Experimental

D,L-Glucitol (and its Hexaacetate) from Product B.—In a plant electroreduction of D-glucose at *p*H 10–13 and below 30° (resultant material designated product B) a crystalline substance was isolated from the mother liquors resulting from the crystallization of D-mannitol. Some purification was effected by crystallization from dioxane–water; m. p. 135–137° (cor.), $[\alpha]^{20}D$ 0° (water).

Anal. Calcd. for $C_6H_{14}O_6$: C, 39.55; H, 7.75. Found: C, 40.28; H, 7.78. Calcd. for a hexitol on periodate oxidation (moles per mole of substance): oxidant consumed, 5; acid formed, 4; formaldehyde, 2. Found: 4.6, 3.9, 2.0, respectively.

A mixed melting point with the below-described synthetic D,L-glucitol (m. p. 135–137°, cor.) was 136–137° (cor.).

An acetate of the isolated hexitol was prepared; m. p. 117–118° (cor.) unchanged on admixture with the below-described D,L-sorbitol hexaacetate of m. p. 116–117° (cor.), $[\alpha]^{20}D$ 0° (*c*, 3.8, U. S. P. chloroform, 2-dm. tube, throughout the visible spectrum).

Anal. Calcd. for $C_6H_8O_6(COCH_3)_6$: C, 49.77; H, 6.03; CH_3CO, 13.81 cc. 0.1 *N* NaOH per 100 mg.; mol. wt., 434. Found: C, 49.98; H, 5.96; CH_3CO, 13.7 cc.; mol. wt. (Rast), 428.

The parent substance was regenerated from its acetate by saponification; m. p. 136–138° (cor.).

L-Glucitol.—A solution of 2.0 g. of D-gulose sirup, obtained by the reduction of crystalline D-gulono-γ-lactone with sodium amalgam, in 15 cc. of water was treated with a suspension of 1.5 g. of kieselguhr-supported nickel catalyst in 15 cc. of absolute ethanol and the mixture was treated for ten hours at 100° at an initial hydrogen pressure of 890 lb. per sq. in. The cooled, filtered solution was concentrated under reduced pressure to a sirup which crystallized slowly from dilute ethanol on concentration in a desiccator; m. p. 89–91° (cor.), $[\alpha]^{29}D$ + 1.7° (*c* 3.6, water).

Anal. Calcd. for $C_6H_{14}O_6$: C, 39.55; H, 7.75. Found: C, 39.39; H, 7.85.

L-Glucitol Hexaacetate.—L-Glucitol was acetylated with acetic anhydride and pyridine and the product was recrystallized from acetone–water; m. p. 98–99° (cor.), $[\alpha]^{27}D$ − 10° (*c* 2.95, U. S. P. chloroform), six-sided prisms.

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.73; H, 6.04.

Synthetic D,L-Glucitol.—Equal amounts of the two enantiomorphous forms of glucitol were mixed, dissolved in water and crystallized by the addition of dioxane; m. p. 135–137° (cor.).

Synthetic D,L-Glucitol Hexaacetate.—Equal amounts of the two enantiomorphous forms of sorbitol hexaacetate were mixed and crystallized from acetone–water; m. p. 116–117° (cor.).

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.77; H, 5.90.

Trimethylene-D,L-glucitol.—An amount of 0.40 g. of D,L-glucitol was dissolved in 1.8 cc. of 40% aqueous formaldehyde and 1.6 g. of dry hydrogen chloride passed into the cooled (ice–salt) solution. The mixture was then heated to 90° over a period of forty-five minutes and maintained at that temperature for ten minutes. Fine needles separated on cooling; yield 0.31 g., m. p. 203–205° (cor.) unchanged on further crystallization from 95% ethanol.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.53; H, 6.51.

Summary

1. L-Glucitol and its hexaacetate have been prepared in pure, crystalline form.

2. D,L-Glucitol (its hexaacetate and trimethylene derivative) has been synthesized in crystalline form.

3. D,L-Glucitol has been identified as a product of the alkaline electroreduction of D-glucose.

COLUMBUS, OHIO
WILMINGTON, DELAWARE RECEIVED JULY 15, 1946

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

N-Methyl-L-glucosaminic Acid[1]

BY M. L. WOLFROM, ALVA THOMPSON[2] AND I. R. HOOPER[3]

The recent discovery that N-methyl-L-glucosamine[4] exists as a component of streptomycin calls attention to the fact that there is no satisfactory method for its preparation. Fischer and Leuchs[5] prepared D-glucosamine (isolated only as a derivative) by reduction of the lactone of D-glucosaminic acid. They synthesized the latter compound and its enantiomorph[6] by the addition of hydrogen cyanide to arabinosylamine with subsequent hydrolysis. E. Votoček and R. Lukeš[7] prepared N-methyl-D-glucosaminic acid by a somewhat similar procedure. They treated an aqueous solution of D-arabinose successively with methylamine and hydrogen cyanide over a period of three weeks. The resulting tar was then removed and the material in solution was hydrolyzed first with hydrochloric acid and then with barium hydroxide to produce, after acidification, an unspecified yield of the amino acid.

