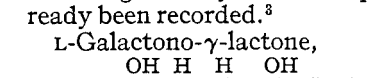
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Synthesis of Perseulose (L-Galaheptulose)[1]

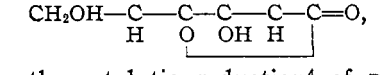
BY M. L. WOLFROM, J. M. BERKEBILE AND A. THOMPSON

The structure of perseulose was established by Hudson and co-workers[2] as L-galaheptulose (L-gala-D-*fructo*-heptose). We report herein its synthesis; the synthesis of its enantiomorph from D-galactonyl chloride pentaacetate has already been recorded.[3]

L-Galactono-γ-lactone,



is obtainable by the catalytic reduction[4] of D-galacturonic acid,



now readily available from commercial citrus or beet pectin through its easily isolable sodium calcium mixed salt.[4,5] The reaction sequence (all substances being crystalline) employed in the synthesis of perseulose was as follows: D-galacturonic acid (I) → L-galactono-γ-lactone (II) → L-galactonamide (III) → L-galactonamide O-pentaacetate (IV) → L-galactonic acid pentaacetate (V) → L-galactonyl chloride pentaacetate (VI) → 1-diazo-1-desoxy-*keto*-L-galaheptulose pentaacetate (VII) → *keto*-L-galaheptulose hexaacetate (VIII) → L-galaheptulose or perseulose (IX). The intermediates IV to VII, inclusive, and the D,L forms of III, IV and VIII are described for the first time. L-Galactonic acid pentaacetate was obtainable by the deamination of L-galactonamide O-pentaacetate according to the general procedure of Hurd and Sowden[6] or alternatively by the acetylation of cadmium L-galactonate with acetic anhydride and hydrogen chloride.[7] *keto*-L-Galaheptulose hexaacetate (VIII) has been reported by Khouvine and Arragon.[8] In the D-series, this substance was recorded[3] as dimorphous but only the lower melting form was encountered in the present work and in that of Khouvine and Arragon.[8] The L-galaheptulose (perseulose) was characterized by melting point, mutarotatory characteristics and phenylosazone.

In the course of this work the tetraacetates of the L and D,L forms of galactono-γ-lactone were prepared. We also report the preparation in crystalline form of D-lyxonic acid tetraacetate.

(1) Paper No. 10 in the series entitled "The Action of Diazomethane upon Acylic Sugar Derivatives"; previous communication, M. L. Wolfrom and A. Thompson, THIS JOURNAL, **68**, 1453 (1946).

(2) R. M. Hann and C. S. Hudson, *ibid.*, **61**, 336 (1939); N. K. Richtmyer, R. M. Hann and C. S. Hudson, *ibid.*, 340.

(3) M. L. Wolfrom, R. L. Brown and E. F. Evans, *ibid.*, **65**, 1021 (1943).

(4) H. S. Isbell, *J. Research Natl. Bur. Standards*, **33**, 45 (1944).

(5) P. P. Regna and B. P. Caldwell, THIS JOURNAL, **66**, 244 (1944); R. Pasternack and P. P. Regna, U. S. Patent 2,338,534 (1944).

(6) C. D. Hurd and J. C. Sowden, THIS JOURNAL, **60**, 235 (1938).

(7) K. Ladenburg, M. Tishler, J. W. Wellman and R. D. Babson, *ibid.*, **66**, 1217 (1944).

(8) Yvonne Khouvine and G. Arragon, *Compt. rend.*, **206**, 917 (1938).

Experimental[9]

L-Galactono-γ-lactone Tetraacetate.—Following the procedures of Regna and Caldwell[5] and of Isbell,[4] D-galacturonic acid, as the hexahydrated sodium calcium mixed salt, was prepared by the enzymic hydrolysis of citrus pectin and reduced catalytically to L-galactonic acid. The latter was isolated as the calcium salt pentahydrate and this was converted in the usual manner to the γ-lactone. Ten grams of L-galactono-γ-lactone[4] was mixed at 0° with 50 ml. of pyridine and 50 ml. of acetic anhydride. After two hours of intermittent agitation the lactone went into solution. The reaction mixture was allowed to stand overnight at ice-box temperature. Upon pouring the solution into 250 ml. of rapidly stirred ice and water, the acetate separated. The precipitated acetate was removed and further material was obtained from the filtrate by chloroform extraction.

