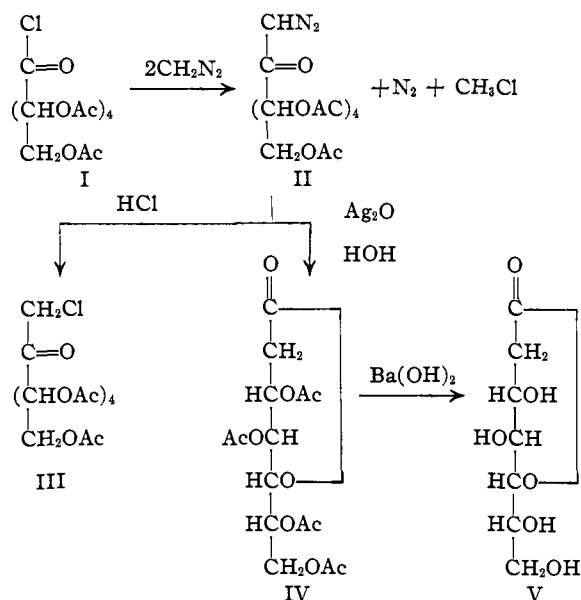


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Action of Diazomethane upon Acyclic Sugar Derivatives.<sup>1</sup> II<sup>2</sup>

BY M. L. WOLFROM, S. W. WAISBROT AND ROBERT L. BROWN

In continuation of our work on the products obtained by the action of diazomethane upon the acid chlorides of fully acetylated sugar acids, we record the synthesis of 1-diazo-1-desoxy-*keto-d*-fructose tetraacetate from *d*-arabonyl chloride tetraacetate and diazomethane.



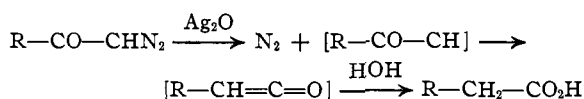
Treatment of the previously reported<sup>2</sup> 1-diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate (II) with ethereal solutions of dry hydrogen chloride and dry hydrogen bromide produced 1-chloro (III) and 1-bromo-*keto-d*-glucoheptulose pentaacetate, respectively. Similar treatment of 1-diazo-1-desoxy-*keto-d*-fructose tetraacetate produced 1-chloro and 1-bromo-*keto-d*-fructose tetraacetate. The chloro derivative III was the uncharacterized compound isolated in crude form from the mother liquors of our original preparations<sup>2</sup> of the diazomethyl ketone II. When the reaction was carried out under nearly anhydrous conditions, only traces of the chloro derivative were obtained. The 1-chloro-*keto-d*-fructose tetraacetate (m. p. 78°, spec. rot. +68°, CHCl<sub>3</sub>) is isomeric with the chloro-*d*-fructose tetraacetate of

(1) An incomplete preliminary report of this work was published in THIS JOURNAL, 63, 632 (1941). The work herein recorded was presented before the Division of Sugar Chemistry and Technology at the 101st Meeting of the American Chemical Society, St. Louis, Missouri, April 10, 1941.

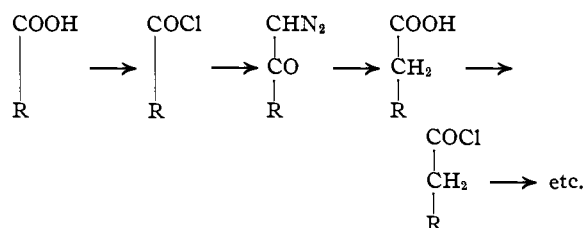
(2) Previous publication in this series: M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, *ibid.*, 63, 201 (1941).

Brauns<sup>3</sup> (m. p. 108°, spec. rot. +45°, CHCl<sub>3</sub>) to which the structural assignment of 6-chloro-*keto-d*-fructose has been made.<sup>4</sup>

In 1912 Wolff<sup>5</sup> described a characteristic rearrangement of diazoketones in their reaction with water or alcoholic ammonia in the presence of catalytic amounts of silver oxide.



It has not been until relatively recent years that the Wolff rearrangement has received any degree of attention. Arndt and co-workers<sup>6</sup> have developed the reaction as a general synthetic method for lengthening the carbon chain.



