When heated at or above its melting point, 8-ethylcaffeine sublimes, forming fine interwoven needles. Like 8-methylcaffeine, it is quite stable toward acids but is easily decomposed in alkalies. Solubility in 100 cc. of water is 0.6 g. at 25° and 2.0 g. at 100°. It is moderately soluble in cold alcohol and quite soluble in boiling alcohol. The crystals came down from either a water or alcohol solution as bundles of very small colorless needles.

Attempts to prepare 8-*n*-propylcaffeine and 8-*n*-butylcaffeine by this method were unsuccessful. When heated in a closed tube at temperatures ranging from 260 to 360°, the materials recovered were unchanged caffeine ether and hydroxycaffeine. Higher temperatures gave decomposition products.

Summary

1. 8-Methylcaffeine has been prepared by heating the 8-alkyl ethers of caffeine with acetic anhydride.

2. 8-Ethylcaffeine has been prepared by heating the 8-alkyl ethers of caffeine (except methoxycaffeine) or hydroxycaffeine with *n*-propionic anhydride.

3. Attempts to prepare 8-*n*-propyl- and 8-*n*-butylcaffeine by the same general procedure have been unsuccessful.

EAST LANSING, MICH. RECEIVED MAY 25, 1934

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

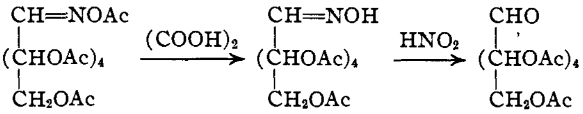
A New Synthesis of Aldehydo Sugar Acetates[1]

BY M. L. WOLFROM, L. W. GEORGES AND S. SOLTZBERG

A number of open chain or *aldehydo* sugar acetates have been synthesized in this Laboratory by the controlled hydrolysis of acetylated sugar mercaptals with mercuric chloride and cadmium carbonate. We wish to report a new method of synthesis for these substances, which may present advantages over the above in certain cases.

Wolfrom and Thompson[2] have shown that *aldehydo*-glucose oxime hexaacetate is formed in low yield by the rather vigorous acetylation of glucose oxime, mild acetylation producing the ring or β-glucose oxime hexaacetate. Acetylation of galactose oxime[3] produces a small amount of β-galactose oxime hexaacetate and a large amount of an approximately equal mixture of *aldehydo*-galactose oxime hexaacetate and galactononitrile pentaacetate, from which it is impossible to separate the former in good yield.

The above work shows that it might be possible to use the sugar oximes as a source for acetylated open chain oximes. We have now found that the latter compounds may be deoximated with the formation of the *aldehydo* sugar acetates. It is first necessary to remove the O-acetyl group of the oxime hexaacetate and this is readily effected with a methanol solution of oxalic acid. The deoximation is then produced with nitrous acid, a reagent first used by Claisen and co-workers.[4]



$$\begin{array}{l}CH{=}NOAc\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array} \xrightarrow{(COOH)_2} \begin{array}{l}CH{=}NOH\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array} \xrightarrow{HNO_2} \begin{array}{l}CHO\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array}$$

When the mixture of acetylated oxime and nitrile obtained from galactose oxime is carried through the above reactions, the resultant mixture of acetylated nitrile and *aldehydo*-galactose pentaacetate is easily separated. The acetylation of glucose oxime does not produce a sufficient amount of the *aldehydo*-glucose oxime hexaacetate to make this reaction a practical source for the compound. However, further acetylation of the oxime of β-glucose tetraacetate produced the above substance as the sole crystalline reaction product.

