[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

1,6-Di-O-phenylsulfonyl-D-mannitol. Its Preparation and Use in the Synthesis of Some Derivatives of D-Mannitol

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1,6-Di-O-phenylsulfonyl-D-mannitol has been converted to 1,6-diaminodideoxy-D-mannitol dihydrochloride (I) under relatively mild conditions without prior blocking of the secondary hydroxyls. In the ammonolysis step a by-product has been isolated which appears to be 1-amino-1-deoxy-3,6-anhydro-D-mannitol benzenesulfonate (X).

1,6-Diaminodideoxy-D-mannitol dihydrochloride (I) has been synthesized by the following reaction sequence[2]: D-mannitol → 1,6-dichlorodideoxy-D-mannitol → 1,6-dichlorodideoxy-2,4:3,5-dimethylene-D-mannitol → 1,6-diaminodideoxy-2,4:3,5-dimethylene-D-mannitol dihydrochloride → I. We now wish to report a more direct synthesis of I and to describe a new intermediate (II) for the preparation of terminally substituted mannitol derivatives.

D-Mannitol was treated with benzenesulfonyl chloride in pyridine at 0° to obtain 1,6-di-O-phenylsulfonyl-D-mannitol (II). Ammonolysis of II in liquid ammonia yielded the benzenesulfonic acid salt of 1,6-diamino-dideoxy-D-mannitol (III) which was converted to I by careful treatment with concentrated hydrochloric acid.

The positions of the sulfonic ester groups in II were established by condensation of II with benzaldehyde in the presence of zinc chloride to give 1,6-di-O-phenylsulfonyl-2,3,4,5-dibenzylidene-D-mannitol (IV), which upon reaction with sodium iodide in acetone yielded the known 1,6-diiodo-2,3,4,5-dibenzylidene-D-mannitol[3] plus a 100% yield of sodium benzenesulfonate.

The diester II also reacts with paraformaldehyde in the presence of benzenesulfonic acid to give 1,6-di-O-phenylsulfonyl-2,4:3,5-dimethylene-D-mannitol (V). Reaction of V with sodium iodide in acetone gave the known 1,6-diiodo derivative.[4] Reaction of II with sodium iodide yielded only sodium benzenesulfonate and an unidentified oil. However it was noted that IV required 4 hours at 100° for complete reaction with sodium iodide and V needed only two hours at 100° while II reacted at room temperature.

The diester II reacts at 25° with aniline to give 1,6-dianilinodideoxy-D-mannitol (VI) in good yield. It was necessary to reflux V with aniline in dioxane for 42 hours in order to get the corresponding 1,6-dianilino-dideoxy-2,4:3,5-dimethylene-D-mannitol (VII) in a similar yield. Ammonolysis of V also proceeded with considerable difficulty. Since V was not soluble in liquid ammonia, the ammonolysis was done in a mixture of dioxane and ethylene glycol dimethyl ether. After several days at room temperature no reaction had occurred. By heating at 45° for five days an oil separated from which was isolated a small amount of 1,6-diaminodideoxy-2,4:3,5-dimethylene-D-mannitol dibenzenesulfonate. With hydrochloric acid, this substance gave a dihydrochloride having the same melting point as that reported by Haworth, *et al.*[2]

When V was refluxed with thiourea in dioxane–alcohol the benzenesulfonic acid salt of 1,6-diisothiouronium-dideoxy-2,4:3,5-dimethylene-D-mannitol (VIII) was formed. Alkaline hydrolysis of VIII yielded 1,6-dithio-2,4:3,5-dimethylene-D-mannitol. On the other hand, II when refluxed with thiourea in ethanol yielded an oily solid that we were not able to purify by crystallization. In the experiments tried it thus appears that II will give the desired reactions with substances that are also solvents, but not with the other reagents unless the free hydroxyl groups are blocked.

In the ammonolysis of II a by-product (X) was isolated. The analysis indicated a possible ring structure containing only one benzenesulfonate radical. It was therefore converted to the hydrochloride XI which was subjected to periodic acid oxidation.[5] There are three possible ring structures that may be assigned to X and XI. The ratio found for IO_4^-/HCO_2H indicates that the compound possesses the 3,6-anhydro ring structure. The by-product X on this basis is probably 1-amino-1-deoxy-3,6-anhydro-D-mannitol benzenesulfonate.

