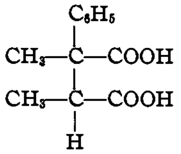
The 142° compound, on oxidation, gave an acid ($C_{12}H_{14}O_4$) which has since been synthesized[2] and proved to be α,α'-dimethyl-α-phenylsuccinic acid,



$$\begin{array}{c} C_6H_5 \\ | \\ CH_3\text{—}C\text{—}COOH \\ | \\ CH_3\text{—}C\text{—}COOH \\ | \\ H \end{array}$$

This synthesis of a compound with two dissimilar asymmetric carbon atoms resulted in a low-melting (159–160°) and a high-melting (170–172°) racemic form of the acid. The high-melting form proved to be identical with the acid obtained by the oxidation of the 142° compound. If the 72° compound is a geometric isomer of the 142° compound, on oxidation it should yield the low-melting form of α,α'-dimethyl-α-phenylsuccinic acid. The 72° compound, which can be obtained in 60–70% yields by boiling an alcoholic solution of the 142° compound with sodium acetate, has been oxidized and gives an acid identical with the low-melting form of α,α'-dimethyl-α-phenylsuccinic acid.

Experimental

2,3,5,6-Tetramethyl-3-phenylcyclohexene-5-dione-1,4

High-Melting Form, 142°.—This compound is the main solid product resulting from the addition of phenylmagnesium bromide to duroquinone.[1] The yield was 16–20%, based on duroquinone reacting.

Low-Melting Form, 72°.—Ten grams of the 142° compound, 6 g. of fused sodium acetate and 150 cc. of 95% alcohol were heated for twenty hours under a reflux condenser. The alcohol was then allowed to evaporate, the sodium acetate dissolved in water, and the remaining solid recrystallized from alcohol. It is more soluble than the 142° compound; yield, 60–70%; m. p. 72–73°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5; mol. wt., 242.1. Found: C, 79.2, 79.9, 78.6; H, 7.5, 7.6, 7.3; mol. wt., 249, 246.

Oxidation.—To five grams of the 72° compound dissolved in 150 cc. of acetone, 7.5 g. of potassium permanganate was added slowly. The mixture was kept between 4–6°, and was shaken almost constantly. The dark brown solution was then allowed to warm up to 20°, when a heavy precipitate of manganese dioxide appeared. After filtering, the precipitate was decomposed with ice, sulfuric acid and sodium bisulfite. The ether extract of this solution was added to the acetone filtrate, and the organic acid extracted from the acetone–ether mixture by means of sodium carbonate solution. Acidifying the sodium carbonate solution and extracting with ether gave 0.7 g. of solid which, after several recrystallizations from 25% alcohol, melted at 158–160°. The synthetic acid[2] melted at 159–160° and a mixture of the two melted at 158–159.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$ (222.1): C, 64.8; H, 6.35. Found: C, 64.2, 64.0; H, 6.4, 6.4. *Eq. wt.* Subs., 0.1115; NaOH (0.1030 *N*) 9.52 cc. = 0.0392 g. NaOH. Eq. wt., 113.7.

Summary

The low-melting form of α,α'-dimethyl-α-phenylsuccinic acid has been obtained by oxidizing the low-melting geometric isomer of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4.

POUGHKEEPSIE, N. Y. RECEIVED JUNE 8, 1934

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[2] H. M. Crawford, THIS JOURNAL, 56, 139 (1934).

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

The Structure of *d*-Glucoheptulose Hexaacetate

BY M. L. WOLFROM AND ALVA THOMPSON

A ketose of α-glucoheptose was synthesized by Bertrand and Nitzberg[1] through the action of the sorbose bacterium on α-glucoheptitol and was named α-glucoheptulose by these workers. Austin[2] prepared the enantiomorph of the above by the action of dilute alkali on *d*-α-glucoheptose and thus allocated his ketose to the *d*-series, a point which the Bertrand synthesis did not decide. This sugar is one of the ketoses that does not exhibit mutarotation.