We have found that the semicarbazones of the *aldehydo*-acetates of glucose and galactose readily undergo oxygen replacements of their semicarbazide part by means of nitrous acid. Acetylation of the semicarbazones of these two sugars produced a good yield of the *aldehydo*-semicarbazone pentaacetates. In the case of glucose, this substance (m. p. 155°; $[\alpha]_D + 97°$, $CHCl_3$) was accompanied by three other products which were isolated in crystalline condition. One was an isomeric pentaacetate (m. p. 236°; $[\alpha]_D -16°$, $CHCl_3$). Another was a tetraacetate (m. p. 171°; $[\alpha]_D -9°$, $CHCl_3$) which produced the pentaacetate melting at 236° on further acetylation

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[1] Presented before the Section of Chemistry at the Forty-fourth Meeting of the Ohio Academy of Science, Columbus, Ohio, March 30, 1934.

[2] M. L. Wolfrom and A. Thompson, THIS JOURNAL, **53**, 622 (1931).

[3] V. Deulofeu, M. L. Wolfrom, P. Cattaneo, C. C. Christman and L. W. Georges, *ibid.*, **55**, 3488 (1933).

[4] L. Claisen and O. Manasse, *Ber.*, **22**, 530 (1889).

Finally, a hexaacetate (m. p. 111°; $[\alpha]_D + 100°$, $CHCl_3$) was obtained. The structure of the isomer melting at 155° was of course determined by its identity with the semicarbazone of *aldehydo*-glucose pentaacetate.[5] The structures of the other three isomers have not been determined but we believe that the hexaacetate is probably a further acetylated *aldehydo* form because of its high dextro rotation and that the other two are the β-ring compounds. Since the main reaction product fortunately was the desired *aldehydo*-glucose semicarbazone pentaacetate, it was not difficult to separate this from the others. The splitting of the acetylated *aldehydo*-glucose semicarbazone with nitrous acid was a very smooth reaction and produced a good yield of highly pure *aldehydo*-glucose pentaacetate.

The extension of these reactions to other sugars is in progress in this Laboratory. We hope to obtain the open chain acetates of those disaccharides and ketoses whose thioacetals are unavailable.

Experimental[6]

Preparation of *Aldehydo-d*-glucose Pentaacetate from β-*d*-Glucose Tetraacetate.—β-Glucose tetraacetate[7] (2.5 g.; 1 mol) was refluxed for two hours in 15 cc. of an ethanol solution of hydroxylamine (2 mols) prepared according to the directions of Wohl.[8] After removal of the ethanol, the resulting sirup was further acetylated by dissolving in 13 cc. of pyridine, adding 9 cc. of acetic anhydride and allowing to stand for two hours at room temperature. The solution was then poured into water, extracted with chloroform and the extract washed successively with solutions of sulfuric acid (3%), sodium bicarbonate and water. After removal of the chloroform, the resulting sirup crystallized on trituration with ethanol and was twice recrystallized from ethanol by the addition of water; yield, 1.4 g.; $[\alpha]_D$ +46°, $CHCl_3$; m. p. 117°. Further purification from ether raised the melting point to 119.5°. The substance was thus identified as *aldehydo*-glucose oxime hexaacetate, for which Wolfrom and Thompson[2] give the constants: m. p. 119.5°; $[\alpha]_D + 46°$, $CHCl_3$.

Aldehydo-glucose oxime hexaacetate (2.5 g.) was dissolved in 65 cc. of a methanol solution of oxalic acid dihydrate (3.3 g.) and refluxed for thirty minutes. The methanol was removed and the residue extracted with several 50-cc. portions of cold water to remove the oxalic acid. The sirupy residue crystallized after several hours of standing in the ice-box; yield, 0.6 g.; m. p. 94–97°. Further recrystallization from methanol by the addition of water produced pure material; m. p. 99°; $[\alpha]_D + 56°$, $CHCl_3$. The substance was thus identified as *aldehydo*-glucose oxime pentaacetate, for which Wolfrom and Thompson[2] give the constants: m. p. 99–99.5°; $[\alpha]_D$ +57°, $CHCl_3$.

