[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY AND FROM THE INSTITUTO DE FISIOLOGIA]

The Acetylation of Galactose Oxime

BY VENANCIO DEULOFEU, M. L. WOLFROM, PEDRO CATTANEO, C. C. CHRISTMAN AND L. W. GEORGES

In a previous publication[1] the product obtained by the low temperature acetylation of the one known form of galactose oxime has been characterized as a homogeneous substance and was termed α-galactose oxime hexa-acetate. Further work initiated by some of us (V. D. and P. C.) has shown that this substance is not homogeneous but consists of mixed crystals of aldehydo-galactose oxime hexa-acetate, reported by Wolfrom, Thompson and Georges,[1] and galactonic acid nitrile penta-acetate. When these two substances are present in about equal proportions they crystallize together and are practically impossible to separate, thus indicating a molecular compound or at least a very bad type of mixed crystal. The compositions of these two substances are so nearly alike that they cannot be differentiated in an equal mixture. Accordingly this problem was thoroughly re-investigated in the two laboratories concerned and we wish to publish the results as a joint communication.

It has now been found that the acetylation of galactose oxime by pyridine and acetic anhydride at low temperatures is a complex reaction and accordingly cannot be used as a proof of structure for galactose oxime. The reaction is intermediate between the low temperature acetylation of glucose oxime and that of the pentose oximes. Glucose oxime produces the ring form of the acetylated oxime, β-glucose oxime hexa-acetate, as has been shown by Wolfrom and Thompson.[2] On the other hand, recent work of Deulofeu[3] has shown that the same conditions applied to the oximes of arabinose and xylose lead exclusively to the acetylated nitriles of these substances. We have also found that further mild acetylation of the oxime of the open chain form of arabinose tetra-acetate leads exclusively to the formation of arabonic acid nitrile penta-acetate. Now the work of Wohl[4] has long ago shown that high temperature acetylation of the sugar oximes leads to the formation of the corresponding acetylated nitriles. It now appears that the temperature at which this reaction takes place may vary considerably with different sugars and that with certain sugars it may occur readily without heating.

The experimental results herein reported show that the mild acetylation of galactose oxime with pyridine and acetic anhydride produces three substances in varying amounts. These are galactonic acid nitrile penta-acetate, aldehydo-galactose oxime hexa-acetate and an isomeric levorota-

---

[1] Wolfrom, Thompson and Georges, THIS JOURNAL, **54**, 4091 (1932).

[2] Wolfrom and Thompson, *ibid.*, **53**, 622 (1931).

[3] Unpublished work.

[4] Wohl, *Ber.*, **26**, 730 (1893).

tory oxime hexa-acetate. The second compound is identical with that obtained by further mild acetylation of the oxime obtained from aldehydogalactose oxime penta-acetate. This method of synthesis is proof of its open chain structure. It produces the acetylated nitrile on mere fusion to slightly above its melting point. This behavior is similar to that shown by the corresponding glucose compound. The levorotatory oxime hexa-acetate may be characterized as a ring structure by its non-identity with the open chain oxime acetate and by the fact that a further investigation of the synthetic step by which the latter was formed failed to detect any of this levorotatory isomer. Like β-glucose oxime hexa-acetate, the substance does not produce the acetylated nitrile on fusion nor on heating with acetic anhydride and sodium acetate.

Thus it is found that in the reaction under consideration both ring and open chain forms are produced. Wolfrom and Thompson[2] also found the same for glucose oxime, except that much more vigorous conditions were required. Although none of the data herein reported can be used to elucidate the structure of galactose oxime, the nature of the water mutarotation of the substance points to a possible ring structure. In that case the ring opens very readily. Increasing evidence is thus being accumulated to show that sugar ring structures tend to open and form open chain derivatives. The recent work of Pacsu[5] and of Brigl and Schinle[6] on fructose is also in harmony with this view.

