versity of Pennsylvania School of Medicine. The compounds were dissolved in ethylene glycol and injected intraperitoneally in white rats.

Menthyl urea in dosage of 220 mg. per kg. caused profound unconsciousness with the abolition of all reflexes. The narcosis appeared at the end of fifteen minutes and was undiminished seven hours after injection. At the end of twenty-two hours the animal had recovered completely and appeared normal. In dosage of 63 mg. per kg. there was definite drowsiness without visible muscular incoördination. The animal was easily aroused at all times and seemed normal when aroused. At twenty hours it was quite normal.

The low solubility of bromoacetylbornylurea and *p*-aminobenzoylmenthylurea made adequate testing impracticable. They had no demonstrable narcotic effects in the dosage used. Larger amounts of the solutions caused ethylene glycol poisoning.

Chloral menthylurea was clearly the most potent. It was the most toxic, slowest acting and most persistent of those tested.

Bornylurea and 2-keto-3-carbamidocamphane acted slowly and weakly with considerable muscular incoördination and the latter seemed to be intensely irritant locally.

Summary

1. *l*-Menthylurea, *d*-bornylurea and 2-keto-3-carbamidocamphane have been prepared by the nitrourea method.

2. The following new derivatives of *l*-menthylurea and *d*-bornylurea have been prepared: acetyl, bromoacetyl, chloral addition product, *p*-nitrobenzoyl and *p*-aminobenzoyl.

3. Preliminary tests on the narcotic effects of some of these ureas indicated that menthylurea was the most promising and may have some value. It acted rapidly without evident after-effects.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Esters of the Aldehydrol Form of Sugars

BY M. L. WOLFROM

Diacetates of aliphatic aldehydes, $RCH(OAc)_2$, have long been known but have been little studied. Some of the earliest work was carried out by Geuther,[1] who prepared these derivatives by heating aliphatic aldehydes with acetic anhydride at relatively high temperatures (180°). Later work[2] showed that the reaction was greatly accelerated by zinc chloride or sodium acetate. Aceto-halogen compounds of aliphatic aldehydes, RCHOAc·X, have also been prepared.[3] From the standpoint of organic structural theory, compounds of this type may be considered as esters of the aldehydrol, $RCH(OH)_2$, irrespective of whether the aldehydrol is an intermediate in their formation.

In the sugar series, the first representative of this type of compound was the crystalline triacetate of gycolaldehyde prepared by H. O. L. Fischer and Dangschat[4] by treating vinyl acetate dibromide with potassium acetate and also directly from the sugar by heating with acetic anhydride. Micheel and co-workers[5] have reported the synthesis of the *d*- and *d,l*- forms of *aldehydo*-galactose heptaacetate as incidental to their important synthetic experiments in the transformation of hexoses into inositols.

Aldehydo-galactose pentaacetate readily forms crystalline carbonyl addition compounds with alcohols and water, the reaction product with the latter being a true aldehydrol.[6] This addition takes place readily at room temperature. We have now found that acetyl halide addition compounds of *aldehydo*-galactose pentaacetate can be readily formed. The resulting compounds are the open chain analogs of the cyclic sugar acetohalogen derivatives and may be named, for example, *aldehydo*-1-chloro-*d*-galactose hexaacetate. In the work herein reported the chloride, bromide and iodide are described. Their rota-

(1) A. Geuther, *Ann.*, **106**, 249 (1858).

(2) G. Kauffmann, *Ber.*, **16**, 683 (1883); M. Descudé, *Compt. rend.*, **133**, 371 (1901).

(3) A. Wurtz, *Ann. chim. phys.*, [3] **49**, 58 (1857); V. Meyer and L. Dulk, *Ann.*, **171**, 65 (1874).

(4) H. O. L. Fischer and Gerda Dangschat, *Ber.*, **62**, 862 (1929).

(5) F. Micheel, H. Ruhkopf and F. Suckfüll, *ibid.*, **68**, 1523 (1935).