The total product was recrystallized from absolute ethanol or toluene; yield 16 g. (83%), m. p. 67–68° (cor.), $[\alpha]^{23}D$ +20° (*c* 4, chloroform), $[\alpha]^{23}D$ +23° (*c* 4, 80 pts. acetone–20 pts. water). These constants are in agreement (opposite sign) with those (m. p. 67–68°, $[\alpha]^{25}D$ −22° in 80% aqueous acetone) recorded[10] for the enantiomorph.

Anal. Calcd. for $C_{14}H_{18}O_{10}$: C, 48.56; H, 5.24. Found: C, 48.57; H, 5.22.

D,L-Galactono-γ-lactone Tetraacetate.—This substance crystallized on cooling a solution in absolute ethanol of equal parts of the enantiomorphs; m. p. 77–78° (cor.), $[\alpha]^{26}D$ 0° (*c* 4, chloroform).

L-Galactonamide O-Pentaacetate.—L-Galactonamide[11] was prepared from the γ-lactone according to the general procedure of Glattfeld and MacMillan[12]; m. p. 175° (cor.); $[\alpha]^{25}D$ −30° (*c* 4, water) in agreement with those (m. p. 170°, $[\alpha]^{18}_{5780}$ −28° in water[11]; m. p. 175°, $[\alpha]^{20}D$ +31.5° for the enantiomorph[12]) previously reported. The amide (10 g.) was acetylated as described above (chloroform extraction omitted) for the acetylation of the γ-lactone; yield 16.8 g. (81%) of crude product of good purity. Pure material was obtained on further crystallization from absolute ethanol or benzene; m. p. 167° (cor.), $[\alpha]^{25}D$ −27° (*c* 4, chloroform) in agreement (opposite sign) with those (m. p. 166–167°, $[\alpha]^{24}D$ +27° in chloroform) reported[6] for the enantiomorph.

D,L-Galactonamide.—This substance crystallized on cooling an 80% ethanolic solution (25 ml.) of 0.7 g. each of the enantiomorphs; m. p. 174° (cor.); $[\alpha]^{26}D$ 0° (*c* 4, water).

D,L-Galactonamide O-Pentaacetate.—This substance crystallized on cooling an ethanolic (absolute) solution of equal parts of the enantiomorphs; m. p. 167° (cor.), $[\alpha]^{26}D$ 0° (*c* 4, chloroform).

L-Galactonic Acid Pentaacetate.—This substance was prepared from L-galactonamide O-pentaacetate by deamination with nitrous anhydride according to the procedure of Hurd and Sowden[6] for the enantiomorph; m. p. 132–133° (cor.), $[\alpha]^{28}D$ −14° (*c* 4, chloroform) in agreement (opposite sign) with those reported[6] (m. p. 131–132°, $[\alpha]^{25}D$ +12° in chloroform) for the enantiomorph.

(9) Unless otherwise noted, all experimental work was performed by Mr. J. M. Berkebile.

(10) F. W. Upson, J. M. Brackenbury and C. Linn, THIS JOURNAL, **58**, 2549 (1936).

(11) R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith and M. Stacey, *J. Chem. Soc.*, 1422 (1933).

(12) J. W. E. Glattfeld and D. MacMillan, THIS JOURNAL, **56**, 2481 (1934).

Anal. Calcd. for $C_{16}H_{22}O_{12}$: C, 47.27; H, 5.46; sapon. value (6 equivs.), 14.8 ml. 0.1 *N* NaOH per 100 mg. Found: C, 47.17; H, 5.44; sapon. value, 14.7 ml.

This substance was alternatively available by acetylation of cadmium L-galactonate with acetic anhydride and hydrogen chloride according to the procedure of Ladenburg and co-workers[7] for the analogous preparation of D-ribonic acid tetraacetate. The final reaction mixture obtained from 60 g. of the cadmium salt was concentrated under reduced pressure to a thick slurry. After adding this residue to 500 ml. of cold (1°) water to dissolve the cadmium salts, it was extracted with three portions of chloroform and the combined extracts were washed with water. The sirup obtained on solvent removal from the dried extract was dissolved in absolute ethanol (50 ml.) and concentrated under reduced pressure to half volume; 200 ml. of toluene was then added and the solution was distilled at atmospheric pressure to a volume of 100 ml.; crystallization was then effected at ice-box temperature; yield 74 g. (80%), m. p. 131–132° (cor.).