In this communication we wish to report the preparation in crystalline form of L-arabinosyl-N-methylamine and N-methyl-L-glucosaminic acid nitrile using anhydrous ethanol as a solvent. By this method, high yields of these intermediate compounds were readily obtained. Hydrolysis of the crystalline nitrile produced a good yield of the acid which was readily isolated in a high degree of purity. N-Methyl-L-glucosaminic acid nitrile was further characterized by the synthesis of its crystalline pentaacetate.

N-Methyl-L-glucosaminic acid nitrile is only the second nitrile in the sugar series to be isolated in the cyanohydrin reaction. Extension of the

(1) A preliminary report of this work has appeared in *Science*, **103**, 276 (1946).

(2) Research Foundation Associate of the Graduate School.

(3) Bristol Laboratories Research Associate of The Ohio State University Research Foundation (Project 224).

(4) F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 536 (1946).

(5) E. Fischer and H. Leuchs, *Ber.*, **36**, 24 (1903).

(6) E. Fischer and H. Leuchs, *ibid.*, **35**, 3787 (1902).

(7) E. Votoček and R. Lukeš, *Coll. Czechoslov. Chem. Commun.*, **7**, 424 (1935); *Chem. Listy*, **29**, 308 (1935).

general procedure herein described should result in the isolation of other members. The other directly isolated cyanohydrin is that of D-fructose, obtained by Kiliani[8] in 1885. D-Gluconic acid nitrile has been synthesized[9] indirectly through the oxime. Two polarimetrically different and interconvertible forms of this substance are known.[10] The nitrile of N-methyl-L-glucosaminic acid shows the same unusual mutarotation (Fig. 1) as does that of the lower-melting form of D-gluconic acid nitrile. It may be postulated that the higher-melting and non-mutarotating form of D-gluconic acid nitrile is the acyclic nitrile, $CH_2OH-(CHOH)_4-C\equiv N$. This substance on heating or on recrystallization from acidic solvents, may shift to a cyclic isomer (I). The substance I might then undergo a complex mutarotation in water of the type shown in Fig. 1. Such a mutarotation indicates a three-membered equilibrium and is of the type found in the chloroform mutarotation of *aldehydo*-D-galactose ethyl hemiacetal.[11] It could be represented by the equilibrium shown below. All of the above postulations would be in accord with the absorption spectra and other data cited by Papadakis.[10]

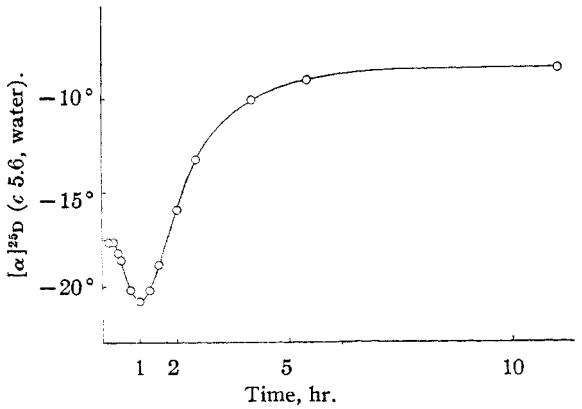


Fig. 1.—Mutarotation of N-methyl-L-glucosaminic acid nitrile.

From the mother liquor of the N-methyl-L-glucosaminic acid nitrile there was obtained an amorphous product that on hydrolysis gave an acid possessing properties different from those of N-methyl-D-glucosaminic acid. When purified this will probably represent the diastereoisomer, N-methyl-D-mannosaminic (epiglucosaminic) acid. This predictable isomer was not isolated in the work of Fischer and Leuchs[5,6] or of Votoček and Lukeš.[7]

Experimental

L-Arabinosyl-N-methylamine.—Twenty-five grams of L-arabinose was suspended in 50 cc. of absolute ethanol and heated on a steam-bath while anhydrous methylamine was bubbled through the mixture until the L-arabinose had dissolved. This required about five minutes. The solution was cooled to room temperature and upon addition of ether the product crystallized; yield 21 g., m. p. 117–118°. After one recrystallization from absolute ethanol (specially dried with Drierite) was m. p. 118–120°, $[\alpha]^{29}D$ +43° (initial, extrapolated) → +51° (final, attained in sixty minutes) (*c* 3.9, water).

