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Summary

A new methyl dimethylene gluconate has been isolated from the sublimate mixture obtained by heating methyl 2,4:3,5-dimethylene-D-gluconate *in vacuo* at 150°. The structure of the new diacetal has been shown to be methyl 2,4:5,6-dimethylene-D-gluconate. The rearrangement of a six-membered methylene acetal ring to a five-membered ring has thus been demonstrated.

The application of the procedure of Hudson and Hann and their associates[6] for the limited acetolysis of the methylene acetals of sugar alcohols to methyl 2,4:3,5-dimethylene-D-gluconate and methyl 2,4:5,6-dimethylene-D-gluconate has resulted in further confirmation of the relative stability of the 2,4-methylene acetal linkage to acetolysis.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY OF THE AMERICAN UNIVERSITY OF BEIRUT]

Sulfanilamide Derivatives Containing Urea, Thiourea or Hydrazide Groupings

BY EVA NIEMIEC[1]

Urea has been used in therapy along with sulfanilamides, its alleged effect being to counteract the action of *p*-aminobenzoic acid. It appeared of interest to prepare sulfanilamides containing urea or related groupings and study their bacteriostatic effects.

In the preparation of sulfanilamidourea (I) and sulfanilamidothiourea (II) from acetylsulfanilyl chloride and the appropriate semicarbazide hydrochloride (condensed in the presence of aqueous sodium acetate), deacetylation was accomplished by boiling for three hours in aqueous alcoholic hydrochloric acid solution. Alkaline hydrolysis causes liberation of ammonia; even ten hours of boiling with concentrated hydrochloric acid results only in partial hydrolysis.

(I) *p*-$H_2NC_6H_4SO_2NHNHCONH_2$
(II) *p*-$H_2NC_6H_4SO_2NHNHCSNH_2$
(III) *p*-$H_2NCH_2C_6H_4SO_2NHNHCONH_2$
(IV) *p*-$CH_3CONHC_6H_4SO_2NHNH_2$
(V) *p*-$CH_3CONHC_6H_4SO_2NHNHCOC_6H_5$
(VI) *p*-$CH_3CONHC_6H_4SO_2NHNHCOCH_3$
(VII) *p*-$CH_3CONHC_6H_4SO_2NHN(COCH_3)_2$
(VIII) *p*-$H_2NC_6H_4SO_2NHNH_2$

Marfanil or homosulfanilamide is interesting because its bacteriostatic action is not counteracted by *p*-aminobenzoic acid; its urea derivative (III) was prepared as above. Sulfanilylhydrazides should be available by either (1) treatment of acetylsulfanilyl chloride with the hydrazide, or (2) acylation of N^4-acetylsulfanilylhydrazine (IV), and hydrolysis at the N^4-position. Haslewood[2] prepared sulfanilylbenzhydrazide using the first method. Since acethydrazide is difficult to prepare, the second method was employed in this work. N^4-Acetylsulfanilylhydrazine[3] was prepared in good yield by grinding hydrazine dihydrochloride in a mortar with dry acetylsulfanilyl chloride and crystalline sodium carbonate.

If N^4-acetylsulfanilylhydrazine is treated in pyridine solution with one mole of benzoyl chloride, N^4-acetylsulfanilylbenzhydrazide[2] (V) is obtained; this yields sulfanilylbenzhydrazide on alkaline hydrolysis. Excess benzoyl chloride gives a product which appears to be a mixture of the mono- and dibenzhydrazide. This is in agreement with the experience of McFadyen and Stevens.[4] Acetylsulfanilylhydrazine in pyridine can be converted into either N^4-acetylsulfanilacethydrazide (VI) or the diacetate VII. When either product is subjected to acid hydrolysis[3] with 12 *N* hydrochloric acid or even with 6 *N* or 3 *N* hydrochloric acid, all acetyl groups are split off and only sulfanilylhydrazine[3] (III) is obtained.

Studies of the bacteriostatic properties of these compounds by Miss Aida Djanian at the Department of Bacteriology of this University indicate that sulfanilamidourea and 4-homosulfanilamidourea are superior to sulfathiazole in their inhibitory action upon *Clostridium welchii*, *Cl. tetani*, *Cl. sporogenes*, and *Cl. chauvei*. Sulfanilamidourea and sulfanilamidothiourea are approximately one-tenth as active against *Streptococcus viridans* as sulfathiazole, whereas homosulfanilamidourea has no inhibitory effect.

Experimental[5]

N^4-Acetylsulfanilamidourea.[6]—A mixture of 5 g. of semicarbazide hydrochloride, 10.5 g. of dry acetylsulfanilyl chloride, and 30 g. of crystalline sodium acetate is thoroughly ground in a mortar with a few cc. of water. The thick paste is then transferred with the minimum amount of water and heated for thirty minutes at 60°. After cooling the product is filtered, washed, and crystallized from boiling water, in which it is not very soluble; needles, m. p. 223–224° with decomposition, yield 6 g.

(1) Part of a Master's thesis submitted to the American University of Beirut, 1946.

(2) Haslewood, *Biochem. J.*, **35**, 1307 (1941).

(3) Curtius and Stoll, *J. prakt. Chem.*, **112**, 1117 (1926).

(4) Compare McFadyen and Stevens, *J. Chem. Soc.*, p. 584 (1936).

(5) All melting points are uncorrected.

