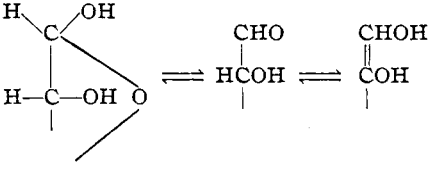
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

ALDEHYDO-*l*-ARABINOSE TETRA-ACETATE[1]

BY M. L. WOLFROM AND MILDRED R. NEWLIN

RECEIVED MAY 21, 1930 PUBLISHED SEPTEMBER 5, 1930

In continuation of the studies being made in this Laboratory on the open-chain forms of the sugar acetates, we wish to report in this paper the synthesis of the crystalline free aldehyde form of *l*-arabinose tetra-acetate. Although the ring formulas for the monosaccharides meet the requirements imposed by experimental data in most cases, there are nevertheless many reactions which are best explained by the assumption of an open-chain form in equilibrium with the ring or lactal structures. This is particularly true of the reactivity of the sugars in alkaline media. The changes that *l*-arabinose undergoes in alkaline solutions have been studied by Nef[2] and by Evans and Conaway.[3] These changes are best explained on the basis of enolic equilibria, which then require an intermediate open-chain formula, as follows



This paper presents evidence that the free aldehyde form of *l*-arabinose is capable of stable existence in the form of its crystalline acetate, $CH_2OAc-(CHOAc)_3-CHO$.

The methods used were similar to those reported in the case of glucose[4] and of galactose.[5] Arabinose ethyl mercaptal was acetylated and the thioethoxy groups replaced by an oxygen atom through reaction with mercuric chloride[6] and water under controlled conditions. The modifications introduced to obtain the arabinose compound consisted in the use of less water in the reaction and a slightly different method of isolation.

The free aldehyde form of *l*-arabinose acetate or aldehydo[5]-*l*-arabinose tetra-acetate crystallizes in prismatic needles and has widely differing constants from the two known lactal acetates of this sugar. Chavanne[7] first obtained crystals of the α-form of arabinose tetra-acetate, but in too

[1] Constructed from a thesis presented by Mildred R. Newlin in candidacy for the degree of Master of Science at The Ohio State University.

[2] J. U. Nef, *Ann.*, **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1914).

[3] R. F. Conaway, Ph.D. Dissertation, The Ohio State University, **1929**.

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

[5] M. L. Wolfrom, *ibid.*, **52**, 2464 (1930).

[6] *Cf.* P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **69**, 175 (1926); **74**, 695 (1927).

[7] G. Chavanne, *Compt. rend.*, **134**, 661 (1902).

small amount to analyze. Hudson and Dale[8] have synthesized and characterized α- and β-*l*-arabinose tetra-acetates. The properties of the three forms are listed in Table I.

TABLE I

PROPERTIES OF THE THREE TETRA-ACETATES OF *l*-ARABINOSE

Form	M. p. °C.	$[\alpha]_D$, Chloroform
α	97	+ 42.5°
β	86	+147.2°
Aldehydo	114	− 65°

The rotation of aldehydo-*l*-arabinose tetra-acetate was stable in acetylene tetrachloride ($[\alpha]_D^{26}$ −58°) solution and in alcohol-free chloroform but underwent a slow change in the dextro direction in methyl alcohol and U. S. P. chloroform. In the former solvent the initial specific rotation was −46°, changing to −29° in five days. That this is due to combination with the alcohol is made probable by the isolation of well-characterized compounds of this type in the case of galactose.[5] The substance readily gave the Schiff aldehyde test and reduced Fehling's solution. A crystalline semicarbazone was formed without loss of an acetyl group. This semicarbazone showed a normal molecular weight by the Rast[9] method. The aldehydo forms of glucose and galactose acetates showed low specific rotations, being −5 and −25° in chloroform, respectively. This was thought to be probably characteristic of the open-chain forms. However, the value −65° obtained for the arabinose acetate, shows that the carbonyl group may produce a relatively high rotation, in spite of the absence of rings.