Austin[3] obtained a strongly dextrorotatory hexaacetate ($[\alpha]_D + 87°$, $CHCl_3$) by the acetylation of this substance with sodium acetate and hot acetic anhydride and named the product α-*d*-glucoheptulose hexaacetate. To our knowledge, this is the only instance recorded in the sugar series where a dextrorotatory acetate was obtained by sodium acetate acetylation. The assignment of an α-ring structure to this acetate was based only upon the dextrorotation exhibited by the substance. The dextrorotatory pentaacetate of *d*-fructose has recently been shown to be an open chain or *keto*-fructose pentaacetate.[4] We have

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[1] G. Bertrand and G. Nitzberg, *Compt. rend.*, 186, 925, 1172, 1774 (1928).

[2] W. C. Austin, THIS JOURNAL, 52, 2106 (1930).

[3] W. C. Austin, *ibid.*, 54, 1925 (1932).

[4] (a) E. Pacsu and F. V. Rich, *ibid.*, 54, 1697 (1932); 55, 3018 (1933); (b) M. L. Wolfrom and A. Thompson, *ibid.*, 56, 880 (1934).

now investigated this acetate of glucoheptulose with the object of proving whether it possesses a cyclic or open chain structure. Our conclusion is that it is a cyclic compound.

We have shown[4b] that open chain *aldehydo*- and *keto*-acetates react readily with ethyl mercaptan in the presence of zinc chloride, two ethyl mercaptan groups entering the molecule without loss of acetyl groups. If the acetate is a ring structure, acetate replacement occurs and an acetylated thioglycoside results. When this reaction was applied to glucoheptulose hexaacetate, two acetate groups were replaced by ethylmercapto groups with the formation of a crystalline thioethyl glucoheptuloside tetraacetate containing a thioethyl ether in the chain. The structure of this sulfur derivative was ascertained by its analysis; by the fact that it could not be further acetylated under stringent conditions; that it was nonreducing but showed reduction after acid hydrolysis; and by the fact that ethyl mercaptan was liberated during the hydrolysis.

We have found in this work that the glucoheptulose hexaacetate of Austin is formed by mild acetylation of the sugar with zinc chloride and acetic anhydride and also with pyridine and acetic anhydride in the cold. The latter fact renders very probable the conclusion that glucoheptulose has the same structure as its hexaacetate. Under certain conditions of pyridine acetylation, a crystalline pentaacetate is obtained. That this pentaacetate has the glycosidic hydroxyl open is proved by the fact that it is identical with the pentaacetate formed by the hydrolysis of the crystalline acetobromoglucoheptulose pentaacetate, which we have now synthesized. The formation of this pentaacetate under mild acetylating conditions indicates that the glycosidic carbon resists acetylation, probably from steric causes. Such an enclosed, potential ketonic hydroxyl may interfere with mutarotation and this may be the explanation for the lack of mutarotation exhibited by the free sugar.

Experimental

Preparation of *d*-Glucoheptulose Hexaacetate.—This substance was prepared according to the directions of Austin.[3] We found that the yield was improved materially if the reaction mixture was stirred mechanically during the acetylation; yield, 8.5 g. of once recrystallized product from 10 g. of sugar; m. p. 115–116°; $[\alpha]^{25}_{D}$ +87° (*c*, 3.0, $CHCl_3$). These constants are in agreement with those obtained by Austin.

The same hexaacetate was obtained in good yield by room temperature acetylation with acetic anhydride and zinc chloride according to the directions of Schlubach and Vorweck[5] for the preparation of *l*-sorbose pentaacetate.