L-Galactonyl Chloride Pentaacetate.—Twenty grams of L-galactonic acid pentaacetate was dissolved in 200 ml. of dry ether, to which was then added 11.3 g. of phosphorus pentachloride. This reaction mixture was warmed and agitated until the phosphorus pentachloride dissolved. The solution was filtered after standing for four hours at room temperature. Six hundred ml. of petroleum ether (b. p. 30–60°) was then added and the mixture maintained at ice-box temperature for twenty-four hours. The crystals were filtered rapidly and adherent solvent removed in a vacuum desiccator; yield 17.4 g. (83%), m. p. 79–80° (cor.). One recrystallization from ether gave pure material; m. p. 81–82° (cor.), $[\alpha]^{24}D$ −3° (*c* 4, chloroform) in agreement (opposite sign) with those (m. p. 80–81°, $[\alpha]^{21}D$ +3°) reported[3] for the enantiomorph.

Anal. Calcd. for $C_{16}H_{21}O_{11}Cl$: C, 45.24; H, 4.98; Cl, 8.35; sapon. value (7 equivs.), 16.5 ml. 0.1 *N* NaOH per 100 mg. Found: C, 45.30; H, 4.93; Cl, 8.01; sapon. value, 16.5 ml.

1-Diazo-1-desoxy-*keto*-L-galaheptulose Pentaacetate.—L-Galactonyl chloride pentaacetate (9.5 g.) in 150 ml. of dry ether was added to a cold solution of 4 g. of diazomethane in 200 ml. of dry ether. The solution stood at room temperature for thirty minutes and was then placed at ice-box temperature for one day. The acetate crystallized and was removed by filtration. The mother liquor was concentrated under reduced pressure to 100 ml. and petroleum ether (100 ml.) added. Upon cooling, a second crop was obtained; total crude yield 7.5 g. (78%), m. p. 132–133° (cor.).

One gram of the above acetate was dissolved in 10 ml. of benzene and chromatographed on a 230 × 35 mm. (diam.)[13] column of Magnesol[14]-Celite[15] (5:1 by wt.) by development with 750 ml. of benzene–ethanol (100:1 by vol.). An alkaline permanganate streak[16] showed a large zone near the bottom and a faint one near the top of the column. The sectioned bottom zone was extracted with acetone and the residue obtained on solvent removal was crystallized from methanol–ether–petroleum ether; crystalline solid of a slight yellow tinge, m. p. 136.5–137.5° (cor.), $[\alpha]^{29}D$ −59° (*c* 4, chloroform) in fair agreement (opposite sign) with those (m. p. 136–137°, $[\alpha]^{23}D$ +64° in chloroform) reported[3] for the enantiomorph.

Anal. Calcd. for $C_{17}H_{22}O_{11}N_2$: C, 47.44; H, 5.15; N, 6.51. Found: C, 47.63; H, 5.06; N, 6.56.

***keto*-L-Galaheptulose Hexaacetate (*keto*-Perseulose Hexaacetate).**—A solution of 1-diazo-1-desoxy-*keto*-L-galaheptulose pentaacetate (9.95 g.) in 150 ml. of glacial acetic acid, to which had been added 0.01 g. of cupric acetate, was heated to about 80° where a vigorous evolution of nitrogen occurred. After heating the solution at reflux for several minutes it was allowed to cool to room temperature. The material was poured into ice and water, extracted with chloroform, and dried over sodium sulfate. Upon evaporation of the solvent under reduced pressure, the residue was dissolved in ethanol and water was added to opalescence. Crystallization occurred during twelve hours at ice-box temperature; yield 8.0 g., m. p. 101–102° (cor.).

The mother liquors were concentrated under reduced pressure to a sirup which was dissolved in 10 ml. of benzene and chromatographed on a 230 × 35 mm. (diam.) column[13] of Magnesol[14]–Celite[15] (5:1 by wt.) by development with 700 ml. of benzene–ethanol (100:1 by vol.). A large zone near the bottom was detected by the alkaline permanganate streak[16] and on elution with acetone yielded crystalline material; yield 0.5 g. or 8.5 g. (85%) total, m. p. 101–102° (cor.). A rechromatogram effected in the same manner yielded pure material; crystalline solid, m. p. 101.5–102.5° (cor.), $[\alpha]^{31}D$ + 21.5° (*c* 2, benzene). Khouvine and Arragon[8] reported m. p. 105°; $[\alpha]^{20}_{5780}$ +20.8° (*c* 4, benzene). Wolfrom and co-workers[3] reported for the enantiomorph: m. p. 101.5–102.5°; $[\alpha]^{23}D$ −20° (*c* 3, benzene). The higher melting polymorph[3] was not encountered.

