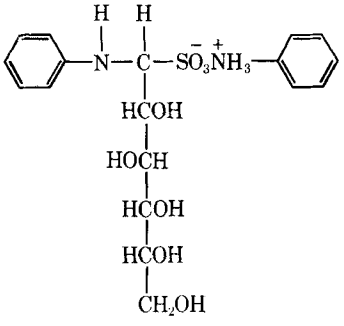
Reactions of Amine Drugs with Sugars I

Reaction of Amphetamine with Aldoses, Glycosylamines, and Bisulfite

By J. C. GRIFFIN* and G. S. BANKER

Amphetamine bisulfite was reacted with D-glucose, D-mannose, *N*-phenylisopropyl-D-mannosylamine, and *N*-phenyl-D-mannosylamine. The effect of an aryl or alkyl amine as the amino substituent at C-1 of the aldose on the formation of amino sulfonates was investigated. Alkyl substitution was found to yield bisulfite addition products, while aryl substitution yielded amino sulfonates. Mannose amphetamine sulfonate and glucose amphetamine sulfonate were synthesized.

THE REACTION of arylamine bisulfites with aldoses has been shown by Ingles (1) to produce amino sulfonates. The structure of an amino sulfonate of this type (D-glycero-D-ido-1-anilino-2,3,4,5,6-pentahydroxyhexylanilinium sulfonate) is shown in I.



I

The hydrolysis characteristics of these compounds (2) were found to be similar to those reported for glycosylamines derived from arylamines (3, 4). Decomposition of the sulfonate structure was observed when the amino sulfonate was dissolved in 10% acetic acid or 0.05 *N* sodium hydroxide solution (2).

The formation of bisulfite addition products, or hydroxysulfonates, by the reaction between inorganic bisulfites and aldehydes is well known (5, 6). The formation of aldose-bisulfite addition products is less well recognized with recent standard texts of organic chemistry (5, 6) indicating that aldoses will not form bisulfite addition products. The chemical literature does not uniformly concur in this view. As early as 1904 Kerp (7) reported the isolation of an impure glucose-sodium bisulfite addition product, while in more recent work Braverman (8) reported the preparation of a pure glucose sodium bisulfite addition product. The preparation of bisulfite addition products of D-glucose, D-galactose, D-mannose, and L-arabinose has also recently been reported by Ingles (9).

The stabilization of pharmaceuticals by the addition of inorganic bisulfites has been common practice for many years (10). The addition of bisulfite to dosage forms containing an amine drug and an aldose could provide the necessary reactants for the formation of aldose-bisulfite addition products as well as amino sulfonates. The implications of this reaction, to modification of amine drug absorption and activity as well as to the browning reaction of sugars, are manifold.

The synthesis of glucose bisulfite compounds of alkoxyamino pyridine by Friedman (11) represents a pharmaceutical application of amino sulfonate formation. The preparation of dialdehyde polysaccharide addition products from various amine bisulfites and dialdehyde starch has been claimed by Borchert (12). These products were of the hydroxy ammonium sulfonate type rather than amino sulfonates. Adams and Garber (13) prepared a number of hydroxy ammonium sulfonates but were unable to obtain products from D-glucose.

The objective of this study was to investigate the reaction of a primary aralkylamine drug with an aldose-bisulfite addition product. The amine drug selected for this phase of the study was dextroamphetamine. The aldose-bisulfite addition product selected was mannose sodium sulfonate.

A further purpose of this work was to examine the reaction of amphetamine bisulfite with the epimeric aldoses, D-glucose and D-mannose, and to examine the effect of an aryl- or alkylamine as

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the *N*-substituted constituent at C-1 of the aldose on the formation of amino sulfonates.

EXPERIMENTAL AND RESULTS

Reactions of Amines with Mannose Sodium Sulfonate

Synthesis of Mannose Sodium Sulfonate—D-Mannose,[1] 18 Gm. (0.1 mole), and sodium bisulfite,[2] 12 Gm. (0.115 mole), were separately dissolved in 18 ml. of distilled water with the aid of heat. The two solutions were mixed immediately after preparation. In 20 min. crystallization began and a solid cake formed in approximately 4 hr. The crystalline mass was separated from the mother liquor by filtration, washed with methanol–water (9:1), and finally with methanol. The product was recrystallized twice from a methanol–water (7:3) solvent system.

The recrystallized material had the following characteristics: m.p. 184°; $[\alpha]_D^{25}$ + 7.2 (c 3, 10% acetic acid); sulfite content [method of Adams and Garber (13)] 27.3% found, 28.1% theory.