(6) M. L. Wolfrom, THIS JOURNAL, **52**, 2464 (1930); *ibid.*, **53**, 2275 (1931); M. L. Wolfrom and W. M. Morgan, *ibid.*, **54**, 3390 (1932).

tions increase in the above order, as could be predicted from the careful work of Brauns[7] on the cyclic acetohalogen sugars. Although these open chain acetohalogen compounds are quite stable, they tend to lose the acyl halide when subjected to metathetical reactions. The ease of carbonyl addition shown by *aldehydo*-galactose pentaacetates, is a property not shared by the other known aldehydo-acetates, but probably such derivatives could be prepared by the use of catalysts and work in this direction is in progress.

We have found that when the *aldehydo*-sugar acetates are subjected to further acetylation, the carbonyl diacetate compounds are obtained. We wish to report herein the glucose and arabinose derivatives, which may be named *aldehydo-d*-glucose heptaacetate and *aldehydo-l*-arabinose hexaacetate. These compounds are very much more stable than the corresponding free carbonyl compounds and are more easily isolated. They may be expected to be formed occasionally in reactions involving cyclic sugar derivatives. On the other hand, Montgomery and Hudson[8] isolated the free carbonyl form of *aldehydo-d-α*-mannoheptose hexaacetate by a relatively mild acetylation of the free sugar with acetic anhydride and sodium acetate. The acetylation methods we have used involve the use of acetic anhydride with pyridine or zinc chloride, the reactions being carried out at room temperature.

Experimental

Aldehydo-1-chloro-*d*-galactose Hexaacetate.[9]—*Aldehydo*-galactose pentaacetate ethyl hemiacetal[6a] (5 g.) was dissolved in 50 cc. of hot acetyl chloride and the cooled solution poured with stirring into about a liter of ice and water. The product separated at once as colorless crystals which were filtered and washed with ice water; yield, 3.4 g. Pure material was obtained after several recrystallizations from ethanol; m. p. 174–175°; $[\alpha]_D^{27}$ −44° (*c*, 4.0; $CHCl_3$). The substance crystallized in individual diamond-shaped plates and showed no tendency to decompose on standing. It was soluble in chloroform and acetone, sparingly so in hot ethanol, and was practically insoluble in ether and petroleum ether.

Anal. Calcd. for $C_6H_7O_6(COCH_3)_6Cl$: Cl, 7.57; saponification value (7 equivalents), 14.9 cc. 0.1 *N* NaOH per 100 mg.; mol. wt., 469. Found: Cl, 7.33; 14.7 cc. 0.1 *N* NaOH; OEt, negative; mol. wt. (Rast), 476.

The same substance was obtained by starting either with the free carbonyl or aldehydrol forms of *aldehydo*-galactose pentaacetate.

Aldehydo-1-bromo-*d*-galactose Hexaacetate.[10]—This substance was prepared as described for the corresponding chloride, except that less acetyl bromide (one-third of the amount used for the corresponding chloride) was employed. The substance showed a tendency to react with ethanol but could be recrystallized from benzene–petroleum ether, acetone–ice water, or chloroform (alcohol free)–petroleum ether. The purified substance crystallized in clusters of needles; m. p. 179–181°; $[\alpha]_D^{27}$ −79° (*c*, 4.0; $CHCl_3$, alcohol-free).

Anal. Calcd. for $C_6H_7O_6(COCH_3)_6Br$: Br, 15.58; saponification value (7 equivalents), 13.6 cc. 0.1 *N* NaOH per 100 mg. Found: Br, 15.62; 13.7 cc. 0.1 *N* NaOH.

That the acetyl halide in this compound was attached on carbon one was determined by shaking the substance (dissolved in 1:1 chloroform–ethanol) with silver carbonate, filtering from silver salts and crystallizing the reaction product (after solvent removal) from ethanol. The reaction product was identified as *aldehydo*-galactose pentaacetate ethyl hemiacetal.