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.19; H, 5.68.

***keto*-D,L-Galaheptulose Hexaacetate (*keto*-D,L-Perseulose Hexaacetate).**—This compound was obtained by crystallizing a mixture of equal amounts of the enantiomorphs from methanol and ether (1:1); m. p. 149.5–150.5° (cor.), $[\alpha]^{24}D$ 0° (*c* 2, benzene).

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.33; H, 5.70.

Perseulose (L-Galaheptulose) and Its Phenylosazone (L-*galacto*-Heptose Phenylosazone[17]).—*keto*-L-Galaheptulose hexaacetate (5 g.) was deacetylated with cold barium hydroxide as described[8] for the enantiomorph except that the barium ion was removed by an excess of carbon dioxide gas followed by filtration and passage of the filtrate successively through 200 g. columns of Amberlites IR-100H[18] and IR-4B[18]; yield 1.5 g. of the hemihydrate,[19] m. p. 102–103° (cor.), $[\alpha]^{23}D$ −102° (extrapolated) → −82°, $k_1 + k_2$ at 23° = 0.028 (min. and dec. log) in agreement with recorded[3] values.

Anal. Calcd. for $2C_7H_{14}O_7 \cdot H_2O$: C, 38.34; H, 6.90. Found: C, 38.19; H, 6.80.

The above crystallization mother liquors were subjected to phenylosazone formation; yield 0.8 g. (≈ 0.5 g. of perseulose or a total yield of 2.0 g. or 78%). Recrystallization from 95% ethanol yielded pure material; m. p. 202° (cor.), $[\alpha]^{25}D$ −36° (pyridine) in agreement with previously recorded[2] (m. p. 202°, $[\alpha]^{20}D$ −35° in pyridine) values.

Anal. Calcd. for $C_{19}H_{24}O_5N_4$: C, 58.73; H, 6.23; N, 14.43. Found: C, 58.91; H, 6.12; N, 14.47.

D-Lyxonic Acid Tetraacetate.[20]—D-Lyxono-γ-lactone[21] (100 g.) was transformed to the amide according to the procedure of Glattfeld and MacMillan.[12] The crude, crystalline product was dried in a vacuum desiccator over concentrated sulfuric acid and was employed directly in the next step; yield 96.5 g. One recrystallization effected from methanol–ethanol containing ammonia yielded material exhibiting $[\alpha]^{21}D$ −10° (*c* 4, water). Hockett

(13) Adsorbent dimensions.

(14) Westvaco Chlorine Products Co., South Charleston, West Virginia.

(15) No. 535, Johns-Manville Co., New York, N. Y.

(16) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(17) Nomenclature of J. C. Sowden, *ibid.*, **69**, 1047 (1947).

(18) Rohm and Haas Co., The Resinous Products Division, Philadelphia, Pennsylvania.

(19) We are indebted to Dr. C. S. Hudson of the National Institute of Health, U. S. Public Health Service, Bethesda, Maryland, for nuclei of perseulose hemihydrate.

(20) Experimental work by Dr. A. Thompson.

(21) A. Thompson and M. L. Wolfrom, THIS JOURNAL, **68**, 1509 (1946).

and co-workers[22] report for D-lyxonamide: m. p. 110°; $[\alpha]^{20}D$ −13.5° (*c* 1, water).

The crude, finely powdered D-lyxonamide was acetylated, in 50-g. portions, by stirring for eight hours at 0° with 365 g. of acetic anhydride containing 20 g. of zinc chloride. The temperature of the mixture was then allowed to rise to room temperature and maintained there until all of the amide was in solution whereupon it was poured into 1 liter of ice and water and allowed to stand for three hours with occasional stirring. The solution was extracted with six 100-ml. portions of chloroform. The combined chloroform extract was washed once with water, dried with anhydrous sodium sulfate and concentrated to a sirup. This sirup has failed to crystallize and was used directly in the next step.