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Experimental

1,6-Di-O-phenylsulfonyl-D-mannitol (II).—In a 1500-cc. Ace Resin kettle a well-stirred mixture of 109.2 g. (0.60 mole) of D-mannitol (dried *in vacuo* over P_2O_5) and 600 cc. (7.44 moles) of anhydrous pyridine was heated (heating mantle) to the boiling point for 15 minutes and then cooled to 0°. Drying tubes were used to prevent the entrance of atmospheric moisture. To the stirred mixture kept at −5 to 0° by means of an ice–salt-bath was added dropwise in 7 hours 165 cc. (1.29 moles) of redistilled benzenesulfonyl chloride. The resulting viscous solution was stirred for 2 hours longer and then allowed to stand overnight at 0°. The mixture was then added with stirring to an excess of ice and 190 cc. (3.6 moles) of sulfuric acid (sp. gr. 1.84). The taffy-like precipitate was dissolved in 900 cc. of chloroform. The chloroform layer was washed with 150-cc. portions of ice-cold water. Usually the product crystallized immediately after the second washing. It was filtered with suction and washed twice with ether. The air-dried product weighed 117–124 g. (42–45%). The product was purified by crystallization from ethanol and then ethylene chloride; m.p. 121–122°, $\alpha^{25}D$ +16.0° (dioxane). Calcd. for $C_{18}H_{22}O_{10}S_2$: S, 13.88. Found: S, 13.75.

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(1) Most of the work herein reported was taken from the Ph.D. thesis of Carl G. Gustafson, Jr.

(2) (a) W. N. Haworth, R. L. Heath and L. F. Wiggins, *J. Chem. Soc.*, 58 (1944); (b) G. M. Jones and L. F. Wiggins, *ibid.*, 364 (1944).

(3) R. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **65**, 1419 (1943).

(4) R. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **65**, 67 (1943).

(5) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 341.

The product II is reasonably stable but in 3 months became sticky (m.p. 95–104°). One crystallization from ethanol raised the m.p. to 121–122°. After 6 months one sample had decomposed to a thick opaque oil.

Ammonolysis of II.—In a pressure bottle, 30 g. (0.066 mole) of II was dissolved in 100 cc. of liquid ammonia at −40°. The bottle was capped, placed in a safety jacket and held for 21 days at 0°. The bottle was then gradually cooled to −40°, opened, and the ammonia evaporated under reduced pressure. The sticky yellow solid was thoroughly shaken with 125 cc. of absolute alcohol, filtered, and the residue washed until white with 10-cc. portions of ethanol, once with ether, and then air-dried. The material weighed 7 g. (21%), m.p. 230–235°. The pure product III was obtained by one crystallization from water–ethanol; m.p. 238–240°, $\alpha^{25}\text{D}$ +10.2° (water). Calcd. for $C_{18}H_{28}O_{10}N_2S_2$: S, 12.92. Found: S, 12.87.

During the filtration of the crude III more ammonia evaporated from the filtrate causing a solid to precipitate. It weighed 3 g. (9.8%), m.p. 165–167°. It is referred to (*vide infra*) as X.

The filtrate from the crude X gave ammonium benzenesulfonate and a yellow oil that was not identified.

1,6-Diamino-dideoxy-D-mannitol Dihydrochloride (I).—In a 50-cc. beaker 17.5 g. of III was suspended in 11 cc. of water. Then 12 cc. of hydrochloric acid (sp. gr. 1.19) was added. The solution was cooled in ice for 30 minutes. The crystals were filtered and washed with four 3-cc. portions of alcohol; yield 8.4 g. (94%), m.p. 238–241°, $\alpha^{25}\text{D}$ +11.5° (water). The m.p. of a mixture with III was 221–229°.

1,6-Di-O-phenylsulfonyl-2,3,4,5-dibenzylidene-D-mannitol (IV).—To an intimate mixture of 5.92 g. (0.0128 mole) of II and 5 g. (0.037 mole) of powdered fused zinc chloride in a wide-mouth glass-stoppered bottle was added 10 cc. of freshly distilled benzaldehyde. The mixture was shaken vigorously for 15 minutes and allowed to stand for 3 days. The material was triturated with 25 cc. of alcohol, filtered and washed copiously with ethanol; yield 7.0 g. (87%). It was purified by two crystallizations from a 1:3 dioxane–alcohol solution; m.p. 181–182°, αD +84.7° (dioxane). Calcd. for $C_{32}H_{30}O_{10}S_2$: S, 10.04. Found: S, 9.93.