Further work on the synthesis and reactivity of the free aldehyde forms of sugar acetates is in progress in this Laboratory.

Experimental

***l*-Arabinose-ethylmercaptal Tetra-acetate.**—Three grams of *l*-arabinose ethyl mercaptal[10] (m. p. 124–126°) was dissolved in 12 cc. of dry pyridine at room temperature and the solution cooled in ice water. To this was added, gradually, 24 cc. of acetic anhydride. Some of the solute precipitated, but redissolved after a short time on standing at 0° with occasional shaking. The solution was then allowed to stand overnight at room temperature. At the end of this period it was poured slowly with stirring into 600 cc. of ice and water. A heavy oil separated which crystallized readily. Recrystallization was effected by dissolving the filtered crude material in methyl alcohol at room temperature, adding water and allowing the mixture to crystallize in the ice box. The yield of the pure product was 4.5 g. or 91%.

The substance crystallizes in prisms and after one recrystallization melted at 79–80°. After another recrystallization the melting point was the same and the specific rotation in chloroform was −30.8° at 27° (0.4005 g. subs. in 10.06 cc. U. S. P. chloroform

[8] C. S. Hudson and J. K. Dale, THIS JOURNAL, **40**, 992 (1918).

[9] K. Rast, *Ber.*, **55**, 1051 (1922).

[10] E. Fischer, *ibid.*, **27**, 673 (1894).

soln., 1.1-dm. tube, $\alpha_D = -1.35°$). After four recrystallizations the melting point was 79–80° and the specific rotation in the same solvent was −29.9° at 26° (0.4008 g. subs. in 10.06 cc. U. S. P. chloroform soln., 1.1-dm. tube, $\alpha_D = -1.31°$). The substance is practically insoluble in cold water, slightly soluble hot, somewhat soluble in ethyl alcohol and petroleum ether, and very soluble in ether, acetone and chloroform.

Anal. Subs., 0.2002: 19.01 cc. 0.1 *N* NaOH. Subs., 0.2001: 19.01 cc. 0.1 *N* NaOH. Calcd. for 100 mg. of $C_5H_6O_4(CH_3CO)_4(SC_2H_5)_2$: cc. 0.1 *N* NaOH, 9.43. Found: 9.49, 9.50.

Aldehydo-*l*-arabinose Tetra-acetate.—An amount of 25 g. of *l*-arabinose-ethyl mercaptal tetra-acetate (m. p. 79–80°) was dissolved in 90 cc. of pure acetone, and 15 cc. of water added. To this was added with mechanical stirring, an excess, 40 to 50 g., of finely powdered alkali-free cadmium carbonate, then a solution of 59 g. of mercuric chloride in 75 cc. of acetone. Stirring was maintained at room temperature for twelve hours, with occasional additions of fresh cadmium carbonate. The mixture was then held for fifteen minutes in a 50° bath, vigorous stirring being maintained. Finally, the solution was refluxed for fifteen minutes. The solution was cooled and filtered, cadmium carbonate being placed in the suction flask before filtering. The filtrate was then concentrated under reduced pressure at 30–35° in the presence of an excess of cadmium carbonate and dried several times by adding fresh acetone and evaporating under reduced pressure. The residue was extracted with warm chloroform and the extract dried a short time with sodium sulfate, adding some norite at the same time. After filtration, the solution was evaporated to dryness at room temperature in a vacuum desiccator. The last traces of chloroform were removed by several treatments with petroleum ether. A partially crystalline mass was thus obtained, from which the crystals were isolated by treatment with alcohol-free, dry ether, which dissolved the sirup. The ether solution was filtered and the crystalline residue washed with ether. The amount of this material was 5 g. and an additional crop of 2 g. was obtained from the ethereal filtrate on standing overnight in the ice box.

