[CONTRIBUTION FROM THE STARCH AND DEXTROSE DIVISION, NORTHERN REGIONAL RESEARCH LABORATORY[1]]

The Preparation of Some Sugar Acid Derivatives of Sulfanilamide

BY C. L. MEHLTRETTER

The reaction of sugar acids with sulfanilamide has been investigated as a possible source of compounds having bacteriostatic activity. The present paper describes the preparation of N^4-D-gluconylsulfanilamide, N^4-(2,3,4,5-diisopropylidene-2-keto-D-gluconyl)-sulfanilamide, N^4-(2,3,4,6-diisopropylidene-2-keto-L-gulonyl)-sulfanilamide, N^4-(2-keto-D-gluconyl)-sulfanilamide, N^4-(2-keto-L-gulonyl)-sulfanilamide and 1-(4-sulfamylphenyl)-pyrrole.

The reaction of D-glucono-δ-lactone with sulfanilamide to form N^4-D-gluconylsulfanilamide was carried out in hot dilute acetic acid solution. This procedure, however, was not applicable to the condensation of 2-keto-D-gluconic acid with sulfanilamide. The diisopropylidene-2-keto acid sulfanilamides were prepared by treating sulfanilamide in pyridine solution with the corresponding diisopropylidene 2-keto acid chlorides.[2] Acid hydrolysis of these products gave the 2-keto acid sulfanilamides.

When potassium acid D-glucosaccharate was heated with sulfanilamide in dilute acetic acid solution in an attempt to synthesize N^4-D-glucosaccharic acid substituted sulfanilamide, 1-(4-sulfamylphenyl)-pyrrole was formed. Support for this structure is the similarity of its ultraviolet absorption spectrum to that of 1-phenylpyrrole[3] and the fact that the latter compound was prepared from potassium acid D-glucosaccharate and aniline under analogous conditions. An examination of these substances for antibacterial activity has yielded unpromising results.

The general method for the acylation of the N^1-amino group of N^4-acylated sulfanilamides with acid chlorides[4] failed completely with the sugar acid chlorides. Thus, when pentaacetyl-D-gluconyl chloride was allowed to react with N^4-acetylsulfanilamide in pyridine, dioxane and acetone solutions the anticipated N^1-pentaacetyl-D-gluconyl-N^4-acetylsulfanilamide was not obtained. The reaction of pentaacetyl-D-gluconamide with N^4-acetylsulfanilyl chloride also was unsuccessful.

Experimental

N^4-D-Gluconylsulfanilamide.—To a hot solution of 172 g. (1 mole) of sulfanilamide in a mixture of 75 ml. of acetic acid and 750 ml. of water was added 196 g. (1.1 mole) of D-glucono-δ-lactone. After heating on the steam-bath for seventeen hours, the solution was cooled at 10° for several hours. A first crop of 112 g. of sulfanilamide was recovered. Concentration of the mother liquor *in vacuo* yielded 49 g. of crude product (m. p. 178–184°). An additional 20 g. was isolated on further concentrating the filtrate. The combined crude products were extracted with hot acetone to remove sulfanilamide, and the solid residue was recrystallized from water. The yield of purified N^4-D-gluconylsulfanilamide was 44 g. (16%); m. p. 199–200°; $[\alpha]^{25}D$ +45.2° (*c*, 1.36; water).

Anal. Calcd. for $C_{12}H_{18}O_8N_2S$: C, 41.2; H, 5.2; N, 8.0. Found: C, 41.4; H, 5.1; N, 7.9.

N^4-(2,3,4,5-Diisopropylidene-2-keto-D-gluconyl)-sulfanilamide.—Potassium 2,3,4,5-diisopropylidene-2-keto-D-gluconate was prepared by the method of Ohle and Berend[5] which was modified by substituting calcium 2-keto-D-gluconate for the barium salt. To a suspension of 193 g. (0.58 mole) of the potassium salt monohydrate in a liter of ether was added 145 ml. (0.29 mole) of 4 *N* sulfuric acid. The mixture was cooled and well agitated. The water layer was removed and further extracted with two 300-ml. portions of ether. The ether extracts were combined, washed free of sulfuric acid with ice water, and dried over anhydrous sodium sulfate. The dry ether solution of diisopropylidene-2-keto-D-gluconic acid was allowed to react with 125 g. (0.6 mole) of phosphorus pentachloride added in small portions with cooling and shaking of the mixture. After two hours excess phosphorus pentachloride was removed by filtration and the clear solution concentrated *in vacuo* to about 800 ml. This solution was added dropwise to a vigorously stirred solution of 100 g. (0.58 mole) of sulfanilamide in 350 ml. of pyridine while cooling the mixture in an ice-bath. When half had been added a gummy substance precipitated which hindered the stirring. By agitating the solution above the gummy material, the remainder of the ether solution could be added and adequately dispersed. The contents of the flask were diluted with one liter of ice water, and 20% sodium hydroxide solution was added to dissolve the gummy mass that was present. The resulting alkaline solution was concentrated *in vacuo* (bath temp. 50°) to remove ether and pyridine. The well-stirred yellow solution was adjusted to *p*H 7 to 8 with 6 *N* hydrochloric acid, and the precipitate that formed was filtered and dried at 50°. The crude product weighed 53 g. (25%); m. p. 207–209°. After recrystallization from 50% ethanol N^4-(2,3,4,5-diisopropylidene-2-keto-D-gluconyl)-sulfanilamide was isolated as colorless prisms; m. p. 211–212°; $[\alpha]^{25}D$ −9.8° (*c*, 2.10; acetone).