***α*-Acetobromo-*d*-glucoheptulose Pentaacetate.**—Glucoheptulose hexaacetate (1 g.) was dissolved in 5 cc. of the halogenating mixture (equal volume of acetic anhyide and glacial acetic acid containing 60 g. of hydrogen bromide per 100 cc. of the mixture) and kept at room temperature for ninety minutes. Chloroform (10 cc.) was then added and the whole poured into ice water, the chloroform layer separated and washed twice with ice water. The sirup obtained after removal of the chloroform crystallized after two days of desiccation. After one recrystallization from ether by the addition of petroleum ether, the substance was obtained in massive rectangular prisms; yield, 0.8 g.; m. p. 97–98°; $[\alpha]^{22}_{D}$ +134.5° (*c*, 2.8; U. S. P. $CHCl_3$). Two further recrystallizations did not alter these constants.

Anal. Calcd. for $C_7H_8O_6Br(COCH_3)_5$: Br, 16.54; saponification value, 12.4 cc. 0.1 *N* NaOH per 100 mg. Found: Br, 16.43; saponification value 12.6 cc.

***α*-*d*-Glucoheptulose Pentaacetate.**—The acetylation of glucoheptulose with pyridine (5 parts) and an excess (10 parts) of acetic anhydride produced the above hexaacetate. With pyridine in excess, a pentaacetate was obtained. Finely powdered glucoheptulose (3 g.) was added to a solution of 30 cc. of pyridine and 21 cc. of acetic anhydride, previously cooled to 0°. The mixture was shaken mechanically at 0° for several hours, during which time the bulk of the sugar dissolved. It was then kept at room temperature for about forty hours and finally poured on ice. The aqueous mixture was extracted with chloroform and the extract washed with water, sodium bisulfate solution, sodium bicarbonate solution and again with water, dried with calcium chloride and the chloroform removed. The resulting sirup crystallized on trituration with petroleum ether and was recrystallized by solution in warm ether and addition of petroleum ether to incipient opalescence; yield, 2.3 g.; m. p. 114–115°; $[\alpha]^{25}_{D}$ +49.0° (*c*, 3.4; $CHCl_3$), without mutarotation. These constants were unchanged on further recrystallization. On admixture with glucoheptulose hexaacetate (m. p. 115–116°), the melting point was depressed to 85–97°. The substance crystallizes in prisms and is readily soluble in chloroform, acetone, alcohol, and warm ether. It is appreciably soluble in warm water and is practically insoluble in petroleum ether.

Anal. Calcd. for $C_7H_9O_7(COCH_3)_5$: acetyl, 11.9 cc. 0.1 *N* NaOH per 100 mg. Found: 12.1 cc.

If the reaction mixture is allowed to become warm during the initial part of the acetylation, considerable hexaacetate is formed. This can be removed almost quantitatively by dissolving the reaction product in hot water and allowing the solution to stand overnight. The hexaacetate crystallizes out while the pentaacetate remains in solution and can be extracted from the mother liquor with chloroform.

Further acetylation of this pentaacetate with acetic anhydride and sodium acetate produces the hexaacetate of Austin. Glucoheptulose pentaacetate (400 mg.) was

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(5) H. H. Schlubach and J. Vorweck, *Ber.*, **66**, 1251 (1933).

heated on the water-bath for thirty minutes with acetic anhydride (4 cc.) and fused sodium acetate (0.2 g.). The product crystallized on pouring the reaction mixture on ice, and was recrystallized from hot water; m. p. 114–115° (mixed m. p. unchanged); $[\alpha]^{21}_{D}$ +86.4° (*c*, 1.4; $CHCl_3$).

This pentaacetate was obtained from the acetobromoglucoheptulose, which proved that the second position was open in the former. Acetobromoglucoheptulose (0.8 g.), silver carbonate (0.6 g.), acetone (5 cc.) and water (3 drops) were placed together and kept for one hour with occasional shaking. After filtration and acetone removal, the resulting sirup crystallized and was recrystallized from ether by the addition of petroleum ether; yield, 0.4 g.; m. p. 113–114°. Pure material was obtained on one more recrystallization; yield, 0.3 g.; m. p. 114–115° (mixed m. p. unchanged); $[\alpha]^{20}_{D}$ +49°, $CHCl_3$.