For purification, the material was dissolved in the minimum amount of warm acetone, and half the volume of anhydrous and alcohol-free ether added. Petroleum ether was then carefully added, crystallization being effected readily. By this procedure 5 g. of the crude material from the ether treatment gave 3.7 g. of product with m. p. 112–114° (corr.) and showing a specific rotation in acetylene tetrachloride soln. of −57.8° at 26° (0.4008 g. subs. in 10.06 cc. acetylene tetrachloride soln., 1.0-dm. tube, $\alpha_D = -2.30°$). After three recrystallizations the melting point was 113–115° (corr.) and the specific rotation in the same solvent was −58.0° at 26° (0.4002 g. subs. in 10.06 cc. acetylene tetrachloride soln., 1.0-dm. tube, $\alpha_D = -2.31°$). After five recrystallizations the melting point remained at 113–115° (corr.).

The substance crystallizes in clusters of prismatic needles. It is slightly soluble in cold water and ethyl alcohol, and readily soluble in these solvents when warmed. It is slightly soluble in warm ether and is practically insoluble in petroleum ether. It dissolves readily in methyl alcohol and with extreme ease in chloroform and acetone. The initial specific rotation of the pure substance in U. S. P. chloroform at 31° was −65.2° (0.4014 g. subs. in 10.06 cc. U. S. P. chloroform soln., 1.0-dm. tube, $\alpha_D = -2.60°$). This value changed slowly in the dextro direction, being −63.3° after thirty minutes. In alcohol-free chloroform solution the specific rotation at 27° of the pure substance was −65.4° (0.4013 g. subs. in 10.06 cc. chloroform soln., 1.0-dm. tube, $\alpha_D = -2.61°$). Another determination at the same temperature gave the value −65.6° (0.4017 g. subs in 10.06 cc. chloroform soln., 1.0-dm. tube, $\alpha_D = -2.62°$). The change in these values in twenty-four hours was negligible. The alcohol-free chloroform was prepared from the U. S. P. grade by washing with water, drying overnight with sodium and calcium

chloride and redistilling. In methyl alcohol solution an initial specific rotation of −46° was obtained, changing slowly in the dextro direction. This change is tabulated in Table II.

TABLE II

CHANGE IN ROTATION OF ALDEHYDO-*l*-ARABINOSE TETRA-ACETATE IN METHYL ALCOHOL SOLUTION

l = 1.0 dm. λ, 5892 Å.

Experiment 1 t = 30°, c = 3.993			Experiment 2 t = 30°, c = 3.995		
Time, hrs.	α, degrees	$[\alpha]_D$, degrees	Time, hrs.	α, degrees	$[\alpha]_D$, degrees
0.03	−1.83	−45.8	0.03	−1.87	−46.8
0.25	−1.82	−45.6	0.25	−1.86	−46.6
0.50	−1.81	−45.3	0.50	−1.85	−46.3
0.75	−1.80	−45.1	..	....	....
1	−1.79	−44.8	1	−1.85	−46.3
1.25	−1.79	−44.8	..	....	....
1.50	−1.77	−44.3	..	....	....
1.75	−1.76	−44.1	..	....	....
19	−1.40	−35.1	..	....	....
24	−1.31	−32.8	24	−1.33	−33.3
72	−1.09	−27.3	..	....	....
..	....	....	96	−1.18	−29.5
..	....	....	120	−1.20	−30.0
144	−0.99	−24.8	144	−1.14	−28.5
168	−0.96	−24.0	168	−1.08	−27.0
192	−0.96	−24.0	..	....	....
216	−0.92	−23.0	..	....	....

Anal. Subs., 0.1000: 12.56 cc. 0.1 *N* NaOH. Subs., 0.1000: 12.76 cc. 0.1 *N* NaOH. Subs., 0.2196: CO_2, 0.3939; H_2O, 0.1176. Calcd. for $C_5H_6O_5(CH_3CO)_4$: C, 49.04; H, 5.69; cc. 0.1 *N* NaOH per 100 mg., 12.6. Found: C, 48.92; H, 5.99; cc. 0.1 *N* NaOH, 12.6, 12.8; S, absent.