Aldehydo-glucose oxime pentaacetate (1.6 g.) was dissolved in 30 cc. of warm ethanol and a warm solution of 5 g. of sodium nitrite in 100 cc. of water added. The solution was placed in a 60° bath and maintained at that temperature with moderate stirring. Dilute hydrochloric acid (14 cc. of 1:1) was added during four minutes. Three minutes later 4 g. of solid sodium nitrite was added, followed after two minutes by 8 cc. of hydrochloric acid (1:1), added fairly slowly. After three minutes, 4 g. of sodium nitrite was added, followed after two minutes by 8 cc. of hydrochloric acid, finally followed after three minutes by 4 g. of sodium nitrite. After two minutes, the solution was removed from the bath and stirred vigorously for ten minutes. After the addition of carboraffin, the filtered solution was extracted with chloroform, the extract dried with calcium chloride and the residue obtained after chloroform removal crystallized by trituration with petroleum ether and standing; yield, 0.9 g. of crude material. After purification from ether the material melted at 119–120° and showed $[\alpha]_D$ +10.6°, MeOH, changing slowly in the dextro direction. The substance was thus identified as *aldehydo*-glucose pentaacetate, for which Wolfrom[5] gives the constants: m. p. 119.5–120.5°: $[\alpha]_D$ +10°, MeOH, changing slowly in the dextro direction.

Acetylation of *d*-Glucose Semicarbazone.—The acetylation of this substance yielded four compounds in varying amounts with the *aldehydo*-glucose semicarbazone pentaacetate being invariably the main product. As Wolfrom[5] recorded only the melting point of this substance, it was prepared again according to his procedure and purified by recrystallization from hot water; m. p. 154.5–155.5°; $[\alpha]^{26}_D$ +96.6° (*c*, 2 g. per 100 cc. U. S. P. $CHCl_3$ soln.). A typical acetylation run will be recorded. Finely powdered glucose semicarbazone dihydrate[9] (44 g.) was added to a solution of 150 cc. of pyridine and 107 cc. of acetic anhydride and stirred rapidly for three hours, solution being then practically completed with a slight temperature rise occurring. The mixture stood for two days at room temperature and was then filtered into one liter of ice water. The separation of this mixture is represented diagrammatically in Fig. 1. The chloroform

TABLE I

CONSTANTS AND ANALYSES OF ACETYLATED GLUCOSE SEMICARBAZONES

Compound		II	III	IV
M. p., °C.		236–237	171–172	110–111.5
$[\alpha]^{25}_D$, $CHCl_3$		−16°, *c* = 1.9	−9°, *c* = 3.8	−100°, *c* = 2.1
Formula		$C_7H_{10}O_6N_3$-$(COCH_3)_5$	$C_7H_{11}O_6N_3$-$(COCH_3)_4$	$C_7H_9O_6N_3$-$(COCH_3)_6$
Nitrogen	Calcd.	9.40	...	...
	Found	9.48	...	...
Acetyl	Calcd.	11.2	9.9	12.3
	Found[a]	11.3	10.1	12.6

[a] Cc. of 0.1 *N* sodium hydroxide per 100 mg. of substance (Freudenberg method).

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[5] M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929).

[6] The experimental work in devising these procedures was carried out first by Mr. Georges for the galactose series and extended to glucose by Mr. Soltzberg.

[7] E. Fischer and K. Hess, *Ber.*, **45**, 912 (1912).

[8] A. Wohl, *ibid.*, **26**, 730 (1893).

[9] (a) R. Breuer, *Ber.*, **31**, 2193 (1898). *Cf.* (b) Maquenne and Goodwin, *Bull. soc. chim.*, [3] **31**, 1075 (1904).

extracts were washed with solutions of potassium bisulfate, sodium bicarbonate and with water. The reacetylation indicated was performed in the same manner as the original.