We have applied the Wolff rearrangement to the acetylated aldonic acids. Treatment of a suspension of II in hot water with catalytic amounts of silver oxide, followed by silver ion removal with hydrogen sulfide and concentration, yielded 2-desoxy-*d*-glucoheptono- $\delta$ -lactone tetraacetate (IV) of specific rotation +39.5° (CHCl<sub>3</sub>). According to Lane and Wallis,<sup>7</sup> this rearrangement may take place with racemization provided that the terminal carbon of the migrating group R contains a hydrogen atom. This structural prerequisite is present in our compound and accordingly a mixture (not necessarily equimolecular) of 2-desoxy-*d*-glucoheptonic acid (or lactone) and 2-desoxy-*d*-mannoheptonic acid (or lactone) would be predictable. Only one product was isolated (ca. 70% yield). In the absence of any evidence for a second product, the 2-desoxy-*d*-glucoheptanolactone structure will be assigned provisionally to the substance isolated.

(3) D. H. Brauns, *ibid.*, 42, 1846 (1920).

(4) E. Pacsu and F. V. Rich, *ibid.*, 55, 3018 (1933).

(5) L. Wolff, *Ann.*, 394, 23 (1912).

(6) F. Arndt and B. Eistert, *Ber.*, 68, 200 (1935).

(7) J. F. Lane and E. S. Wallis, *J. Org. Chem.*, 6, 443 (1941).

Saponification of IV with barium hydrate, followed by removal of barium ion with sulfuric acid and concentration, yielded crystalline 2-desoxy-*d*-glucoheptonolactone (V) of specific rotation  $+20^\circ$  ( $H_2O$ ). The analytical data definitely indicate a lactone structure for IV and V. If, in accordance with the principles of Hudson's lactone rule, the rotations of these compounds are due almost in their entirety to the position of the lactone ring, then ring closure in IV and V must be on the right (as represented in the Fischer projection formula). The acceptance of such an hypothesis favors assignment to IV and V of a *delta* lactone structure, since carbon four in these structures is on the left. The *delta* lactones of the normal sugar acids are relatively unstable and exhibit moderately rapid hydrolysis. Further evidence for the 1,5 ring in IV, then, lies in the fact that it was found to be rapidly titratable to a stable end-point within a period of one and one-half minutes from the time of solution in acetone-water. It was found that V was too slowly soluble to allow rapid titration but was titratable to a stable end-point within four and one-half to five minutes. Contrary to expectation, IV exhibited no mutarotation in either methanol or aqueous acetone. V was too slowly soluble in water for early polarimetric readings in that medium; however, no mutarotation was observed after an initial rotation of  $+20^\circ$  at twenty minutes. Attempts were made to follow lactonization of the free acid by the general method of Levene and Simms.<sup>8</sup> An initial reading at three minutes gave a specific rotation of  $+20^\circ$ . Thereafter there was no observable mutarotation over a period of eighty hours.

Explanation of the apparently anomalous optical behavior of IV and V may lie in an effective increase in the rate of hydrolysis due to the influence of the 2-desoxy carbon. Again, the explanation may lie in an extraordinary similarity in rotation between the lactone and its acid, in the event of which Hudson's lactone rule would not be applicable. The expectation would be that in V *gamma* lactone formation would be sufficiently slow to be readily observable and an appreciable quantity of the *gamma* lactone in the equilibrium mixture should yield a more negative value. As more information is obtained concerning the little known group of 2-desoxy sugar acids, it may well be that their behavior will be found to differ

markedly from that of the normal sugar acids. Thus, an abnormally high rate of hydrolysis has been found<sup>9</sup> for the glycopyranosides of the 2-desoxy sugars in comparison with the rate exhibited by the normal sugar pyranosides.

Further extension of these reactions is in progress in this Laboratory.

### Experimental

**1-Diazo-1-desoxy-*keto-d*-fructose Tetraacetate.**—*d*-Araonic acid tetraacetate<sup>10</sup> (7.1 g.), prepared according to the excellent method of Robbins and Upson,<sup>11</sup> was dissolved in 20 cc. of benzene and 3 cc. (2 moles) of thionyl chloride added. The solution was warmed until the evolution of hydrogen chloride ceased, as shown by ammonia test. The excess thionyl chloride was removed by solvent concentration under reduced pressure followed by repeated additions of benzene and subsequent removal in the same manner. The sirupy residue was dissolved in 50 cc. of anhydrous ether and the solution cooled to  $0^\circ$ . Two moles of diazomethane gas was then added and the solution allowed to stand overnight. At the end of this period, some separated polymethylenes were removed by filtration and the filtrate was concentrated with a stream of dry air until crystallization occurred. The cream-colored crystals were removed by filtration and washed with cold ether; yield 5.7 g.; m. p.  $88.5-89^\circ$ . Pure material was obtained on recrystallization from methanol-ether; yield 5 g.; m. p.  $93-94^\circ$ ; spec. rot.  $-11^\circ$  ( $23^\circ$ ,  $c$  4, abs.  $CHCl_3$ ).<sup>12</sup>

The purified substance possessed a slight cream color. It was soluble in alcohol, acetone and warm ether but was insoluble in petroleum ether and water. It reduced boiling Fehling solution.