Aldehydo-*l*-arabinose-semicarbazone Tetra-acetate.—An amount of 4 g. (1 mole) of aldehydo-*l*-arabinose tetra-acetate (m. p. 113–115°) was dissolved in 40 cc. of warm water and cooled rapidly to room temperature. A mixture of 2 g. (1.3 moles) of semicarbazide hydrochloride and 2.5 g. (2 moles) of potassium acetate was added and the solution shaken vigorously. The crystalline semicarbazone began to separate rapidly after three to four minutes in the form of glittering four-sided plates. After one recrystallization from methyl alcohol the melting point was 184–187° (corr.) and this value was unchanged on a second recrystallization from hot water. The substance is moderately soluble in chloroform and acetone, soluble in warm water and warm alcohol, and is practically insoluble in ether and petroleum ether.

Molecular weight (Rast). 0.0106 g. subs. in 0.1017 g. of camphor depressed the m. p. 10.5°. Mol. wt. calcd. for $C_{14}H_{21}O_9N_3$: 375. Found: 396.

Anal. Subs., 0.2007: N_2, 19.50 (742.2 mm., 20°). Subs., 0.1000: cc. 0.1 *N* NaOH, 10.8, 10.7. Calcd. for $C_6H_9O_5N_3(CH_3CO)_4$: N, 11.20, cc. 0.1 *N* NaOH per 100 mg., 10.7. Found: N, 10.96, cc. 0.1 *N* NaOH, 10.8, 10.7.

Summary

1. A new form of *l*-arabinose tetra-acetate has been synthesized in pure crystalline condition.

2. Evidence is presented that this substance possesses the free aldehyde structure.

3. The crystalline semicarbazone of this aldehyde has been prepared in pure form.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE CHEMISTRY OF DIARYL SULFIDES. III. THE SYNTHESIS OF THIOTHYRONINE[1]

BY GEORGE H. LAW AND TREAT B. JOHNSON

RECEIVED MAY 22, 1930 PUBLISHED SEPTEMBER 5, 1930

In two previous papers from this Laboratory,[2] attention has been directed to the remarkable effect of diaryl-sulfide groupings in organic compounds which have been shown to have therapeutic value as germicides or antiseptics. The outstanding derivative thus far studied is *p*-hydroxydiphenyl-sulfide which was found to possess a germicidal activity equivalent to a phenol coefficient of 115. As a result of the discovery of this unexpected increase in germicidal power, and on account of the growing interest in the biochemistry of organic sulfur groupings in general, we have now extended further our researches in this field, and have begun a study of practical methods for synthesizing sulfur-ether-α-amino acid combinations corresponding in structure to the naturally occurring protein acids, phenyl-alanine and tyrosine, and also the sulfur analog of the hormone—*thyroxine*. In this paper we describe methods of synthesizing the two new α-aminoacids—*p*-methyl-*p'*-diphenylsulfide-β-alanine and *p*-hydroxy-*p'*-diphenylsulfide-β-alanine or *thiothyronine* (desiodo-thyroxine), which are expressed by formulas I and II, respectively. The amino acid II is

$CH_3C_6H_4SC_6H_4CH_2CH(NH_2)COOH$ (I) $\qquad$ $HOC_6H_4SC_6H_4CH_2CH(NH_2)COOH$ (II)

$HOC_6H_4OC_6H_4CH_2CH(NH_2)COOH$ (III) $\qquad$ $HSC_6H_4CH_2CH(NH_2)COOH$ (IV)

the sulfur analog of thyronine III already described by Harington,[3] and is the first aromatic sulfur-ether derivative of the amino acid thiotyrosine IV to be described. A method for preparing *thiotyrosine* IV was first described in a paper from the Yale laboratory by Johnson and Brautlecht[4] in 1912, and so far as the authors are aware no attention has been paid to

[1] Constructed from a dissertation presented by George Hartland Law in June, 1929, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

[2] Hilbert and Johnson, THIS JOURNAL, **51**, 1526 (1929); Bass and Johnson, *ibid.*, **52**, 1146 (1930).

[3] Harington, *Biochem. J.*, **20**, 300 (1926); **22**, 1429 (1928); *C. A.*, **23**, 1631 (1929).

[4] Johnson and Brautlecht, *J. Biol. Chem.*, **12**, 175 (1912).