Aldehydo-1-iodo-*d*-galactose Hexaacetate.[10]—*Aldehydo*-galactose pentaacetate (4 g.) was added with stirring to 17 g. of acetyl iodide and the resultant thin paste was poured into ice and water. The yellow crystals that separated were purified by repeated recrystallization from chloroform (alcohol-free) by the addition of petroleum ether; m. p. 152–153°; $[\alpha]_D^{25}$ −111° (*c*, 2; $CHCl_3$, alcohol-free). These constants are provisional as the substance was unstable and difficult to purify.

Anal. Calcd. for $C_6H_7O_6(COCH_3)_6I$: I, 22.66. Found: I, 22.10.

Aldehydo-*d*-glucose Heptaacetate.[11]—*Aldehydo*-glucose pentaacetate[12] (10 g.) was dissolved in 250 cc. of dry pyridine, the solution allowed to stand for two hours and then 125 cc. of acetic anhydride added and the whole allowed to stand overnight (fifteen hours). The dark solution was then poured into one liter of ice and water and the clear aqueous solution extracted with chloroform. The extract was washed with 5% sulfuric acid until free from pyridine, followed by washing with a solution of sodium bicarbonate and finally with water. The extract was dried and after removal of the chloroform the resultant sirup was dissolved in hot ethanol (carboraffin) and on cooling this solution a mass of fine white crystals separated. Further crops could be obtained by concentration of the mother liquor; yield (3 crops), 2.8 g. The substance was readily recrystallized from warm ethanol, the pure material showing the constants: m. p. 118.5–119.5°; $[\alpha]_D^{25}$ +8° (*c*, 4; $CHCl_3$).

The substance crystallized in prisms and rather large crystals (3 mm. long) could be formed on slow evaporation of an alcoholic solution. The substance was very soluble in chloroform, acetone, glacial acetic acid; was soluble, when heated, in water, ethanol, ether, and heptane; and was practically insoluble in petroleum ether.

Anal. Calcd. for $C_6H_7O_7(CH_3CO)_7$: C, 48.76; H, 5.74; acetyl, 14.2 cc. 0.1 *N* NaOH per 100 mg. Found: C, 48.79; H, 5.65; acetyl, 14.2 cc.

(7) D. H. Brauns, *Bur. Standards J. Research*, **7**, 573 (1931).

(8) Edna Montgomery and C. S. Hudson, THIS JOURNAL, **56**, 2463 (1934).

(9) W. M. Morgan, Ph.D. Dissertation, The Ohio State University, June, 1932.

(10) J. L. Quinn, Ph.D. Dissertation, The Ohio State University, Dec., 1934.

(11) R. L. Whistler, M. Sc. Thesis, The Ohio State University, Aug., 1935.

(12) M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929).

That the substance was not an acetylated enolic or alkali-interconverted sugar was determined by the fact that it did not decolorize a solution of bromine in carbon tetrachloride and on deacetylation with sodium ethylate followed by reacetylation with warm acetic anhydride and sodium acetate, β-glucose pentaacetate (m. p. 131°; $[\alpha]_D$ +4°, $CHCl_3$) was produced.

The substance was also formed, although in lower yield, by the room temperature acetylation of *aldehydo*-glucose pentaacetate with acetic anhydride and zinc chloride. *Aldehydo*-glucose pentaacetate (2 g.) was added to a solution of 1 g. of freshly fused zinc chloride in 40 cc. of acetic anhydride and the solution allowed to stand overnight (fifteen hours). The solution was then poured on cracked ice and neutralized with sodium bicarbonate, extracted with chloroform and the extract washed with water and dried. The sirup obtained after solvent removal was crystallized from hot ethanol (carboraffin); yield, 0.2 g.; m. p. 117.5–118.5°; $[\alpha]_D$ +8° (*c*, 3; $CHCl_3$).