The compound is soluble in water and hot ethanol but is insoluble in ether.

Anal. Calcd. for $C_6H_{13}O_4N$: C, 44.16; H, 8.03; N, 8.58. Found: C, 43.95; H, 8.17; N, 8.47.

N-Methyl-L-glucosaminic Acid Nitrile.—One hundred grams of L-arabinose was suspended in 200 cc. of absolute ethanol and heated on a steam-bath. A stream of anhydrous methylamine was passed through the mixture until the L-arabinose had dissolved. (The nitrile can be prepared from L-arabinosyl-N-methylamine but it is not necessary to isolate the latter compound at this point.) The solution was then cooled to room temperature and 45 cc. of anhydrous liquid hydrogen cyanide added. After about thirty minutes, the product crystallized. (An amorphous product, now under investigation, was obtained from the mother liquor.) It was filtered and washed with cold ethanol and ether; yield 65 g., m. p. 113°, $[\alpha]^{25}D$ −17.5° (initial) → −21° (1 hr.) → −8.3° (final) (*c* 5.6, water) (*cf.* Fig. 1).

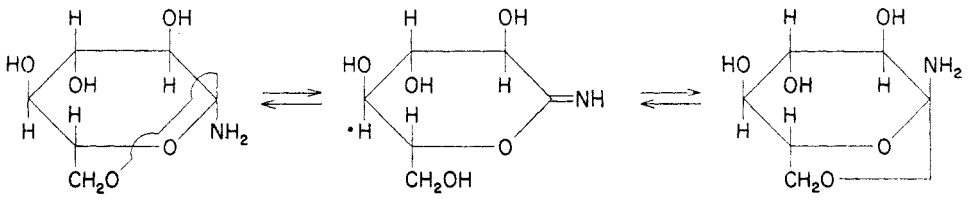
The compound is soluble in water and hot ethanol but is insoluble in ether. It can be recrystallized from ethanol. However, because of its marked instability the material so obtained appears to be less pure than that produced by the first crystallization.

Anal. Calcd. for $C_7H_{14}O_4N_2$: C, 44.20; H, 7.42; N, 14.73. Found: C, 44.09; H, 7.40; N, 14.62.

N-Methyl-L-glucosaminic Acid Nitrile Pentaacetate.—Thirty-four grams of N-methyl-L-glucosaminic acid nitrile was placed in a mixture of 100 cc. of dry pyridine and 200 cc. of acetic anhydride and kept cool in an ice-bath until the evolution of heat had stopped. It was then held at room temperature for eighteen hours. The mixture was poured into 500 cc. of ice and water whereupon it immediately crystallized; yield 57 g., m. p. 130–132°. It was recrystallized from 95% ethanol. The constants of the pure material are: m. p. 132–134°, $[\alpha]^{23}D$ −38° (*c* 4.2, chloroform, no mutarotation).

Anal. Calcd. for $C_{17}H_{24}O_9N_2$: C, 50.99; H, 6.04; N, 7.00. Found: C, 51.10; H, 5.98; N, 6.98.

The substance could also be prepared, but in lower yield,



I

(8) H. Kiliani, *Ber.*, **18**, 3066 (1885).

(9) G. Zemplén, *ibid.*, **60B**, 171 (1927); A. Wohl and O. Wollenberg, *Ann.*, **500**, 281 (1933).

(10) P. E. Papadakis and H. J. Cohen, THIS JOURNAL, **60**, 765 (1938); P. E. Papadakis, *ibid.*, **64**, 1950 (1942).

(11) M. L. Wolfrom, *ibid.*, **53**, 2275 (1931); *cf.* R. J. Dimler and K. P. Link, *ibid.*, **62**, 1216 (1940).

by hot acetylation with sodium acetate and acetic anhydride.