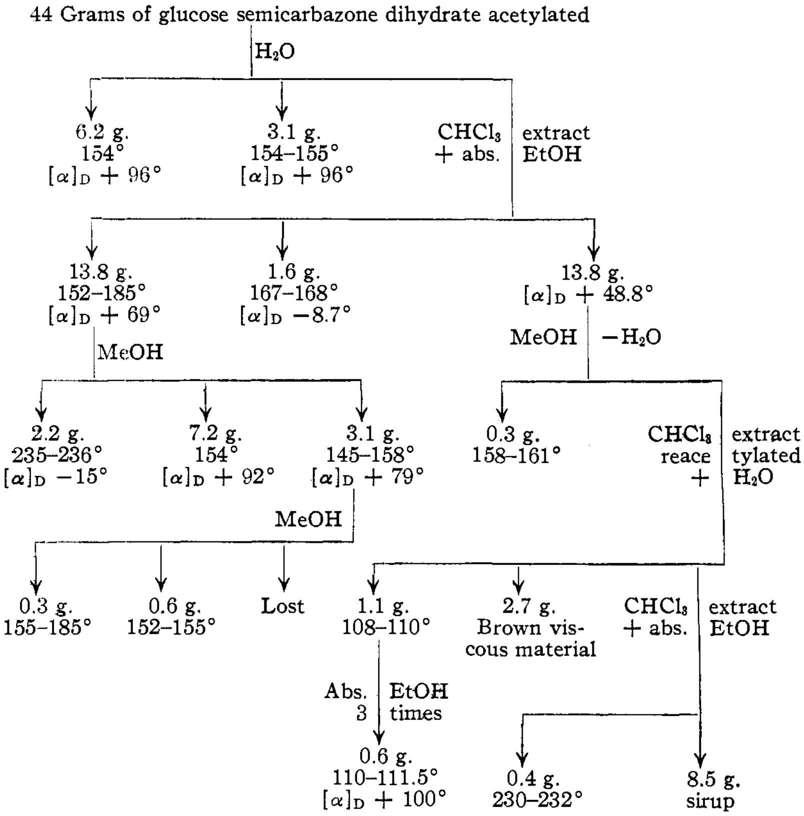

Fig. 1.—Separation of the acetylation products of glucose semicarbazone.

There was thus obtained in good purity 16.5 g. of *aldehydo*-glucose semicarbazone pentaacetate (I), 2.6 g. of II, 1.6 g. of III and 0.6 g. of IV. The last three substances were purified to constant rotation and melting point and analyzed. The results are tabulated in Table I. The tetraacetate III produces the pentaacetate II on further acetylation. III (120 mg.) was acetylated at 40° for twenty-four hours with 1.2 cc. of pyridine and 0.6 cc. of acetic anhydride. The product crystallized from the reaction mixture; yield, 50 mg.; m. p. 235°. After recrystallization from hot water the melting point was 236° (mixed m. p. unchanged). From previous work with acetylated sugar oximes, it appears probable that II and III are ring structures. IV is probably I with an acetyl group on one of the nitrogen atoms. It is evident that the acetylation of glucose semicarbazone is a complex reaction.

Preparation of ***Aldehydo-d*****-glucose Pentaacetate from** ***Aldehydo-d*****-glucose Semicarbazone Pentaacetate.**—*Aldehydo*-glucose semicarbazone pentaacetate (1.6 g.) was dissolved in 50 cc. of hot water, cooled rapidly to room temperature and treated with sodium nitrite and hydrochloric acid as described previously under the corresponding oxime, except that the reaction was carried out at room temperature; yield, 1.0 g.; m. p. 118–119.5°. The product was recrystallized from acetone, ether and petroleum ether[5]; m. p. 119–120.5°; $[\alpha]^{23}_{D}$ −4.2° (*c*, 3.3; alcohol-free $CHCl_3$). These constants indicate that the substance was very pure *aldehydo*-glucose pentaacetate.