Reaction of Amphetamine with Mannose Sodium Sulfonate—Mannose sodium sulfonate, 2.8 Gm. (0.01 mole) was added directly to 1.95 Gm. (0.0144 mole) of amphetamine base[3] and the mixture thoroughly mixed. A paste was obtained initially which gradually solidified as a white mass.

The crude product was extracted with 100 ml. of ether for 24 hr. to remove unreacted amphetamine. The ether extract contained 158 mg. of unreacted amphetamine.

The amphetamine content of the crude product was 38.7% as determined by hydrolyzing the adduct with base and extracting the liberated amine with chloroform. Sulfite content of the product was 18.9%. Theoretical values for the condensation product, amphetamine mannose sodium sulfonate, are: amphetamine, 39.0%; sulfite, 19.9%.

The infrared absorption spectrum of the compound between 9.75 and 12.25 μ, as determined by KBr pellet, is shown in Fig. 1 (spectrum A). Also shown in Fig. 1 are the absorption spectra in this region for amphetamine sodium sulfite (B), physical mixture of amphetamine sodium sulfite and mannose sodium sulfonate (C), and mannose sodium sulfonate (D). Amphetamine sodium sulfite was prepared by the addition of amphetamine base to an equimolar amount of sodium bisulfite.

Reaction of Amine Bisulfites with Aldoses

Preparation of Mannose Amphetamine Sulfonate—Amphetamine base, 13.6 Gm. (0.1 mole), was added to 14 ml. of water, and sulfur dioxide[4] from a compressed gas cylinder was bubbled through the suspension. Considerable evolution of heat and the formation of a white solid resulted almost immediately upon introduction of the sulfur dioxide. The white solid redissolved and formed a clear, slightly yellow solution on continued addition of sulfur dioxide. A solution of D-mannose, 9 Gm. (0.05 mole), in 9 ml. of water was prepared with the aid of heat and the mannose solution added to the amphetamine bisulfite solution. Crystallization began in approximately 2 min., and a solid cake was present in the beaker within 20 min. The crude product was suspended in 250 ml. of 95% ethanol and stirred for 1 hr. The product was separated by filtration and dried.

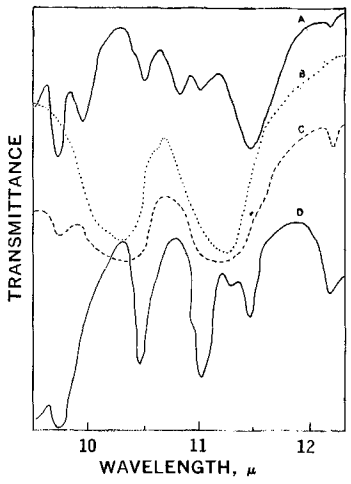


Fig. 1—Infrared absorption spectra. Key: A, *isolated compound;* B, *amphetamine sodium sulfite;* C, *physical mixture of amphetamine sodium sulfite and mannose sodium sulfonate;* D, *mannose sodium sulfonate.*

Free sulfite could not be detected in the product (14) after recrystallizing twice from methanol–water (8:2). Total combined sulfite, determined iodometrically, was 19.8%; theoretical 20.14% for mannose amphetamine sulfonate. Aqueous solutions of the compound gave a positive test for sugar with reagent tablets.[5] The melting point of the recrystallized material was 137°.

The ultraviolet absorption spectrum of the recrystallized product exhibited the characteristic absorption peaks of amphetamine. Amphetamine content, as determined by a chloroform extraction technique from alkaline solution, was 34.6%; theoretical value 34.0% for mannose amphetamine sulfonate.

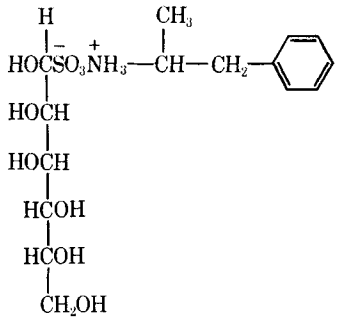
The infrared absorption of the compound in KBr disk showed the following absorption peaks: 3 μ, —OH, —NH; 5.1 μ, amine salt (15); 8.7 μ, R—SO_3^-; 13.5 and 14.5 μ, monosubstituted benzene.

The infrared absorption spectrum of the compound in potassium bromide disk appeared to be consistent with structure II.