Anal. Calcd. for $C_{18}H_{24}O_8N_2S$: C, 50.5; H, 5.6; N, 6.5. Found: C, 50.6; H, 5.6; N, 6.4.

N^4-(2-Keto-D-gluconyl)-sulfanilamide.—A mixture of 41 g. of the diisopropylidene derivative and 250 ml. of *N* hydrochloric acid was refluxed for five minutes. The hot solution was filtered from 8 g. of unreacted derivative and decolorized with carbon. Crystallization of the product as colorless long prisms occurred on cooling to 10°. The air-dried compound, N^4-(2-keto-D-gluconyl)-sulfanilamide monohydrate, weighed 18 g. (63%); m. p. 153–154°. Recrystallization from water did not change the melting point. On drying the product over phosphorus pentoxide at 100° and 1 mm. pressure for four hours, anhydrous N^4-(2-keto-D-gluconyl)-sulfanilamide was formed; m. p. 192–193°; $[\alpha]^{25}D$ −22.4° (*c*, 1.90; 50% ethanol).

Anal. Calcd. for $C_{12}H_{16}O_8N_2S$: C, 41.4; H, 4.6; N, 8.0. Found: C, 41.5; H, 4.7; N, 8.0.

N^4-(2,3,4,6-Diisopropylidene-2-keto-L-gulonyl)-sulfanilamide.—A suspension of 27.4 g. (0.1 mole) of 2,3,4,6-diisopropylidene-2-keto-L-gulonic acid in 150 ml. of dry ether was treated with 21 g. (0.1 mole) of phosphorus

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Ohle, *Ber.*, **63**, 847 (1930).

(3) Blicke and Powers, THIS JOURNAL, **66**, 304 (1944).

(4) Crossley, Northey and Hultquist, *ibid.*, **61**, 2950 (1939); Stockton and Lochte, *ibid.*, **67**, 160 (1945).

(5) Ohle and Berend, *Ber.*, **60**, 1165 (1927).

pentachloride, added in small portions with cooling and shaking of the mixture. After thirty minutes the slight excess of phosphorus pentachloride was removed by filtration. The clear filtrate was added dropwise to a vigorously stirred solution of 17.2 g. (0.1 mole) of sulfanilamide in 75 ml. of pyridine. A gummy precipitate was obtained. The reaction mixture was diluted with 200 ml. of water, the ether distilled off, and concentrated sodium hydroxide solution added to dissolve the gummy material. This alkaline solution was concentrated *in vacuo* to remove pyridine. The sirupy residue, diluted with water, was adjusted to *p*H 8 with 6 *N* hydrochloric acid while being stirred vigorously. The product that precipitated weighed 9.2 g.; m. p. 135–150°. Recrystallization from dilute ethanol gave 6.6 g. of N^4-(2,3,4,6-diisopropylidene-2-keto-L-gulonyl)-sulfanilamide (15.5%); m. p. 172–173°; $[\alpha]^{25}D$ +16.8° (*c*, 1.90; acetone).

Anal. Calcd. for $C_{18}H_{24}O_8N_2S$: C, 50.5; H, 5.6; N, 6.5. Found: C, 50.8; H, 5.8; N, 6.5.

N^4-(2-Keto-L-gulonyl)-sulfanilamide.—A suspension of 10 g. of N^4-(2,3,4,6-diisopropylidene-2-keto-L-gulonyl)-sulfanilamide in a mixture of 200 ml. of water and 1 ml. of concentrated hydrochloric acid was heated on the steam-bath for thirty minutes. On cooling the resulting solution, 5 g. of a crystalline product deposited (61%); m. p. 199°. Two recrystallizations from water gave colorless prisms of N^4-(2-keto-L-gulonyl)-sulfanilamide; m. p. 210–211° (dec.). A water solution of this substance reduced hot Fehling solution.