*Anal.* Calcd. for  $C_{14}H_{16}O_8N_2$ : C, 46.93; H, 5.06; N, 7.82. Found: C, 46.93; H, 5.21; N, 7.67.

**1-Chloro-*keto-d*-fructose Tetraacetate.**—Two grams of 1-diazo-1-desoxy-*keto-d*-fructose tetraacetate was suspended in anhydrous ether and dry hydrogen chloride passed into the solution until the evolution of nitrogen ceased. The solution was cooled and an equal amount of petroleum ether was then added. The crystals which formed were removed by filtration and washed with ether-petroleum ether; yield 1.5 g.; m. p.  $75-77^\circ$ . Pure material was obtained on two further crystallizations from ether-petroleum ether; yield 1 g.; m. p.  $77.5-78^\circ$ ; spec. rot.  $+68^\circ$  ( $22^\circ$ ,  $c$  4, abs.  $CHCl_3$ ).

The substance reduced boiling Fehling solution but no precipitate formed on boiling with alcoholic silver nitrate.

*Anal.* Calcd. for  $C_{14}H_{16}O_8Cl$ : C, 45.85; H, 5.22; Cl, 9.66. Found: C, 45.81; H, 5.40; Cl, 9.50.

**1-Bromo-*keto-d*-fructose Tetraacetate.**—1-Diazo-1-desoxy-*keto-d*-fructose tetraacetate (3.5 g.) was treated in the same manner as in the above-described synthesis of the corresponding 1-chloro derivative, using hydrogen bro-

(9) M. Bergmann and W. Breuers, *Ann.*, **470**, 38 (1929); P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **88**, 791 (1930).

(10) C. D. Hurd and J. C. Sowden, *This Journal*, **60**, 235 (1938).

(11) G. Robbins and F. Upson, *ibid.*, **62**, 1074 (1940); cf. J. M. Brakenbury and F. Upson, *ibid.*, **55**, 2512 (1933).

(12) All rotations are recorded to the D-line of sodium light,  $23^\circ$  is the temperature,  $c$  is the concentration in g. per 100 cc. of soln.

(8) P. A. Levene and H. S. Simms, *J. Biol. Chem.*, **65**, 31 (1925).

vide instead of hydrogen chloride. The product which crystallized was removed by filtration and washed with ether-petroleum ether; yield 3.4 g.; m. p. 67.5–68°. Pure material was obtained on crystallization from ether; yield 3 g.; m. p. 68°; spec. rot. +62.5° (26°, *c* 4, abs. CHCl<sub>3</sub>).

The substance reduced boiling Fehling solution but no precipitate formed on boiling with alcoholic silver nitrate.

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>O<sub>9</sub>Br: Br, 19.43. Found: Br, 19.12.

**1-Chloro-*keto-d*-glucoheptulose Pentaacetate (III).**—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate<sup>2</sup> (1.0 g.) was suspended in anhydrous ether (15 cc.) and dry hydrogen chloride gas was passed into the solution until the compound was dissolved. The solution was then allowed to stand for two hours, after which the excess hydrogen chloride was removed by washing with aqueous sodium bicarbonate solution. An equal volume of petroleum ether was added to the dried (sodium sulfate) ethereal solution and the crystalline product which formed was removed by filtration and washed with petroleum ether; yield 0.6 g.; m. p. 100–101°; spec. rot. –5.5° (22°, *c* 5, abs. CHCl<sub>3</sub>). These constants were unchanged on two further crystallizations from ether-petroleum ether.

The substance was soluble in the common solvents except petroleum ether and water. It reduced boiling Fehling solution. No precipitate was formed on boiling with alcoholic silver nitrate.

*Anal.* Calcd. for C<sub>17</sub>H<sub>23</sub>O<sub>11</sub>Cl: C, 46.52; H, 5.28; Cl, 8.08. Found: C, 46.52; H, 5.28; Cl, 8.05.

This substance was the uncharacterized compound isolated in crude form from the mother liquors of our original preparations<sup>2</sup> of 1-diazo-1-desoxy-*d*-glucoheptulose pentaacetate (II). When the preparation of II was carried out under nearly anhydrous conditions only traces of the chloro compound were obtained.

**1-Bromo-*keto-d*-glucoheptulose Pentaacetate.**—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate (3.5 g.) was treated in the same manner as in the synthesis of the corresponding 1-chloro derivative, using hydrogen bromide in place of hydrogen chloride. The product which crystallized was removed by filtration and washed with ether-petroleum ether; yield 3.3 g.; m. p. 80–82°. Pure material was obtained on three recrystallizations from ether-petroleum ether; m. p. 86–87°; spec. rot. –4° (24°, *c* 5, abs. CHCl<sub>3</sub>).