Preparation of Glucose Amphetamine Sulfonate—A solution of amphetamine bisulfite, prepared from 13.6 Gm. (0.1 mole) amphetamine base, 14 ml. of water, and sulfur dioxide gas was added to a solution of D-glucose,[6] hydrous, 9.9 Gm. (0.05 mole), in 9 ml. of water. The solution was allowed to stand in an open beaker at room temperature. Crystallization began in about 4 hr. and was allowed to continue for 18 hr. The product was separated and washed in 250 ml. of ethanol (95%).

The characteristics of the isolated reaction product

[1] Nutritional Biochemicals Corp., Cleveland, Ohio.
[2] Mallinckrodt Chemical Co., St. Louis, Mo.
[3] Prepared from dextroamphetamine sulfate, Sigma Chemical Co., St. Louis, Mo.
[4] The Matheson Co., Inc., Joliet, Ill.
[5] Marketed as Clinitest tablets by the Ames Co., Inc., Elkhart, Ind.
[6] Mallinckrodt Chemical Co., St. Louis, Mo.



II

corresponded to those of mannose amphetamine sulfonate described above. Crystallization was, however, observed to be considerably slower than with the mannose reaction.

Anal.—Calcd. for $C_{15}H_{27}NO_9S$: C, 45.32; H, 6.85. Found: C, 46.5; H, 6.89.

Reactions of Amine Bisulfite with Glycosylamines

Reaction of N - Phenylisopropyl - D - mannosylamine with Amphetamine Bisulfite—A solution of *N*-phenylisopropyl-D-mannosylamine was prepared by refluxing a mixture of D-mannose (5.4 Gm., 0.03 mole), amphetamine (4.0 Gm., 0.03 mole), and methanol (25 ml.) for 20 min. after solution of the sugar was effected. A solution of amphetamine bisulfite, prepared from amphetamine base (4.0 Gm., 0.03 mole), water (0.54 ml., 0.03 mole), methanol (2 ml.), and sulfur dioxide was added to the *N*-phenylisopropyl-D-mannosylamine solution. The resulting solution was placed on a rotary vacuum evaporator and concentrated to small volume. The concentrated solution was placed in an open beaker and allowed to stand at room temperature. Crystallization started within a few minutes and was allowed to continue for 24 hr. The resulting crystalline product was separated, washed with ether, and recrystallized from 95% ethanol.

Physical and chemical characteristics of the recrystallized product were identical to those of mannose amphetamine sulfonate described previously.

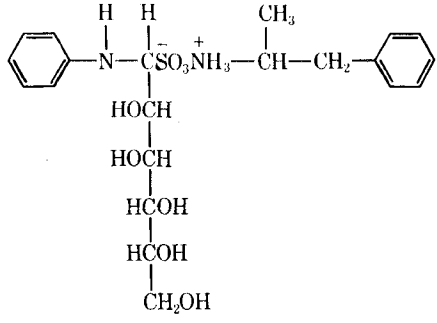
Reaction of N-Phenyl-D-mannosylamine with Amphetamine Bisulfite—A solution of *N*-phenyl-D-mannosylamine was prepared by refluxing a mixture of aniline,[7] 0.93 Gm. (0.01 mole), D-mannose, 1.8 Gm. (0.01 mole), and 10 ml. of methanol for 30 min. The mixture formed a clear solution in approximately 10 min. A white precipitate formed from the clear solution after refluxing for 25 min. Distilled water, 5 ml., was added to the reaction mixture and refluxing was continued. A clear solution resulted in 5 min. and refluxing was terminated at this point.

Sulfur dioxide was bubbled through a mixture of amphetamine, 1.36 Gm. (0.01 mole), distilled water, 0.18 ml. (0.01 mole), and methanol, 3 ml. A clear solution of amphetamine bisulfite resulted and was added to the preformed *N*-phenyl-D-mannosylamine. The solution was refluxed for 4 hr., transferred to a 50-ml. beaker, and allowed to stand at room temperature. Crystallization started within a few minutes and was allowed to continue for 24 hr.

The crystalline material was removed by filtration and washed first with methanol, then with absolute ethanol, and finally with ethyl ether. The product was recrystallized from methanol–water (8:2) and dried in a vacuum desiccator over calcium sulfate.

Sulfite content found, 16.3%; theoretical 16.9% for the amino sulfonate.

The ultraviolet absorption spectrum of the crystalline product dissolved in pH 10 buffer indicated the presence of both aniline and amphetamine chromophores and strongly suggests the structural formula III.



III

DISCUSSION

The reaction of an arylamine bisulfite with an aldose produces, as the normal reaction product, an amino sulfonate. The aralkylamine bisulfite, amphetamine bisulfite, when reacted with the aldoses, D-mannose and D-glucose, was observed to form a bisulfite addition product rather than an amino sulfonate.