Experimental

Acetylation of Galactose Oxime at 25°.—Galactose oxime (5 g.) was added to a solution of 30 cc. of pyridine and 20 cc. of acetic anhydride and the whole mechanically shaken with the flask immersed in a large reservoir of water at 23°. A thermometer in the solution did not rise above 25°. Solution was effected in a few hours. The solution was then allowed to stand overnight at room temperature (27°), no further heat of reaction being developed. At the end of this period the crystals formed were removed by filtration and washed with cold pyridine followed by petroleum ether, the washings being discarded; yield, 2.0 g.; m. p. 145.5–146.5° (m. p. 146–147° on admixture with aldehydogalactose oxime hexa-acetate of m. p. 146° and $[\alpha]_D$ +23.3°, $CHCl_3$, prepared from aldehydogalactose penta-acetate); $[\alpha]^{24}_D$ +23.6°, $CHCl_3$ (c, 3.993; α +3.76°; l, 4 dm.). The filtrate from the above filtration was poured into ice and water and the crystalline material removed by filtration; yield, 5.2 g.; m. p. 110–125°; $[\alpha]^{23}_D$ +14.3°, $CHCl_3$ (c, 4.004; α + 2.30°; l, 4 dm.). In this experiment the aqueous filtrate was discarded.

The above procedure was repeated with three 5-g. runs of galactose oxime. In this case, however, only 0.3 g. of aldehydo-galactose oxime hexa-acetate crystallized out of the combined acetylation reagents even after standing in the ice box; m. p. 145–146° (144–146° mixed with aldehydogalactose oxime hexa-acetate of m. p. 144–145°). The water-insoluble material obtained weighed 20.7 g.; m. p. 110–125°; $[\alpha]^{22}_D$ +13.0°, $CHCl_3$ (c, 3.990; α +2.08°; l, 4 dm.). The aqueous filtrate was extracted with chloroform and the extract concentrated under reduced pressure at room temperature

---

(5) Pacsu and Rich, THIS JOURNAL, **54**, 1697 (1932).

(6) Brigl and Schinle, *Ber.*, **66**, 325 (1933).

to a thick magma of sirup and crystals containing pyridine. These were stirred with cold water, filtered and washed with ice water and recrystallized from alcohol by the addition of water; yield, 3.3 g.; m. p. 106°; $[\alpha]^{22}_{D}$ −27.4°, $CHCl_3$ (*c*, 4.073; α −4.46°, *l*, 4 dm.). After two recrystallizations from absolute alcohol the substance melted at 105° and showed $[\alpha]^{21}_{D}$ −27.3°, $CHCl_3$ (*c*, 3.973; α −4.34°, *l*, 4 dm.). After two further recrystallizations from acetone by the addition of water the melting point was 106° and the rotation was $[\alpha]^{23}_{D}$ −27.5°, $CHCl_3$ (*c*, 3.995; α −4.40°; *l*, 4 dm.). The substance crystallized in colorless, individual, complicated prisms and was apparently very pure.

Anal. Subs., 0.3419: N_2, 10.00 cc. (729.1 mm., 23°). Acetyl: Subs., 0.3036: 40.67 cc. 0.1 *N* NaOH (by distillation at constant volume with 15% H_3PO_4). Subs., 0.2600: 34.36 cc. (Freudenberg method).[7] Calcd. for $C_6H_7O_6N(CH_3CO)_6$: N, 3.14. Found: 3.14. Calcd. for acetyl, 0.1000: 13.4 cc. 0.1 *N* NaOH. Found: 13.4, 13.2.

The levorotatory isomer may be isolated from the water-insoluble fraction by the following procedure. An amount of 14 g. of this material ($[\alpha]_D$ +13 to +14°, $CHCl_3$; m. p. 110–125°) was digested with 400 cc. of hot water, filtered, cooled to 0° and filtered again. The filtrate was extracted with chloroform to yield 4.4 g. of extracted crude levorotatory material. After repeated alcohol recrystallization there was obtained from this 0.9 g. of pure product; m. p. 106°; $[\alpha]_D$ −27.5°, $CHCl_3$. The substance was very soluble in chloroform and acetone; soluble in benzene and hot alcohol and hot water, moderately so in ether and practically insoluble in petroleum ether.

