine and 12 cc. of acetic anhydride was cooled to 0° and 3 g. of solid α-galactose oxime added. The mixture was shaken mechanically at 0° for several hours and then placed overnight in the ice box. At the end of that period a considerable portion of the oxime had not dissolved. The supernatant liquor was poured into 60 cc. of ice water. The product crystallized readily. It was filtered and washed with cold water; yield, 0.6 g. On one recrystallization from alcohol and water the melting point was 130–131° and showed no depression on admixture with material (m. p. 130°) obtained by room temperature acetylation.

Anal. Subs., 0.5060: 67.50 cc. of 0.1 N NaOH; subs., 0.3120: N_2, 11.5 cc. (746.1 mm., 31°). Calcd. for $C_6H_7O_6N(COCH_3)_6$: 13.4 cc. of 0.1 N NaOH per 100 mg.; N, 3.14. Found: 13.3 cc. 0.1 N NaOH; N, 3.88. The acetyl or saponification value was determined by distillation at constant volume with 15% phosphoric acid.

Aldehydo-galactose Oxime Pentaacetate Monohydrate.—Seven grams (1 mole) of aldehydo-galactose pentaacetate ethyl hemi-acetal was dissolved in 90 cc. of warm water, cooled to room temperature and a solid mixture of 3.5 g. of potassium acetate (2 mols) and 1.7 g. of hydroxylamine hydrochloride (1.5 mols) added to the solution and the mixture shaken until the added solids were dissolved. A heavy crystallization was immediately initiated on scratching the sides of the container. The crystals were removed by filtration and washed with cold water; yield, 4.5 g.; m. p. 104–106°; $[\alpha]_D^{29}$ +32.0° (c, 2.499; α +0.80°; 1-dm. tube; U. S. P. CHCl$_3$). After three recrystallizations from dilute alcohol, the melting point was 112–114° and the rotation was $[\alpha]_D^{29}$ +32.0° (c, 2.53; α +0.81°; 1-dm. tube; U. S. P. CHCl$_3$). This melting point was unchanged by further recrystallization. The substance showed no tendency to mutarotate in chloroform solution, thus differing from aldehydogalactose pentaacetate aldehydrol. The compound crystallized in lustrous, six-sided, diamond-shaped plates and was very soluble in chloroform and acetone, soluble in benzene and ether, moderately so in ethyl alcohol and warm water and was practically insoluble in petroleum ether.

Anal. Subs., 0.2394: CO_2, 0.4013; H_2O, 0.1290. Subs., 0.3196: 10.40 cc. N_2 (744 mm., 22°). Subs., 0.2601, 0.2000: 31.00, 23.30 cc. 0.1 N NaOH. Calcd. for $C_6H_8O_6N(COCH_3)_5 \cdot H_2O$: C, 45.36; H, 5.95; N, 3.28; 11.8 cc. 0.1 N NaOH per 100 mg. subs. Found: C, 45.71; H, 6.03; N, 3.60; 11.9, 11.7 cc. 0.1 N NaOH.

[11] United States Pharmacopoeia.

The substance lost the equivalent of one mole of water on heating over sulfuric acid to constant weight under reduced pressure at 96–97°.

Anal. Subs., 0.2424: loss in weight, 0.0103. Subs., 0.1580: loss in weight. 0.0067. Calcd.: H_2O, 4.25. Found: 4.25, 4.24.

De-acetylation of the hydrated substance yielded α-galactose oxime. Aldehydo-galactose oxime pentaacetate monohydrate (5 g.) was dissolved in 125 cc. of methanol and cooled in an ice–salt mixture. Dry ammonia gas was then passed through the solution for about forty minutes. The flask was placed in the ice box overnight and the next day was evaporated to dryness in a vacuum desiccator at room temperature. The acetamide formed in the reaction was extracted from the residue with cold methanol. The yield of the crude galactose oxime so obtained was 1.3 g. melting at 160–165°. On one recrystallization from hot water the melting point was raised to 176–178°, which is the melting point of authentic α-galactose oxime. In water solution the rotation of the product was $[\alpha]_D^{26}$ +83° (extrapolated) $\longrightarrow$ +14.1° (c, 1.134; α +0.16° (final); 1-dm. tube). The values previously found for α-galactose oxime were $[\alpha]_D$ +84° $\longrightarrow$ 14.5°.

Aldehydo-galactose Oxime Pentaacetate.—This substance was prepared from the monohydrate by heating under reduced pressure over calcium chloride at 95–97°. Under these conditions the product did not fuse, the crystals merely appearing to lose their luster. On recrystallization from dry benzene the substance melted at 118–120°. The rotation in U. S. P. chloroform was $[\alpha]_D^{25}$ +34.0° (c, 4.994; α +1.70°; 1-dm. tube). Another sample gave the value $[\alpha]_D^{26}$ +34.0° (c, 5.146; α +1.75°; 1-dm. tube).