The above sirup (from 50 g. of D-lyxonamide), following the general deamination procedure of Hurd and Sowden,[6] was dissolved in five times its weight of glacial acetic acid and divided into 50-ml. portions. Oxides of nitrogen, generated by the action of concentrated sulfuric acid on sodium nitrite, were bubbled into the acetic acid solutions until a dark green color persisted whereupon the flow of gas was stopped and the solutions were allowed to stand at room temperature for four hours. The combined acetic acid solution was evaporated under reduced pressure at 50° to a sirup. The sirup was dissolved in an excess of aqueous sodium bicarbonate and extracted with chloroform, the extract being discarded. The bicarbonate solution was then acidified with dilute hydrochloric acid and again extracted several times with chloroform. The combined chloroform extract was dried with anhydrous sodium sulfate and concentrated again to a thick sirup. The last traces of chloroform were removed by distilling the sirup with toluene under reduced pressure. The sirup was crystallized from toluene; yield 84.5 g. from 100 g. of D-lyxono-γ-lactone. Three recrystallizations from toluene yielded pure material; m. p. 113.5–115°, $[\alpha]^{22}D$ +19° (*c* 5.5, chloroform).

Anal. Calcd. for $C_{13}H_{18}O_{10}$: C, 46.71; H, 5.43; sapon. value (5 equivs.), 14.96 ml. 0.1 *N* NaOH per 100 mg. Found: C, 46.76; H, 5.26; sapon. value, 14.83 ml.

Acknowledgment.—One of us (A. T.) acknowledges fellowship fund support granted by The Ohio State University Research Foundation to the University for aid in fundamental research (Project 7670-107).

(22) R. C. Hockett, J. B. Ames and A. Scattergood, *Abstracts Papers Am. Chem. Soc.*, **109**, 2R (1946).

Summary

1. A synthesis of perseulose (L-galaheptulose) from L-galactono-γ-lactone is described.

2. The following substances are also described: D,L-galactonamide; the tetraacetates of D-lyxonic acid, L-galactono-γ-lactone and D,L-galactono-γ-lactone; the O-pentaacetates of L-galactonamide, D,L-galactonamide, L-galactonic acid, L-galactonyl chloride and 1-diazo-1-desoxy-*keto*-L-galaheptulose; and the hexaacetate of *keto*-D,L-galaheptulose.

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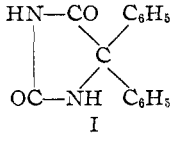
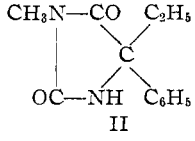
Conversion of Alkyl 2-Anilino-2-phenylethyl Ketones into Hydantoins[1]

BY HENRY R. HENZE AND E. MURRAY WILLIAMS[2]

Although hydantoin is physiologically innocuous,[3] many of its derivatives have been shown to have activity as anticonvulsants[4] and two (I and II) are actually in general use in the control of epilepsy of the *grande mal* type. Disubstitution of



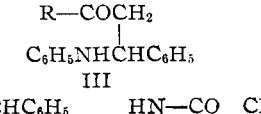
I



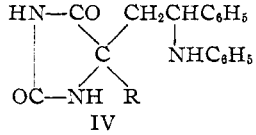
II

alkyl or aryl groups at the 5-position of the hydantoin nucleus is likely to produce derivatives of limited solubility in water or acidic solutions, so it is really the more water-soluble sodium salt of 5,5-diphenylhydantoin (I) which is employed. However, in the case of a trisubstituted (3,5,5-) derivative, such as II, formation of a more soluble alkali-metal salt is impossible. Another approach to the problem of producing derivatives of more desirable solubility has been the incorporation, at the 5-position, of a grouping capable of yielding soluble salts with acids. For example, we have previously prepared hydantoins possessing 5-mono- or 5,5-disubstituted heterocyclic nitrogen groups.[5] Or the 5-alkyl or -aryl groupings have been further substituted with certain amino derivatives.

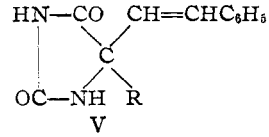
The availability of a series of anilino-substituted ketones (III), from reaction of benzalaniline with aliphatic ketones in the presence of boron trifluoride etherate,[6] suggested the possibility of their conversion into 5-alkyl-5-(2-anilino-2-phenylethyl) hydantoins through interaction with a cyanide and ammonium carbonate. The products of such reaction were found to be 5,5-disubstituted hydantoins, but not of the structure anticipated (IV).



III



IV



V

(1) From the M.A. thesis of E. M. Williams, January, 1949.

(2) Present address: Tennessee Eastman Co., Kingsport, Tenn.

(3) Lewis, *J. Biol. Chem.*, **13**, 547 (1913).

(4) Merritt, Tracy and Putnam, *Epilepsia*, 51 (1945).

(5) Unpublished results by Henze, *et al.*, include various pyridyl, quinolyl, isoquinolyl and polyaza products.

(6) Snyder, Kornberg and Romig, THIS JOURNAL, **61**, 3556 (1939)