The remaining material obtained in the acetylation of the galactose oxime consisted mainly of the crystalline fraction rotating around +30° in chloroform and melting around 130°. This is identical with that previously described by Wolfrom, Thompson and Georges as α-galactose oxime hexa-acetate but it is now found to be mixed crystals containing the aldehydogalactose oxime hexaacetate and galactonic acid nitrile pentaacetate in approximately an equimolecular proportion. A constant, but not sharp, melting point at 130–131° is obtained on recrystallization from alcohol by the addition of water. By repeated ether treatment the aldehydogalactose oxime hexa-acetate of m. p. 145–146° could be obtained in very low yield from the less soluble ether fractions. The presence of the more soluble acetylated nitrile was demonstrated by the analytical method of Zemplén,[8] which gave a corrected figure of approximately 50%. This method gives low values, but it serves as an excellent semi-quantitative method for the detection of the acetylated nitrile, as a control showed that the aldehydogalactose oxime hexaacetate gave only a trace of silver cyanide. The rotation of the mixture is also in agreement for that calculated for an approximately equimolecular mixture of the two compounds. A known mixture of the two substances behaved in a similar manner and the microscopic appearance of the crystalline mixture was also similar. As an example of the nature of this fraction, the following may be cited. Pure galactonic acid nitrile penta-acetate (2.3 g.) and aldehydo-galactose oxime hexa-acetate (2.7 g.) were mixed to obtain an equimolecular mixture and recrystallized from alcohol. The rotation of the product was $[\alpha]_D$ +32.1°, $CHCl_3$. This was recrystallized twice more from alcohol; $[\alpha]_D$ +32.5°, $CHCl_3$. An ether recrystallization was then effected; 0.7 g.; m. p. 135–137° (m. p. 127–129° on admixture with galactonic acid nitrile penta-acetate of m. p. 137–138°); $[\alpha]_D$ +31.9°, $CHCl_3$. No appreciable separation was thus effected.

The acetylated nitrile was obtained by pyridine (6 parts) and acetic anhydride (4 parts) acetylation of galactose oxime at 110° for one hour. The crystalline product obtained by pouring the reaction mixture into water was recrystallized several times from alcohol; m. p. 138° (m. p. 138° on admixture with galactonic acid nitrile penta-acetate

---

[7] Freudenberg and Harder, *Ann.*, **433**, 230 (1923).

[8] Zemplén, *Ber.*, **59**, 1259 (1926).

of m. p. 138°, but melting at 125° with aldehydo-galactose oxime hexa-acetate of m. p. 145–146°).

The acetylation of the oxime at 0° was difficult because of its very low solubility in the acetylating reagents at this temperature. An investigation of the reaction product obtained gave a very low yield of the open chain oxime hexa-acetate, but the main product was the +30° mixture.

Acetylation of Galactose Oxime with Sodium Acetate.—Sodium acetate (10 g.) and 70 cc. of acetic anhydride were mixed and heated to boiling. The source of heat was then withdrawn and 10 g. of finely powdered galactose oxime added in small portions so as to maintain the mixture at or just short of the boiling point by the reaction heat evolved. After the addition, the dark solution was poured into one liter of water, chipped ice added and the mixture allowed to stand for a few hours. The dark brown crystalline precipitate was removed by filtration and washed with ice water (11.7 g.). The filtrate was partially neutralized by the addition of 75 g. of sodium bicarbonate and extracted with chloroform. On evaporation of the extract under reduced pressure a crystalline product was obtained. After one recrystallization from alcohol 2.7 g. of crystals was obtained; m. p. 105°; $[\alpha]^{23}_{\mathrm{D}}$ −24.7°, CHCl$_3$ (*c*, 4.274; α −2.11°; *l*, 2 dm.). After two further alcohol recrystallizations, there was obtained 1.9 g. of substance; m. p. 106°; $[\alpha]^{25}_{\mathrm{D}}$ −27.6° (*c*, 4.022; α −4.45°; *l*, 4 dm.).

The crude water-insoluble fraction above was recrystallized once from alcohol (carboraffin, repeatedly), once from hot dilute alcohol, and thrice from alcohol by the addition of water; yield, 3.6 g.; m. p. 138–139°; $[\alpha]^{25}_{\mathrm{D}}$ +43.2°, CHCl$_3$ (*c*, 4.056; α +7.01°; *l*, 4 dm.). These constants may be accepted for pure galactonic acid nitrile penta-acetate. The melting point given by Wohl and List[9] was 135°. These workers did not cite any rotation. The properties of the product were in agreement with those given by Wohl and List. Thus the vigorous acetylation of galactose oxime produces the acetylated nitrile and also the levorotatory oxime hexa-acetate. This behavior is similar to that of glucose oxime.

Reactivity of Aldehydogalactose Oxime Hexa-acetate.—This compound produced the acetylated nitrile on fusion. Three 2-g. lots of pure aldehydogalactose oxime hexa-acetate were carefully heated to slightly above the melting point, whereupon a vigorous evolution of acetic acid was noted. On cooling the melt readily crystallized and the product was thrice recrystallized from alcohol; yield, 2.0 g.; m. p. 137–138° (m. p. 138–139° on admixture with authentic acetylated nitrile of m. p. 138–139°; $[\alpha]^{22}_{\mathrm{D}}$ +42.8°, CHCl$_3$ (*c*, 4.007; α +3.43°; *l*, 2 dm.).