Reaction of IV with Sodium Iodide.—A solution of 2 g. of IV and 3.0 g. of sodium iodide in 50 ml. of purified acetone was heated for four hours at 100° in a pressure bottle. After cooling, a theoretical yield of sodium benzenesulfonate was separated by filtration and washed with acetone. The combined filtrates were concentrated to dryness *in vacuo* and the residue washed with water. The water-insoluble portion was recrystallized from 1:3 chloroform–ether; m.p. 182–183°, lit.[3] 184–186° (cor.), $\alpha^{25}\text{D}$ +57.1° (chloroform).

1,6-Di-*p*-phenylsulfonyl-2,4:3,5-dimethylene-D-mannitol (V).—To a mixture of 8.0 g. (0.017 mole) of II, 2 g. (0.06 mole) of paraformaldehyde and 5 g. (0.037 mole) of fused zinc chloride was added 20 g. (0.13 mole) of molten benzenesulfonic acid. The materials were thoroughly mixed by shaking in a wide-mouth glass-stoppered bottle, kept in a water-bath at 50° for 20 minutes and allowed to stand for 3 days. The solid mass was triturated with water and filtered. The solid was extracted with two 30-cc. portions of boiling dioxane. The residue from distillation of the dioxane was crystallized from alcohol to give V, m.p. 140–142°, αD +71.6° (dioxane). Calcd. for $C_{20}H_{22}O_{10}S_2$: C, 49.4; H, 4.6. Found: C, 49.7; H, 4.5.

Reaction with Sodium Iodide.—A mixture of 0.97 g. (0.0020 mole) of V and 1.5 g. (0.010 mole) of sodium iodide was dissolved in 50 cc. of purified acetone and heated 2 hours at 100° in a pressure bottle surrounded by an iron jacket. After gradual cooling to room temperature 0.73 g. (100%) of sodium benzenesulfonate was collected by filtration. The residue from the distillation of acetone was triturated with water, filtered and crystallized from dioxane; m.p. 196–197°, αD +53.0° (chloroform). This agrees with the data for 1,6-diiododideoxy-2,4,3:5-dimethylene-D-mannitol obtained by Hudson and co-workers[6] who used the ditosyl derivative.

When II was used in place of V reaction took place at room temperature to give sodium benzenesulfonate and an unstable red oil.

1,6-Dianilino-dideoxy-D-mannitol (VI).—A mixture of 4.62 g. (0.010 mole) of II and 50 cc. of cold freshly distilled aniline was shaken for 10 minutes and the solution was stored in a dark place at room temperature. After 6 days the long needle-like crystals which had separated from the orange-colored solution were filtered and washed with dry ether. A second crop was obtained by dilution with 10 volumes of dry ether. The water-soluble component of both crops was recrystallized from alcohol to give 2.2 g. (65%) of pure VI, m.p. 171–172°, αD +59.3° (dioxane). Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.4; H, 7.3; N, 8.4. Found: C, 64.5; H, 7.0; N, 8.3.

1,6-Dianilino-dideoxy-2,4:3,5-dimethylene-D-mannitol (VII).—A mixture of 2.4 g. (0.0050 mole) of V, 10 cc. (0.11 mole) of aniline and 20 cc. of dioxane was refluxed 48 hours from a bath at 110°; 2.6 g. of aniline benzenesulfonate was filtered from the cooled mixture. The filtrate was treated with 7 cc. of hydrochloric acid (sp. gr. 1.19) and 35 cc. of water. The solution was extracted with four 25-cc. portions of ether. The red oil from the dry (sodium sulfate) ether extract was dissolved in 25 cc. of alcohol to start crystallization and the whole was decolorized by boiling 10 minutes with activated charcoal. The crystals (VII) from the cooled filtrate weighed 1.1 g. (62%) from which pure VII was obtained by one more crystallization from alcohol; m.p. 124°, $\alpha^{25}\text{D}$ +135° (dioxane). Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; N, 7.9. Found: C, 67.1; H, 6.8; N, 7.6.

Ammonolysis of V.—A solution of 5 g. (0.010 mole) of V in 150 cc. of ethylene glycol dimethyl ether in a pressure bottle was saturated with ammonia at −25°. It was heated at 44° in a safety jacket for 5 days. The heavy yellow oil (3 g.) that separated was heated with 10 cc. of a 5% solution of barium hydroxide for 2 hours. The residue from the removal of water *in vacuo* was extracted with chloroform. The residual oil from the chloroform solution was dissolved in water and acidified with hydrochloric acid (sp. gr. 1.19). Dilution with alcohol gave the hydrochloride, dec. p. 220–224°. This corresponds to that obtained by Haworth and co-workers[7] for 1,6-diamino-dideoxy-2,4:-3,5-dimethylene-D-mannitol dihydrochloride.