Reaction between *d*-Glucoheptulose Hexaacetate and Ethyl Mercaptan.—Freshly fused zinc chloride (0.4 g.) was placed in a glass tube, followed by 3 cc. of ethyl mercaptan, 2 g. of soluble anhydrite and 1 g. of glucoheptulose hexaacetate. The tube was finally rinsed down with 3 cc. more of ethyl mercaptan, sealed and kept at room temperature for eighteen hours. The ethyl mercaptan was previously dried over soluble anhydrite.[6] The tube was then opened and the contents poured into a saturated solution of sodium bicarbonate. The precipitate and filtrate were extracted with chloroform, the extract washed with water, dried and the solvent removed with a stream of dry air. Petroleum ether was added to the resulting sirup and removed in the same manner. On repetition of the latter treatment, the product was obtained crystalline. Pure material was obtained after several recrystallizations from methanol by the addition of water; m. p. 92–93°; $[\alpha]^{25}_{D}$ +65° (*c*, 2.9; $CHCl_3$).

Anal. Calcd. for $C_{11}H_{18}O_5S_2(COCH_3)_4$: S, 13.75; acetyl, 8.58 cc. 0.1 *N* NaOH per 100 mg. Found: S, 13.49; acetyl, 8.60 cc.

The above substance was recovered unchanged after acetylation with 10 parts of dry pyridine and 20 parts of acetic anhydride for twenty-four hours at 40°. This proves that the compound contained no free hydroxyl groups. The substance showed no Fehling reduction, but was strongly reducing after acid hydrolysis. The odor of ethyl mercaptan was noted during the hydrolysis. This shows that the glycosidic hydroxyl was replaced by an ethylmercapto group.

Summary

1. α-Acetobromo-*d*-glucoheptulose and α-*d*-glucoheptulose pentaacetate have been synthesized in pure crystalline form.

2. Glucoheptulose hexaacetate reacts with ethyl mercaptan to form a crystalline product in which two acetate groups have been replaced with ethylmercapto groups.

3. The above constitutes evidence that glucoheptulose hexaacetate is a cyclic compound.

4. Evidence is given that glucoheptulose pentaacetate is a cyclic compound with an open glycosidic hydroxyl group.

COLUMBUS, OHIO RECEIVED JUNE 11, 1934

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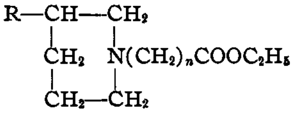
[6] W. A. Hammond and J. R. Withrow, *Ind. Eng. Chem.*, **25**, 1112 (1933).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

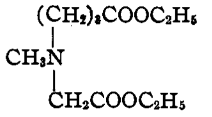
The Acetoacetic Ester Condensation. VIII. The Condensation of ω-Piperidino Esters

BY W. B. THOMAS AND S. M. MCELVAIN

In a study of the cyclization of certain 3-carbethoxypiperidino esters, it was found[1] that while ethyl β-(3-carbethoxypiperidino)-propionate (I, R is carbethoxy, *n* is 2) in xylene reacted vigorously with metallic sodium, the corresponding acetate (in which *n* is 1) remained practically unchanged when refluxed in xylene with either metallic sodium or sodium ethoxide.

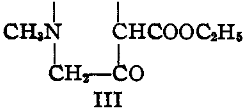


I



$CH_3N[(CH_2)_2COOC_2H_5]CH_2COOC_2H_5$

II



III

This apparent inability of the α-amino ester to enter into an acetoacetic ester condensation later led to the conclusion that the cyclization of such an ester as II would produce the 4-carbethoxy-3-piperidone (III) rather than the isomeric 2-carbethoxy derivative.[2] However, before such a conclusion could be made into a generalization it seemed necessary to study the behavior of various types of simple amino esters in the acetoacetic ester condensation.

The present paper reports the results obtained with a series of ω-piperidino esters (I) in which R is hydrogen, *n* varies from 1 to 4. The first at-

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[1] McElvain and Adams, THIS JOURNAL, **45**, 2746 (1923).

[2] Prill and McElvain, *ibid.*, **55**, 1233 (1933).