N-Methyl-L-glucosaminic Acid.—Fifty grams of N-methyl-L-glucosaminic acid nitrile was dissolved in 100 cc. of concentrated hydrochloric acid (d. 1.19) with cooling. The solution was then evaporated under reduced pressure to a sirup. All but traces of the hydrochloric acid were removed by alternate solution in water and evaporation under reduced pressure. The sirup was dissolved in 200 cc. of water, 95 g. of barium hydroxide octahydrate added, and the solution boiled until the odor of ammonia could no longer be detected. The barium ion was precipitated exactly by the addition of sulfuric acid. Activated carbon was added and the hot mixture filtered. The solution was treated with lead carbonate until it no longer effervesced. Decolorizing carbon was added again, the solution filtered, and evaporated under reduced pressure to 100 cc. It was allowed to stand in the ice-box overnight. The separated lead chloride was removed by filtration. The solution was warmed and treated with silver carbonate to remove the remainder of the chloride ion and the mixture filtered. The lead and silver ions were precipitated with hydrogen sulfide and the colorless liquid evaporated under reduced pressure at a temperature below 50° to a thin sirup. Absolute ethanol was added and the evaporation continued until a heavy crop of crystalline acid formed. The crystalline material was removed by filtration. More crystals were obtained by the addition of ethanol to the mother liquor and further evaporation; yield 32 g., m. p. 234–236° (dec.), $[\alpha]^{25}D$ −3.0° (*c* 4.1, water); no mutarotation. Pure material was obtained on two recrystallizations from water-ethanol; m. p. 236° (dec.), $[\alpha]^{24}D$ −4.6° (*c* 4.0, water); $[\alpha]^{29}D$ −3.0° (initial, extrapolated) → −9.1° (final) (*c* 10.8, 2.5% hydrochloric acid). These constants are in agreement (opposite sign) with those cited by Votoček and Lukeš[7] for the enantiomorph and with the melting point cited by Folkers and co-workers.[4]

The substance is soluble in water, very slightly soluble in ethanol and is insoluble in ether.

Anal. Calcd. for $C_7H_{15}O_6N$: C, 40.19; H, 7.23; N, 6.70. Found: C, 40.22; H, 7.25; N, 6.64.

Acknowledgment.—We are indebted to Mr. W. J. Polglase for the analytical data recorded.

Summary

1. An effective method for the preparation of N-methyl-L-glucosaminic acid is reported.

2. L-Arabinosyl-N-methylamine and N-methyl-L-glucosaminic acid nitrile (and its pentaacetate) have been synthesized in crystalline form.

3. Postulations are made concerning the nature of the isomeric forms of D-gluconic acid nitrile.

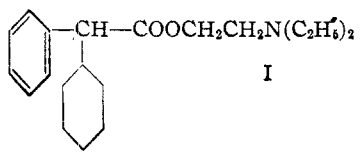
COLUMBUS, OHIO RECEIVED AUGUST 12, 1946

[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

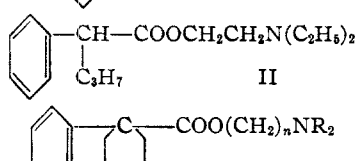
Antispasmodics. Derivatives of 1-Phenylcycloparaffincarboxylic Acids

BY ARTHUR W. WESTON

Basic alkyl esters of substituted acetic acids have been studied extensively in a search for a synthetic antispasmodic drug which would combine both a musculotropic and neurotropic action within the same molecule.[1] Two compounds possessing this dual activity to an appreciable degree are Trasentin-6H (I) and Propavine (II).

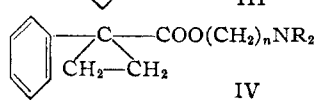


I



II

III



IV

In an effort to find a potent antispasmodic drug, basic alkyl esters of 1-phenylcyclohexanecarboxylic acid (III) and 1-phenylcyclopropanecarboxylic acid (IV), which are somewhat related structurally to I and II, were synthesized and examined for their antispasmodic activity. For purposes of comparison, some basic alkyl thioesters and amides of these acids were also prepared.

After this work was completed, a report[2] on the investigation of a series of compounds derived from 1-phenylcyclohexanecarboxylic acid appeared. One of the esters prepared in the present work, β-diethylaminoethyl 1-phenylcyclohexanecarboxylate, was described therein.

1-Phenylcyclohexanenitrile, one of the starting materials, was obtained by a modification of the published method[3] in which phenylacetonitrile was condensed with pentamethylene bromide in the presence of sodamide. By employing a relatively large volume of solvent, it was found that the tendency for intermolecular condensation was diminished. This resulted in an increased yield of the 1-phenylcyclohexanenitrile. Whether higher dilutions would have still further improved this conversion was not investigated. Hydrolysis of the nitrile was accomplished with 48% hydrobromic acid. Case[3] reported a 22.2% over-all yield of 1-phenylcyclohexanecarboxylic acid from phenylacetonitrile. By the present method a 52% yield was realized.

The 1-phenylcyclopropanenitrile was prepared, according to the directions of Knowles and Cloke[4] as modified by Case,[3] from phenylacetonitrile and

(1) For recent reviews see Raymond, *J. Am. Pharm. Assoc. Sci. Ed.*, **32**, 249 (1943); Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

(2) Rubin and Wishinsky, THIS JOURNAL, **68**, 828 (1946).

(3) Case, *ibid.*, **56**, 715 (1934).

(4) Knowles and Cloke, *ibid.*, **54**, 2028 (1932).