A possible explanation of this difference in reaction products may be developed by an examination of the probable reaction mechanisms. Amino sulfonate formation may take place as a result of nucleophilic substitution of the amine at C-1 of the aldose, followed by addition of bisulfite. The strongly basic alkylamine bisulfites exist primarily as the protonated amine, in the system studied, and are thus no longer capable of nucleophilic substitution. The reaction products would thus appear to be limited to bisulfite addition products.

The reactions of *N*-phenyl-D-mannosylamine and *N* - phenylisopropyl - D - mannosylamine with amphetamine bisulfite provide information relative to the effect of the *N*-substituted constituent at C-1 of the aldose on the stability of amino sulfonates. The successful formation of the amino sulfonate, *N*-phenyl-D-mannose amphetamine sulfonate, and the failure to form the corresponding *N*-phenylisopropyl-D-mannose amphetamine sulfonate indicates that amino sulfonate synthesis requires, under the conditions used in this portion of the study, an arylamine as the *N*-substituted constituent at C-1 of the aldose.

Differences in the infrared spectra and absence of free amphetamine base in the product isolated from direct addition of amphetamine base to mannose sodium sulfonate would indicate that a new

[7] General Chemical Division, Allied Chemical and Dye Corp., New York, N. Y.

compound had been formed, possibly of the amino sulfonate type.

Failure to isolate an amino sulfonate from *N*-phenylisopropyl - D - mannosylamine and amphetamine bisulfite would suggest that the mannosylamine had reacted with bisulfite to form an unstable amino sulfonate. The amino sulfonate would then undergo expulsion of the amine, as in the hydrolytic reactions of glycosylamines (16), to form the more stable aldose bisulfite addition product. The reaction was undoubtedly driven in this direction as a result of the insolubility of the aldose bisulfite addition product which was observed to crystallize out of the reaction solution.

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Reactions of Amine Drugs with Sugars II

Synthesis and *In Vivo* Evaluation of Mannose Amphetamine Sulfonate and *N*-Phenylisopropyl-D-mannamine

By J. C. GRIFFIN* and G. S. BANKER

Mannose amphetamine sulfonate was synthesized from the reaction of amphetamine bisulfite with D-mannose. *N*-Phenylisopropyl-D-mannamine was synthesized by catalytic hydrogenation of *N*-phenylisopropyl-D-mannosylamine. The products were evaluated *in vivo* by the Williamson activity cage method. Mannose amphetamine sulfonate was found to have a significantly longer duration of activity and produced a higher level of mean activity, from 3.5 hr. to 4.5 hr. after administration, than dextroamphetamine sulfate. *N*-Phenylisopropyl-D-mannamine was found to be orally inactive at dosage levels of 10 and 50 mg./Kg. of body weight.

ADAMS *et al.* (1, 2) have extensively investigated the reaction of various amine bisulfites with aldehydes and ketones. The products isolated, using aldehydes such as benzaldehyde, were of the α-hydroxy sulfonate type. They were, however, unsuccessful in obtaining products with D-glucose. The formation of alkylamine bisulfite addition products with aldoses has been reported by Ingles (3).

The preparation of glycamines by catalytic hydrogenation of *N*-glucosides of alkylamines has been reported by a number of workers (4, 5). Mitts and Hixon (6) have reported on the properties of a number of alkylglucamines obtained by catalytic hydrogenation of glucosylamines.

The purpose of this work was the synthesis and *in vivo* evaluation of an aldose bisulfite addition product and a glycamine derived from an alkylamine drug.

EXPERIMENTAL

Synthesis of Mannose Amphetamine Sulfonate—The synthesis of this product was carried out by reacting dextroamphetamine bisulfite with D-mannose as described in the first paper of this series (7).

Synthesis of N-Phenylisopropyl-D-mannamine—*N*-Phenylisopropyl-D-mannosylamine was prepared by reacting dextroamphetamine,[1] 6.80 Gm. (0.05 mole), with D-mannose,[2] 9.00 Gm. (0.05 mole), in methanol, 5 ml., at 60–65° for 30 min. The resulting light amber colored solution of the mannosylamine was used without further purification for the catalytic hydrogenation.

Hydrogenation of the mannosylamine was carried

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[1] Prepared from dextroamphetamine sulfate, Sigma Chemical Co., St. Louis, Mo.

[2] Nutritional Biochemicals Corp., Cleveland, Ohio.