Preparation of ***Aldehydo-d*****-galactose Pentaacetate Ethyl Hemiacetal from** ***d*****-Galactose Oxime.**—Galactose oxime[10] (10 g.) was stirred mechanically for ten hours with a solution of 60 cc. of pyridine and 40 cc. of acetic anhydride, the temperature of the reaction being maintained at 20° by suitable cooling. The clear solution was poured into 500 cc. of ice and water and the crystalline product removed by filtration; yield 14.5 g.; m. p. 100–115°. This material was digested with 400 cc. of hot water and filtered. Three grams of crystalline material separated from the filtrate. This was identified as β-galactose oxime hexaacetate[3] and after one recrystallization from absolute ethanol gave the constants: m. p. 106–107°; $[\alpha]^{22}_{D}$ −26.1° (*c*, 4.5; $CHCl_3$).

The water-insoluble residue (8.5 g.; m. p. 127–130°; $[\alpha]_D$ +28°, $CHCl_3$) was treated with a methanol solution of oxalic acid as described previously for *aldehydo*-glucose oxime hexaacetate and yielded a crystalline product; yield, 5 g.; m. p. 92–96°; $[\alpha]_D$ +36.6°, $CHCl_3$). These constants indicate that the product was an approximately equal mixture of *aldehydo*-galactose oxime pentaacetate monohydrate and galactononitrile pentaacetate.

The above product (5 g.) was dissolved in 15 cc. of ethanol, 90 cc. of hot water and 8 g. of sodium nitrite added, and the solution cooled to 80°. Some solids began to separate at this temperature. A solution of 8 cc. of concentrated hydrochloric acid (sp. gr. 1.2) in 12 cc. of water was added to the solution in small portions with shaking after each addition and the solution subsequently stirred for fifteen minutes. On cooling, a heavy crystallization was effected and removed by filtration; yield, 3 g. of crude acetylated nitrile. After several recrystallizations from dilute ethanol and from hot water the pure galactononitrile pentaacetate was obtained; $[\alpha]^{25}_{D}$ +41.8° (*c*, 3.5; $CHCl_3$); m. p. 137–138° (mixed m. p. unchanged).

The material remaining in the filtrate was removed by chloroform extraction; yield, 1.2 g. of crystalline material. Pure material was obtained after several recrystallizations from absolute ethanol; $[\alpha]^{22}_{D}$ $+1.2° \longrightarrow +13.7°$ (*c*, 1.0; MeOH; 45 hours) m. p. 134–135° (mixed m. p. unchanged but m. p. 130–133° on admixture with authentic galactononitrile pentaacetate of m. p. 138–139°). The product was thus identified as *aldehydo*-galactose pentaacetate ethyl hemiacetal, for which Wolfrom[11] gives

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[10] A. Wohl and E. List, *Ber.*, **30**, 3103 (1897).

[11] M. L. Wolfrom, This Journal, **52**, 2464 (1930).

the constants: m. p. 133–134°; $[\alpha]_D$ 0° ⟶ +14°, MeOH.

Aldehydo-galactose pentaacetate ethyl hemiacetal was also prepared from its oxime monohydrate by the Claisen[4] procedure, using glacial acetic acid and sodium nitrite, in approximately the same yield as in the above deoximation procedure. The oxime acetate (2 g.) was dissolved in 30 cc. of glacial acetic acid and a solution of 2 g. of sodium nitrite in 10 cc. of water added over a period of ten minutes. The solution was stirred for forty minutes at room temperature and then for ten minutes at 40°. It was then poured into 150 cc. of water, chloroform added and also 40 g. of sodium bicarbonate. The product was then worked up as above; yield, 1.6 g. of crude material; m. p. 134–135°, after recrystallization from absolute ethanol.

Preparation of *Aldehydo-d*-galactose Ethyl Hemiacetal from *d*-Galactose Semicarbazone.—Galactose semicarbazone proved to be very insoluble in the acetylating reagents and rather vigorous conditions were required to effect its acetylation. As Wolfrom[11] recorded only the melting point for *aldehydo*-galactose semicarbazone pentaacetate, this substance was prepared again and recrystallized from hot water to constant rotation. The melting point, around 200° (dec.), was unreliable but the rotation, unchanged on recrystallization, was $[\alpha]^{25}_D$ +89° (*c*, 2.2; $CHCl_3$).