(6) After the completion of these experiments, Roth and Degering, THIS JOURNAL, **67**, 126 (1945), reported the preparation of this compound in comparable yield in pyridine solution

Anal. Calcd. for $C_9H_{12}N_4O_4S$: N, 20.58. Found: N, 20.41, 20.05.

Sulfanilamidourea (I).—N^4-Acetylsulfanilamidourea (6.0 g.) is refluxed for three hours with 21 cc. of concentrated hydrochloric acid (density 1.19) and 70 cc. of 95% alcohol. The crystals that separate on cooling are filtered and neutralized with sodium carbonate to litmus. The needles that separate on cooling are recrystallized from boiling water; m. p. 229° with decomposition; yield 4.5 g.

Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.38; N, 24.34. Found: C, 37.1, 37.2; H, 4.6, 4.7; N, 24.25, 24.20.

N^4-Acetylsulfanilamidothiourea.[6]—A mixture of 5 g. of thiosemicarbazide, 13 g. of acetylsulfanilyl chloride, and 23 g. of crystalline sodium acetate is allowed to react as described for the urea derivative; needles (from water), m. p. 186°; yield 2 g.

Anal. Calcd. for $C_9H_{12}N_4O_3S_2$: C, 37.49; H, 4.20; N, 19.43. Found: C, 37.1, 36.8; H, 4.6, 4.9; N, 19.0, 18.8.

Sulfanilamidothiourea (II).—The hydrolysis is carried out exactly as described for the urea derivative; needles (from water) m. p. 224–225° with decomposition.

Anal. Calcd. for $C_7H_{10}N_4O_2S_2$: C, 34.13; H, 4.09; N, 22.75. Found: C, 34.45, 34.30; H, 4.3, 4.3; N, 23.0, 23.2.

N^4-Acetyl-4-homosulfanilamidourea.—A mixture of 7 g. of N-acetyl-4-homosulfanilyl chloride,[7] 7 g. of semicarbazide hydrochloride, and 20 g. of crystalline sodium acetate is treated as described for the lower homolog. The product is crystallized from boiling water, in which it is quite soluble; rods, m. p. 193–194° with decomposition; yield 5 g. The air-dried product contains 1 mole of water of crystallization, which is removed by drying in vacuum over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{10}H_{14}N_4O_4S \cdot H_2O$: N, 18.41. Found: N, 18.5, 18.2.

4-Homosulfanilamidourea Hydrochloride (III).—One gram of N^4-acetyl-4-homosulfanilamidourea is refluxed for eight to nine hours with concentrated hydrochloric acid and 56 cc. of absolute alcohol. On cooling the hydrochloride separated in the form of clusters melting at 225–226° with decomposition; yield 0.7 g.

Anal. Calcd. for $C_8H_{13}N_4O_3SCl$: N, 19.96. Found: N, 19.8, 19.9.

N^4-Acetylsulfanilylhydrazine (IV).—Hydrazine dihydrochloride (5 g.), dry acetylsulfanilyl chloride (12 g.), and crystalline sodium carbonate (28 g.) are ground in a mortar. The reaction is marked by a strong evolution of gas. When the gas stops evolving a few cc. of water is added and the reaction mixture is left for one hour at room temperature. The product is filtered, washed with water, and crystallized from 500 cc. of boiling water; plates, m. p. 183–184° with decomposition. Prolonged boiling results in decomposition of the product.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.9, 42.1; H, 4.9, 5.3; N, 18.2, 18.4.

N^4-Acetylsulfanilylbenzhydrazide (V).—N^4-Acetylsulfanilylhydrazine (1 g.) is dissolved in a minimum amount of dry pyridine. The solution is cooled and treated slowly with 0.5 cc. of benzoyl chloride. After standing for twenty-four hours at room temperature the pyridine is removed *in vacuo*. The residue is treated with dilute hydrochloric acid and the precipitate is collected and crystallized three times from water or alcohol; m. p. 219–220° with decomposition; yield 0.5 g. It shows no depression with Haslewood's product.

N^4-Acetylsulfanilylmonoacethydrazide (VI).—To a cooled solution of 3 g. of N^4-acetylsulfanilylhydrazine in dry pyridine, 0.93 cc. of acetyl chloride is slowly added. After standing for twenty-four hours and after evacuation of the pyridine, the residue is treated with dilute hydrochloric acid and kept for several hours in the icebox. The product is filtered and crystallized twice from water; m. p. 204–205° with decomposition.

Anal. Calcd. for $C_{10}H_{13}O_4N_3S$: N, 15.49. Found: N, 15.79, 15.68.

N^4-Acetylsulfanilyldiacethydrazide (VII).—N^4-Acetylsulfanilhydrazine (3 g.) in pyridine is treated without cooling with acetic anhydride (3 cc.). The procedure is the same as for the monoacethydrazide; needles (from water), m. p. 191–192° with decomposition.

Anal. Calcd. for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.83; N, 13.41. Found: C, 45.8, 46.1; H, 4.8, 4.6; N, 13.6, 13.3.

Summary

Sulfanilamidourea, sulfanilamidothiourea, and 4-homosulfanilamidourea were prepared and tested for bacteriostatic activity.

A simplified method for the preparation of N^4-acetylsulfanilylhydrazine is described. The latter compound can be used for the preparation of sulfanilylbenzhydrazide and of N^4-acetylsulfanilylmono- and diacethydrazide. Acid hydrolysis of the last two compounds yields sulfanilylhydrazine.

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(7) Bergeim and Braker, THIS JOURNAL, **66**, 1459 (1944).