This compound was slightly less soluble than the corresponding chloro derivative. It reduced boiling Fehling solution and yielded no precipitate on boiling with alcoholic silver nitrate.

*Anal.* Calcd. for C<sub>17</sub>H<sub>23</sub>O<sub>11</sub>Br: Br, 16.54. Found: Br, 16.72.

**2-Desoxy-*d*-glucoheptonolactone Tetraacetate (IV).**—1-Diazo-1-desoxy-*d*-glucoheptulose pentaacetate (1 g.) was suspended in 40 cc. of water with 0.2 g. of silver oxide. The mixture was warmed to about 70° and 0.2 g. of silver oxide was added portionwise over a period of fifteen minutes. The mixture was then refluxed for fifteen minutes, after which the silver oxide was removed by filtration. The silver ion was removed with hydrogen sulfide, followed by filtration. The clear filtrate was then concentrated to about 15 cc. The fibrous crystals that formed were re-

moved by filtration and washed with water; yield 0.5 g.; m. p. 129–130°, unchanged on further recrystallization from hot water; spec. rot. +40° (20°, *c* 4, abs. chloroform, no detectable mutarotation). The mother liquors on further concentration yielded 0.1 g. of additional material.

The substance did not reduce boiling Fehling solution.

*Anal.* Calcd. for C<sub>7</sub>H<sub>9</sub>O<sub>8</sub>(CH<sub>3</sub>CO)<sub>4</sub> (lactone tetraacetate): C, 50.00; H, 5.60; saponification value (five equivalents), 13.88 cc. 0.1 *N* sodium hydroxide per 100 mg. Calcd. for C<sub>7</sub>H<sub>9</sub>O<sub>7</sub>(CH<sub>3</sub>CO)<sub>5</sub> (acid pentaacetate): C, 48.57; H, 5.75; saponification value (six equivalents), 14.27 cc. Found: C, 49.76; H, 5.58; saponification value, 13.8 cc.

The analytical data indicate that in the course of the rearrangement one mole of acetic acid was lost, presumably by lactonization. In a study of the position of ring closure the following experiments were performed.

(a) 2-Desoxy-*d*-glucoheptonolactone tetraacetate (0.2766 g.) was dissolved in acetone (50 cc.). Boiled distilled water (100 cc.) was quickly added and the solution immediately titrated to a phenolphthalein end-point. Time elapsed from introduction of the acetone to complete neutralization was one minute and thirty seconds. A volume of 7.75 cc. of 0.1005 *N* sodium hydroxide which, less a blank of 0.15 cc., gives a volume of 7.60 cc. required for neutralization. The neutralization equivalent calculated therefrom is 362.1; theory for the lactone tetraacetate, 360.3. That the compound was instantaneously titratable is evidence in support of a *delta*-lactone structure.

(b) In absolute methanol solution there was no observable mutarotation (initial reading, four minutes) over a period of forty-five hours; spec. rot. +34° (22°, *c* 2.5).

(c) A sample of the lactone was dissolved in dry acetone (8 cc.) and made up to 15.00 cc. with water. There was no observable mutarotation (initial reading, six minutes) over a period of twenty hours; spec. rot. +35° (23°, *c* 4).

**2-Desoxy-*d*-glucoheptonolactone (V).**—2-Desoxy-*d*-glucoheptonolactone tetraacetate (5 g.) was treated with an equivalent amount of a saturated barium hydrate solution (10.95 g. of barium hydrate octahydrate) and allowed to stand at room temperature overnight. The barium ion was then removed with an equivalent amount of sulfuric acid (69.4 cc. *N*) and the barium sulfate removed by filtration. The clear filtrate was concentrated to about 10 cc. and on cooling crystallization ensued; yield 1 g.; m. p. 170°, unchanged on further recrystallizations effected by solution in water and subsequent concentration; spec. rot. +20° (26°, *c* 5, H<sub>2</sub>O, no mutarotation).

The compound was soluble in warm water and insoluble in the common organic solvents except glacial acetic acid.

*Anal.* Calcd. for C<sub>7</sub>H<sub>12</sub>O<sub>6</sub> (lactone): C, 43.75; H, 6.29; sapon. equiv., 192. Calcd. for C<sub>7</sub>H<sub>14</sub>O<sub>7</sub> (acid): C, 40.00; H, 6.71; sapon. equiv., 210. Found: C, 43.44; H, 6.27; sapon. equiv., 196.