Galactose semicarbazone[9b] (4 g.) was added to a mixture of 32 cc. of pyridine and 16 cc. of acetic anhydride, stirred for forty hours in a 55° bath, and poured into 500 cc. of ice and water containing 32 cc. of glacial acetic acid. The crystalline product was removed by filtration; yield, 3.2 g.; m. p. 185–190°; $[\alpha]_D$ + 63°, $CHCl_3$. This product was a mixture, but it was found that it was unnecessary to separate it into its components for use in the next step.

The acetylated galactose semicarbazone (1.6 g.) was dissolved in 25 cc. of warm ethanol and treated with sodium nitrite and hydrochloric acid as described under the deoximation of *aldehydo*-glucose oxime pentaacetate, except that the reaction was carried out at 70°. Absolute ethanol (20 cc.) was added to the chloroform extract and this yielded 1 g. of crystalline product on evaporation at room temperature. The products from several such runs were combined and twice recrystallized from absolute ethanol; m. p. 134–135°; $[\alpha]^{22}_D$ +1.2° ⟶ +13.7° (*c*, 1.0; MeOH; 45 hours). The product was thus identified as very pure *aldehydo*-galactose pentaacetate ethyl hemiacetal.

Summary

1. Acetylation of the semicarbazone of galactose produces appreciable amounts of the corresponding *aldehydo* acetate.

2. Acetylation of glucose semicarbazone produces mainly *aldehydo*-glucose semicarbazone pentaacetate, accompanied by smaller amounts of a semicarbazone tetraacetate, hexaacetate and an isomeric pentaacetate.

3. Acetylation of the sirupy oxime of β-glucose tetraacetate produces *aldehydo*-glucose oxime hexaacetate.

4. The O-acetyl group on the oximes of *aldehydo*-glucose and galactose hexaacetates may be selectively hydrolyzed.

5. A new synthesis of *aldehydo* sugar acetates is established for glucose and galactose by the action of nitrous acid on the *aldehydo*-pentaacetates of their oximes and semicarbazones.

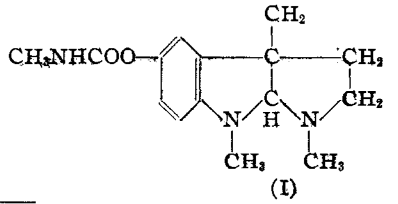
COLUMBUS, OHIO RECEIVED MAY 28, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

Studies in the Indole Series. II. The Alkylation of 1-Methyl-3-formyloxindole and a Synthesis of the Basic Ring Structure of Physostigmine[1]

BY PERCY L. JULIAN, JOSEF PIKL AND DOYLE BOGGESS

The literature records no efforts at direct alkylation of oxindoles, and this gap in our knowledge of these substances appears to us decidedly embarrassing in view of (1) recent attempts to effect a smooth and complete synthesis of the alkaloid, physostigmine, (I),[2] (2) the existing doubt as to the structure of the amino acid, oxytryptophane, for which formula (II) is a possibility.[3] It was with a view toward contributing to the solution of these two problems that the present work was undertaken.



(I)

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[1] This paper is an abstract of a portion of a thesis presented by Doyle Boggess to the Graduate Council of DePauw University in May, 1934, in partial fulfilment of the requirements for the degree of Master of Arts.

[2] King, Robinson and Suginome, *J. Chem. Soc.*, 298–336; 1433 (1932). (Reference there to earlier papers.) Hoshino and Tamura, *Proc. Imp. Acad. Japan*, **8**, 17 (1932); *Ann.*, **500**, 42 (1933).

[3] Abderhalden and Kempe, *Z. physiol. Chem.*, **52**, 212 (1907); Abderhalden and Sickel, *ibid.*, **138**, 108–117 (1924); Fischer and Smeykal, *Ber.*, **56**, 3470 (1923).