The substance also underwent nitrile formation on heating with sodium acetate and acetic anhydride. A mixture of 4.2 g. of aldehydogalactose oxime hexa-acetate, 4.2 g. of fused sodium acetate and 17 cc. of acetic anhydride was heated in an oil-bath for twenty minutes at 137–138°. The dark mixture was then poured into ice water and the resulting dark colored sirup washed twice with water. The residue was dissolved in 250 cc. of boiling water, treated with norite and filtered. Crystals of the nitrile acetate separated on cooling; yield, 0.9 g.; m. p. 136–138° (unchanged on admixture with galactonic acid nitrile penta-acetate of m. p. 136–137°); $[\alpha]^{28}_{\mathrm{D}}$ +43.7°, CHCl$_3$ (*c*, 3.93; α +1.72°; *l*, 1 dm.).

Although vigorous acetylation conditions transform the aldehydogalactose oxime hexa-acetate into the acetylated nitrile, this transformation is not effected by certain of the mild conditions which are sufficient to transform the free oxime. The substance was recovered unchanged under the following conditions with the previously cited proportions of pyridine and acetic anhydride: fifteen hours at 50°; one minute at boiling; one hour at 70°. However, on heating at 110° for one hour the previously cited mixture with the 130° melting point was obtained.

---

(9) Wohl and List, *Ber.*, **30**, 3101 (1897).

Reactivity of the Levorotatory Form of Galactose Oxime Hexa-acetate.—In order to be certain that this substance was not a readily interconvertible *syn* or *anti* form of the aldehydogalactose oxime hexa-acetate of m. p. 146°, the further acetylation of aldehydogalactose oxime penta-acetate monohydrate was re-investigated. It was found that the yield reported by Wolfrom, Thompson and Georges[1] could readily be raised and a thorough investigation of all mother liquors failed to yield a trace of this readily isolable levorotatory isomer.

On heating this oxime hexa-acetate of m. p. 106° and $[\alpha]_D$ −27°, $CHCl_3$, above its melting point it merely darkened and decomposed without any noticeably vigorous evolution of acetic acid. The substance did not undergo nitrile formation and was recovered unchanged on heating with sodium acetate and acetic anhydride for some time at 145–149°.

Aldehydo-*l*-arabinose Oxime Tetra-acetate.—Aldehydo-*l*-arabinose tetra-acetate[10] (9.5 g.) was dissolved in 180 cc. of warm water, cooled to room temperature and a solid mixture of 2.1 g. of hydroxylamine hydrochloride and 4.5 g. of potassium acetate added with shaking. After solution of the solids, the sides of the flask were scratched, and after about five minutes the solution became turbid and fine crystals separated. These were filtered and washed with water; yield, 5.0 g.; m. p. 131–134°. The substance was twice recrystallized from hot water; m. p. 137–139°; $[\alpha]^{22}_D$ −5.2°, $CHCl_3$ (*c*, 5.111; α −1.07°; *l*, 4 dm.). After another recrystallization the melting point was 136–137°; $[\alpha]^{26}_D$ −5.2°, $CHCl_3$ (*c*, 4.371; α −1.06°; *l*, 4 dm.). The substance was very soluble in chloroform, acetone and methyl alcohol, soluble in ether, moderately so in hot water and practically insoluble in petroleum ether.

Anal. Subs., 0.2568: N_2, 10.55 cc. (741.7 mm., 23°). Acetyl: subs., 0.3099: 37.56 cc. 0.1 *N* NaOH (by distillation at constant volume with 15% H_3PO_4). Calcd. for $C_5H_7O_5N(COCH_3)_4$: N, 4.20. Found: 4.49. Calcd. for acetyl: 12.0 cc. 0.1 *N* NaOH per 100 mg. Found: 12.1 cc.