Anal. Subs., 0.2050, 0.1945: 25.2, 23.8 cc. 0.1 N NaOH. Calcd. for $C_6H_8O_6N$-$(COCH_3)_5$: 12.35 cc. 0.1 N NaOH per 100 mg. subs. Found: 12.3, 12.2 cc. On recrystallization from hot water the monohydrate was reformed, as the following acetyl values show: subs., 0.2000, 0.1794: 23.9, 21.3 cc. 0.1 N NaOH. Calcd., 11.8 cc. per 100 mg. Found: 11.9, 11.9 cc.

Aldehydo-galactose Oxime Hexaacetate.—Five grams of aldehydo-galactose oxime pentaacetate monohydrate was added to a mixture of 15 cc. of acetic anhydride and 30 cc. of pyridine, previously cooled to 0°. After solution of the solid the solution was placed in the ice box for one hour. The mixture was then poured into water. The product crystallized immediately and was filtered and washed with water; yield, 3.8 g.; m. p. 144–145°. After one recrystallization performed by dissolving in alcohol and adding water, the substance melted at 146°. Another portion of the crude material was recrystallized four times from acetone, once from alcohol, and again from acetone. The melting point of the final product was then 144–146°. The original product crystallized from the water solution showed a rotation in U. S. P. chloroform solution of $[\alpha]_D^{27}$ +23.7° (c, 2.023; α +0.48°; 1-dm. tube) without mutarotation. The rotation of the purified product in the same solvent was $[\alpha]_D^{24}$ +22.5° (c, 4.00: α +0.91°; 1-dm. tube). The substance is very soluble in chloroform; soluble in acetone; slightly soluble in methyl and ethyl alcohol; practically insoluble in ether, benzene, water and petroleum ether. The solubilities were thus quite different from those of α-galactose oxime hexaacetate. A mixed melting point of the substance (m. p. 145–146°) with α-galactose oxime hexaacetate (m. p. 129–130°) was 138–143°.

Anal. Subs., 0.2628: 35.00 cc. 0.1 N NaOH. Subs., 0.3091: N_2, 9.72 cc. (744 mm., 23°). Calcd. for $C_6H_7O_6N(COCH_3)_6$: 13.4 cc. 0.1 N NaOH per 100 mg.; N, 3.13. Found: 13.3 cc.; N, 3.45. The acetyl or saponification value was determined by distillation at constant volume with 15% phosphoric acid.

This substance was de-acetylated in the manner recorded for the hydrated oxime pentaacetate and likewise produced α-galactose oxime. The melting point of the purified product was 177–178°, melting at 176–178° in admixture with authentic α-galactose oxime (m. p. 176–178°).

Summary

1. α-Galactose oxime hexaacetate and the hexaacetate and penta-acetate of aldehydo-galactose oxime have been synthesized in pure crystalline form.

2.   It is shown that the two oxime hexaacetates above are isomers of the ring–open chain type.

3.   The mole of water in the hydrate of aldehydo-galactose oxime penta-acetate has been shown to be held by non-constitutional or secondary valence forces.

4.   Galactose oxime has been shown to possess a ring structure of the α-type.

5.   The acetylated aldehydo-galactose oximes revert to the ring form on alkaline de-acetylation.

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A POTENTIOMETRIC STUDY OF SCHOLL'S ANTHROXYL RADICALS

BY LOUIS F. FIESER AND WAI YUN YOUNG

It is generally agreed that the primary oxidation products of all of the monatomic phenols are radicals having univalent oxygen atoms ("oxyls"). The radicals ordinarily are too unstable to have any but a transitory existence, for the free valence shifts from oxygen to carbon and the carbyl radical undergoes various secondary changes.   In chlorophenanthrol Goldschmidt and Steigerwald[1] found a compound in which, probably because of the blocking of the positions ortho and para to the oxygen atom, this wandering of the free valence does not occur.   Their phenanthroxyls, however, were not completely stable, but associated to form dimolecular peroxides.   It remained for Scholl to discover a type of radical which does not manifest even this second kind of instability.[2]   That his blue-violet aryl-hydroxyl-*peri*-hydrofurano-anthroxyls of the type of I are strictly monomeric may be due to the spatial characteristics of the anthracene

O⁻ … OH structures

O—C(OH)Ar   O—C(OH)Ar
        I   II

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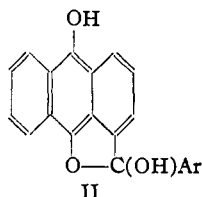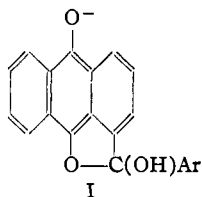
[1] Goldschmidt and Steigerwald, *Ann.*, **438**, 202 (1924).

[2] Scholl, *Ber.*, **64**, 1158 (1931).