The lactone was too slowly soluble in water to allow early initial polarimetric readings in that medium. No mutarotation was observed after a reading of +20° at twenty minutes. Attempts were made to follow lactonization of the free acid, according to the general procedure of Levene and Simms.<sup>8</sup> The lactone (0.4717 g.) was suspended in water and 4.70 cc. of 0.5008 *N* sodium hydroxide was added. The compound went into solution slowly and

after about four minutes the alkaline color of phenolphthalein faded. Two additional drops (0.1 cc.) of base were required for complete neutralization (total 4.8 cc.). A further 0.2 cc. of alkali was added followed by the addition of an equivalent volume (5.00 cc.) of 0.5007 *N* hydrochloric acid. The solution was quickly made up to 15.00 cc. and the polarimetric reading taken (initial reading, three minutes); spec. rot. +20.1° (23°, *c* 3.1). Thereafter there was no observable mutarotation over a period of eighty hours.

We acknowledge the general assistance of Messrs. Percy McWain (N.Y.A. Project O.S.U. 170) and Clarence M. Clevenger.

### Summary

1. 1-Diazo-1-desoxy-*keto-d*-fructose tetraacetate has been synthesized by the action of diazomethane upon *d*-arabonyl chloride tetraacetate.
2. The 1-chloro and the 1-bromo derivatives

of the *keto*-forms of *d*-fructose and of *d*-glucoheptulose acetates have been synthesized by the action of the hydrogen halides upon the corresponding diazomethyl ketone acetates (II).

3. 1-Diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate (II) underwent the Wolff rearrangement to produce a lactone form of 2-desoxyglucoheptonic acid tetraacetate, from which 2-desoxyglucoheptonolactone was obtained by saponification.

4. The above 2-desoxyaldonolactone and its acetate exhibited anomalous properties.

5. The above reactions represent transformations from the aldose series to (a) the ketose series and to (b) the 2-desoxyaldonic acid series.

COLUMBUS, OHIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

## Anthochlor Pigments. III. The Pigments of *Cosmos Sulphureus*

BY T. A. GEISSMAN

Previous studies on the sap-soluble flower pigments of certain species of *Compositae* have shown that the petals of these species contain substances which form intensely red salts with alkalis. For convenience these pigments have been described by the term "anthochlor." The tetrahydroxychalcone butein (I) has been identified as one member of this class of pigments and has been isolated from *Dahlia variabilis*<sup>1</sup> and from two species of *Coreopsis*.<sup>2</sup>

It was noted in the paper describing the studies on *Coreopsis gigantea*<sup>2b</sup> that in this flower a second substance accompanies butein, and it was suggested on the basis of the analytical figures for its crystalline acetate that this substance was a pentahydroxychalcone hexoside. This compound has now been isolated from the ray florets of *Cosmos sulphureus* ("Orange Flare"). *C. sulphureus* is a garden annual whose bright orange rays and yellow disk florets give the anthochlor reaction with alkali. Ether extraction of the dried, powdered rays yielded the glycoside as a yellow amorphous powder which separated from the ether during the extraction. Further treatment of the ether-extracted rays by a somewhat more lengthy procedure yielded an additional

amount of the pigment. It formed a white crystalline acetate identical with that of the pigment previously isolated from *Coreopsis gigantea*. It is proposed to call this pigment "coreopsin."

The previously reported analytical figures on the basis of which coreopsin was assumed to be a pentahydroxychalcone hexoside were somewhat in error since it has been found that the aglycone of the pigment is butein. Hydrolysis of coreopsin acetate (the acetate was chosen since it is readily crystallized while the pigment itself has been obtained only in an amorphous, although apparently homogeneous, condition), followed by acetylation of the ether-extractable products, yielded the triacetate of butin (II), the flavanone isomeric with butein. The formation of butin in the hydrolysis is undoubtedly due to the isomerization of the butein first produced from the glycoside. The isomerization of *o*-hydroxychalcones to the corresponding flavanones under these conditions is a well-known reaction<sup>3</sup> and the sample of butin triacetate used for purposes of comparison was synthesized by treating a sample of synthetic butein under conditions identical with those used for the hydrolysis of the glycoside. That coreopsin is a glycoside of butein and not of butin

(1) Price, *J. Chem. Soc.*, 1018 (1939).

(2) (a) Geissman, *THIS JOURNAL*, **63**, 656 (1941); (b) **63**, 2689 (1941).

(3) (a) Perkin and Hummel, *J. Chem. Soc.*, **85**, 1462 (1904); (b) Göschke and Tambor, *Ber.*, **45**, 186 (1912). These describe the preparation of butin.