Aldehydo-*l*-arabinose Hexaacetate.[11]—*Aldehydo-l*-arabinose tetraacetate[13] (20 g.) was acetylated with a solution of 20 g. of zinc chloride (freshly fused) in one liter of acetic anhydride as described above for the preparation of glucose heptaacetate. The resultant sirup was crystallized from hot ethanol; yield, 9 g.; m. p. 85°. Pure material was obtained by solution in just sufficient hot ethanol so that no crystallization occurred on cooling and repeatedly adding water in small quantities to the above solution at ice box temperature; m. p. 89.5°; $[\alpha]_D^{27}$ −27° (*c*, 4; $CHCl_3$). The solubilities of this substance were similar to those of the corresponding glucose compound.

Anal. Calcd. for $C_6H_6O_6(CH_3CO)_6$: C, 48.57; H, 5.76; acetyl, 14.3 cc. 0.1 *N* NaOH per 100 mg. Found: C, 48.57; H, 5.68; acetyl, 14.3 cc.

The experimental work herein reported was carried on in this Laboratory rather incidentally over a considerable period of time and I wish to make due acknowledgment to the assistance rendered by Messrs. W. M. Morgan, J. L. Quinn, R. L. Whistler and M. Konigsberg.

Summary

1. The chloride, bromide and iodide forms of *aldehydo-d*-galactose hexaacetate 1-halide have been synthesized in crystalline form. It is pointed out that these substances are the open chain analogs of the cyclic acetohalogen sugars.

2. *Aldehydo-d*-glucose heptaacetate and *aldehydo-l*-arabinose hexaacetate have been synthesized in pure crystalline form. It is pointed out that these compounds may be expected to be formed in reactions involving the cyclic forms of the sugars, rather than the free carbonyl or *aldehydo*-structures.

COLUMBUS, OHIO RECEIVED OCTOBER 4, 1935

(13) M. L. Wolfrom and Mildred R. Newlin, THIS JOURNAL, **52**, 3619 (1930).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Iodine Substitution Products of Vanillin and Some of their Derivatives

BY L. CHAS. RAIFORD AND EUGENE H. WELLS

In work published from this Laboratory[1] the chlorine and bromine substitution products of vanillin demanded by theory were prepared and characterized by a study of their interactions with typical amino compounds. Steric hindrance[2] was noted only when both ortho positions in the aldehyde were substituted, and was then less pronounced than expected. In the present work the iodine derivatives have been examined. The high yields of products indicated little, if any, hindrance.

The Action of Iodine on Vanillin.—Carles[3] treated vanillin with warm alcoholic solutions of iodine of different concentrations and obtained products that analyzed for mono- and diiodovanillin, respectively. He did not determine the structures of these compounds or study them further, and they are recorded as having the halogen in unknown positions.[4] The monoiodo derivative was reported to melt at 174° and was probably an impure sample of that, m. p. 180°, obtained by Hann[5] and reported as 5-iodovanillin, but without proof of structure. No melting point was given for the diiodo compound. Carles' work has been repeated and, while the monoiodo

(1) Raiford and Lichty, THIS JOURNAL, **52**, 4576 (1930). Other references to these studies are given there.

(2) Hantzsch [*Ber.*, **23**, 2776 (1890)] could not condense *sym*-tribromo- and trinitroaniline with benzaldehyde, but Lowy and coworkers [THIS JOURNAL, **43**, 1961 (1921)] found that when the nitro radical was in the aldehyde, condensation with aniline did take place, though they studied no aldehyde containing a substituent other than the nitro radical. Their results may not be typical for Meyer [*Z. physik. Chem.*, **24**, 219 (1897)] found that while hindrance in esterification of *o*-substituted benzoic acids was often proportional to the weight of the *o*-substituent, that produced by the nitro group was much greater than expected. On the other hand, Fischer and Giebe [*Ber.*, **31**, 546 (1898)] found that the *o*-nitro radical in benzaldehyde favors acetal formation.

(3) Carles, *Bull. soc. chim.*, [2] **17**, 14 (1872).

(4) Beilstein, "Handbuch org. Chem.," Vierte Auflage, 1925, VIII, p. 251.

(5) Hann, THIS JOURNAL, **47**, 2000 (1925).