Anal. Calcd. for $C_{12}H_{16}O_8N_2S$: C, 41.4; H, 4.6; N, 8.0. Found: C, 41.7; H, 4.8; N, 8.1.

1-(4-Sulfamylphenyl)-pyrrole.—One mole (172 g.) of sulfanilamide was dissolved in a boiling mixture of 1250 ml. of water and 100 ml. of acetic acid and treated with 1 mole (248 g.) of potassium acid D-glucosaccharate. The solution was heated on a steam-bath for sixteen hours and cooled to room temperature. The solid material which separated was recrystallized from 5% sodium hydroxide solution. The yield of 1-(4-sulfamylphenyl)-pyrrole was 55 g. (25%); m. p. 246–247°. Another recrystallization raised the melting point to 247–248°. Several grams more were obtained on concentrating the mother liquor.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.0; H, 4.5; N, 12.6; S, 14.4. Found: C, 54.1; H, 4.5; N, 12.7; S, 14.4.

Acknowledgment.—The author is indebted to Dr. F. F. Blicke of the University of Michigan for the sample of 1-phenylpyrrole,[3] to Charles Pfizer and Company, Inc., for furnishing a supply of diisopropylidene-2-keto-L-gulonic acid, and to Dr. L. B. Lockwood of the Fermentation Division of this Laboratory for the sample of calcium 2-keto-D-gluconate. He is also grateful to Dr. R. D. Coghill of the Abbott Laboratories for the antibacterial tests. The microanalyses were performed by Mr. C. H. Van Etten and the absorption spectra work by Miss Ruth Johnston of this Laboratory.

Summary

1. N^4-Acyl-sulfanilamides have been synthesized by the reaction of sulfanilamide with D-glucono-δ-lactone and the acid chlorides of diisopropylidene-2-keto-D-gluconic and diisopropylidene-2-keto-L-gulonic acids. Acid hydrolysis of the latter two compounds produced N^4-(2-keto-D-gluconyl)-sulfanilamide and N^4-(2-keto-L-gulonyl)-sulfanilamide, respectively. None of these products have significant bacteriostatic properties.

2. An attempt to prepare N^4-D-glucosaccharic acid substituted sulfanilamide by the condensation of potassium acid D-glucosaccharate with sulfanilamide yielded 1-(4-sulfamylphenyl)-pyrrole.

PEORIA, ILLINOIS RECEIVED MARCH 12, 1947

[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

Diaryl Acetylenic Ketones

BY CHARLES L. BICKEL

A recent paper from this Laboratory reported the preparation of *o*-chlorophenylbenzoylacetylene from α-bromo-*o*-chlorobenzalacetophenone by the action of potassium hydroxide in a mixture of acetone and water.[1] One other acetylenic ketone has been prepared from a compound with the same carbon skeletal structure, Fuson[2] reporting the isolation of mesitylbenzoylacetylene from the products obtained by treating the enol methyl ethers of 2,4,6-trimethylbenzoylacetonitrile with phenylmagnesium bromide. The immediate precursor of this acetylenic ketone is, however, not yet identified.

The general methods of preparing acetylenic ketones involve either the condensation of a metal acetylide with an acid halide,[3,4,5,6] or the condensation of the acid chloride of a propiolic acid with an aryl group by the Friedel–Crafts reaction[7]

$$R{-}C{\equiv}C{-}Na + ClCOR' \longrightarrow R{-}C{\equiv}C{-}COR'$$

$$R{-}C{\equiv}C{-}COCl + H{-}R' \longrightarrow R{-}C{\equiv}C{-}COR'$$

In general, α-bromo ethylenic ketones can be prepared more easily than the substances from which acetylenic ketones have previously been obtained. The present paper describes the preparation of four acetylenic ketones from the corresponding α-bromo ketones and thus indicates that this method of preparation may be of general application. Further work on this problem is in progress and will be reported at a later date.

The α-bromo derivatives of benzalacetophenone, *p*-methoxybenzalacetophenone, benzal-*p*-methoxyacetophenone and benzal-*p*-bromoacetophenone give the corresponding acetylenic

(1) Bickel, THIS JOURNAL, **69**, 73 (1947).
(2) Fuson, Ullyot and Hickson, *ibid.*, **61**, 410 (1939).
(3) Nef, *Ann.*, **308**, 276 (1899).
(4) Manchot, *ibid.*, **387**, 285 (1912).
(5) Barat, *J. Indian Chem. Soc.*, **7**, 851 (1930).
(6) Fuson and Meek, *J. Org. Chem.*, **10**, 551 (1945).
(7) Watson, *J. Chem. Soc.*, **85**, 1319 (1904).