1,6-Diisothiouronium-dideoxy-2,4:3,5-dimethylene-D-mannitol Benzenesulfonate (VIII).—To a boiling solution of 2.43 g. (0.005 mole) of V in 7 cc. of dioxane was added a solution of 0.76 g. (0.010 mole) of thiourea in 13 cc. of hot alcohol. The mixture was refluxed 18 hours. The cooled solution set to a solid mass when diluted with dioxane. The filtered product was crystallized from hot alcohol; yield 2.5 g. (78%). No crystalline product was obtained when this reaction was applied to II; m.p. 181–182°. Calcd. for $C_{22}H_{30}O_{10}N_4S_4$: N, 8.76. Found: N, 8.64.

Alkaline Hydrolysis of VIII.—In 10 cc. of 10% sodium hydroxide there was dissolved without warming 3.1 g. (0.0046 mole) of VIII. It was allowed to stand for 6 hours, then cooled to 0°, acidified with hydrochloric acid (sp. gr. 1.19) and stirred until white crystals separated. The product was filtered and washed with small portions of water at 0°. The product (IX) was crystallized from hot alcohol; yield 0.75 g. (75%), m.p. 101–102°. Calcd. for $C_8H_{14}O_4S_2$: C, 40.3; H, 5.9. Found: C, 40.5; H, 6.0.

Partial Identification of X.—The by-product (m.p. 165–167°) from the ammonolysis of II was purified by crystallization from alcohol; m.p. 166–168°, $\alpha^{25}\text{D}$ −11.3° (water).

Anal. Calcd. for $C_{12}H_{19}O_7NS$: C, 45.17; H, 5.96; S, 9.99. Found: C, 44.95; H, 6.12; S, 10.01.

The benzenesulfonate radical was replaced by chloride to give XI as described for the conversion of III to I; m.p. 166–167°, αD −11.5° (water).

Anal. Calcd. for $C_6H_{14}O_4NCl$: C, 36.10; H, 7.07. Found: C, 36.32; H, 7.09.

In a 50-cc. volumetric flask was dissolved 0.2523 g. (0.00126 mole) of XI in 25 cc. of water. It was cooled in ice and with constant swirling 10.0 cc. of 0.4617 *N* sodium metaperiodate was added. The solution was diluted to 50 cc. with water and thoroughly mixed. Aliquots (2.0 cc.) were diluted with 1.0 cc. of 20% potassium iodide solution, 15 cc. of 0.0924 *N* arsenite solution and 5 cc. of 0.20 *M* sodium bicarbonate solution. After standing at room temperature they were titrated with 0.09144 *N* iodine solution. Another aliquot (5.0 cc.) was titrated with 0.1294 *N* sodium hydroxide using methyl red as indicator to determine the amount of formic acid liberated.

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(6) W. T. Haskins, R. M. Hann and C. S. Hudson, This Journal, **65**, 67 (1943).

(7) W. N. Haworth, R. L. Heath and L. F. Wiggins, *J. Chem. Soc.*, 155 (1944).

Time, min.	IO_4^- cons.,[a] equiv.	HCO_2H lib.,[a] equiv.
5	1.74	
60	1.81	0.04
360	1.82	.15
1440	1.82	.17

[a] Standardization runs were conducted with mannitol and with I. In each case the oxidation was almost complete in 5 minutes and essentially complete in 1 hour. In no case was more than 90% of the theoretical value obtained.

Ring structure	2, 6	3, 6	4, 6
Equiv. IO_4^- required	2	2	2
Equiv. HCO_2H expected	1	0	1

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[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

The Reactions of Maleic Anhydride with Hydrazine Hydrate[1]

BY HENRY FEUER, EMIL H. WHITE AND JOHN E. WYMAN[2]