Mild Acetylation of Aldehydo-*l*-arabinose Oxime Tetra-acetate.—Further acetylation of this substance according to the methods successfully used with the corresponding compounds in the glucose and galactose series produced *l*-arabonic acid nitrile tetra-acetate. Aldehydo-*l*-arabinose oxime tetra-acetate (2.7 g.) was added to a mixture of 7 cc. of acetic anhydride and 14 cc. of pyridine, previously cooled to 0°. The substance dissolved readily and the solution was allowed to stand at ice box temperature for three hours and was then poured into 150 cc. of ice water; yield, 1.2 g.; m. p. 113–115°. The substance was recrystallized from hot water; m. p. 120–121° (m. p. 120–121° on admixture with *l*-arabonic acid nitrile tetra-acetate of m. p. 120–121°); $[\alpha]^{28}_D$ +2.8°, $CHCl_3$ (*c*, 0.88; α +0.10°; *l*, 4 dm.). Wohl[11] gave the melting point of 117–118° for this substance but did not record its rotation. The chloroform rotation of the purified product prepared according to these authors' directions was $[\alpha]^{24}_D$ +3.4°, $CHCl_3$ (*c*, 5.061; α +0.70°; *l*, 4 dm.) and the melting point was found to be 120–121°. The product is therefore identified as the acetylated nitrile.

Anal. Acetyl: subs., 0.2560: 32.79 cc. 0.1 *N* NaOH (H_3PO_4 method). Calcd. for $C_4H_5O_4(COCH_3)_4CN$: 12.7 cc. 0.1 *N* NaOH per 100 mg. Found: 12.8 cc.

Summary

1. Aldehydo-*l*-arabinose oxime tetra-acetate and a new isomeric form of galactose oxime hexa-acetate have been synthesized in pure crystalline form. Evidence is given that the latter compound is very probably a ring isomer.

---

(10) Wolfrom and Newlin, This Journal, **52**, 3619 (1930).

(11) Wohl, *Ber.*, **26**, 744 (1893).

2. Mild pyridine acetylation of galactose oxime produces aldehydo-galactose oxime hexa-acetate, galactonic acid nitrile penta-acetate and the isomeric galactose oxime hexa-acetate (m. p. 106°; $[\alpha]_D$ −27°, $CHCl_3$). Vigorous acetylation produces the last two compounds.
3. Aldehydo-galactose oxime hexa-acetate undergoes nitrile formation but this behavior is not shown by the levorotatory oxime hexa-acetate.
4. The previously reported α-galactose oxime hexa-acetate is a mixture and accordingly the dependent proof that galactose oxime possesses an *alpha* ring structure is invalidated.
5. Mild acetylation of aldehydo-*l*-arabinose oxime tetra-acetate produces *l*-arabonic acid nitrile tetra-acetate.

COLUMBUS, OHIO
BUENOS AIRES, ARGENTINA

RECEIVED MAY 10, 1933
PUBLISHED AUGUST 5, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

Aldehyde–Amide Condensation. I. Reactions between Aldehydes and Acetamide

BY WILLIAM A. NOYES AND DON B. FORMAN

The best known aldehyde–amide condensations are those that take place between urea and formaldehyde to give polymeric compounds. However, amides have been condensed with aldehydes to form bimolecular compounds. This is illustrated by the reactions of acetamide with formaldehyde,[1] acetaldehyde,[2] propylaldehyde[3] and benzaldehyde.[4,5]

These reactions have been found to be general for alkyl and aryl aldehydes, as the accompanying table will show. In each case, a small amount of acetic acid catalyzes the condensations, which take place according to the following equation

$$RCHO + 2CH_3CONH_2 \longrightarrow (CH_3CONH)_2CHR + H_2O$$

TABLE I

THE YIELDS ARE BASED UPON THE ACETAMIDE USED

Aldehyde	Product, diacetamide	M. p., °C.	Yield, %	Nitrogen analyses, % Calcd.	Found
Form-	Methylene-	197.5–198	54	21.53	21.42
Acet-	Ethylidene-	180	44	19.42	18.97
Propyl-	Propylidene-	190–190.5	7.5	17.72	16.94
Butyl-	Butylidene-	189	11.5	16.28	16.17
Isovaleryl-	1-Methylbutylidene-4-	184	26	15.05	15.04
Heptyl-	Heptylidene-	171–172	6.5	13.08	13.18
Benz-	Benzylidene-	238	48	13.59	14.00

---

(1) G. Pulvermacher, *Ber.*, **25**, 304 (1892).
(2) V. v. Richter, *ibid.*, **5**, 477 (1872).
(3) A. Reich, *Monatsh.*, **25**, 933 (1904).
(4) K. Bulow, *Ber.*, **26**, 1973 (1893).
(5) Roth, *Ann.*, **154**, 72 (1870).