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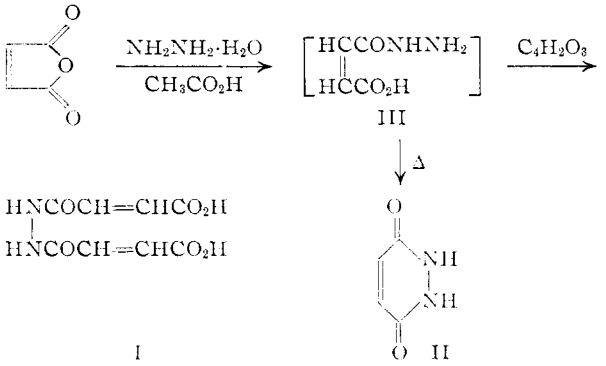
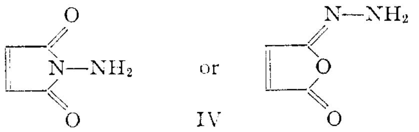
Depending on the conditions employed, maleic anhydride and hydrazine hydrate react to give 1,2-dimaleic acid hydrazine (I), maleic hydrazide, (1,2-dihydro-3,6-pyridazinedione) (II) and a yellow colored complex mixture which contains a small amount of I. Compound I was converted by hydrogenation to the known 1,2-disuccinic acid hydrazine and by refluxing in water to II.

In 1951, we reported the reactions of succinic anhydride with hydrazine hydrate.[3] Since then, we have investigated the reactions of maleic anhydride with hydrazine hydrate, and have found that they differ in some respects from those of succinic anhydride. The differences, however, can be accounted for by the facile ring closures that occur in the maleic acid series.

When hydrazine hydrate is added to two moles of maleic anhydride dissolved in acetic acid, 1,2-dimaleic acid hydrazine (I) is formed in good yield. Hydrogenation of I yields the known 1,2-disuccinic acid hydrazine.[3] When an equimolar mixture of maleic anhydride and hydrazine hydrate is heated in acetic acid, an excellent yield of maleic hydrazide[4] (II) is obtained. Maleic monohydrazide (III) is a likely intermediate in the formation of both I and II.



A similar procedure for the synthesis of II was reported recently by Hinterbauer.[5] The author reported the formation of a yellow intermediate which he considered to be N-aminomaleimide (IV).[6] We have repeated his directions and have found instead that under the conditions used (hydrazine hydrate added to the anhydride), the yellow intermediate is the linear hydrazide I. At higher temperatures, I is converted into II and maleic acid, a reaction that occurs even in a water solution (*vide infra*). The structure of IV was not established by Curtius[6] and we have not obtained it in any of our reactions.



When maleic anhydride and hydrazine hydrate are mixed in ether or in alcohol solvents, a canary yellow precipitate forms; this reaction was first reported by Curtius.[6] Our evidence indicates that the solid is a mixture of products. The infrared spectrum of a sample in a potassium bromide pellet had a moderately strong band centered at 5.90 μ (characteristic of –CON– groups) and an intense broad band at 6.40 μ ($-CO_2^-$ group). Most of the solid was soluble in water; the insoluble part was largely the linear hydrazide I. Some of the solid could be recrystallized with difficulty from methanol, and its elemental analysis agreed with maleic monohydrazide (III). When the solid was refluxed in methanol with maleic anhydride, two compounds were obtained, the linear hydrazide I and maleic hydrazide (II).

Treatment of the aqueous solution of the yellow precipitate with benzaldehyde yielded benzalazine

$$C_6H_5CH{=}N{-}N{=}CHC_6H_5$$

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[1] (a) From the Ph.D. thesis of John E. Wyman, Purdue University, 1956; (b) presented before the Division of Organic Chemistry at the Miami Meeting of the American Chemical Society, April, 1957.

[2] Purdue Research Foundation Fellow, 1954–1955, Monsanto Chemical Co. Fellow, 1955–1956.

[3] H. Feuer, G. B. Bachman and E. H. White, THIS JOURNAL, **73**, 4716 (1951).

[4] This compound has also been prepared by the reaction of maleic anhydride with mineral acid salts of hydrazine: (a) R. H. Mizzoni and P. E. Spoerri, THIS JOURNAL, **73**, 1873 (1951); (b) W. D. Harris and D. L. Schoene, U. S. Patent 2,575,954, Nov. 20 (1951); (c) Yu. A. Baskakov and N. N. Melnikov, *J. Gen. Chem. of U.S.S.R.*, **24**, 1216 (1954).

[5] H. Hinterbauer, Austrian Patent 176,563, Nov. 10, 1953; *C. A.*, **48**, 10785 (1954).

[6] T. Curtius and H. H. Foesterling, *J. prakt. Chem.*, **51**, 371 (1895).