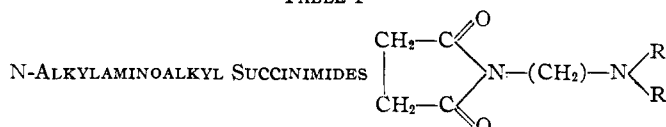


TABLE I



R	n	Formula	B.p.,		Carbon, %		Hydrogen, %		Nitrogen, %		Hydrochloride M.p., °C.
			°C.	Mm.	Calcd.	Found	Calcd.	Found	Calcd.	Found	
CH ₃	2	C ₈ H ₁₄ N ₂ O ₂ ^b	93-97	2	56.45	56.51	8.29	8.03	16.46	16.53	198-199
C ₂ H ₅	2	C ₁₀ H ₁₈ N ₂ O ₂	122-124	3	60.58	60.44	9.15	8.97	14.13	13.94	208-209
CH ₃	3	C ₉ H ₁₆ N ₂ O ₂	105-107	2	58.67	58.41	8.75	8.59	15.21	14.91	196-197
C ₄ H ₉ O ^a	2	C ₁₀ H ₁₆ N ₂ O ₃	140-144	2	56.59	56.85	7.60	7.53	13.20	13.03	217-218

^a Morpholino. ^b M.p. 40-41°.

TABLE II



R	n	Formula	B.p.,		Carbon, %		Hydrogen, %		Nitrogen, %		HCl M.p., °C.	Dimethiodide analysis		M.p., °C.
			°C.	Mm.	Calcd.	Found	Calcd.	Found	Calcd.	Found		Calcd.	Found	
CH ₃	2	C ₈ H ₁₈ N ₂	92-94	48	67.55	67.52	12.76	12.64	19.69	19.58	294-295	6.57	6.60	261-262
C ₂ H ₅	2	C ₁₀ H ₂₂ N ₂	56-58	3	70.53	70.68	13.02	12.75	16.45	16.89	245-246	6.16	6.37	228-229
CH ₃	3	C ₉ H ₂₀ N ₂	50-55	3	69.17	69.06	12.90	12.72	17.93	17.65	264-265	6.36	6.20	295-297
C ₄ H ₉ O ^a	2	C ₁₀ H ₂₀ N ₂ O	78-80	2	65.17	65.00	10.94	10.73	15.20	15.39	295-296	5.98	6.02	245-246

^a Morpholino.

ence the reduction of imides with lithium aluminum hydride had proved to give excellent yields in other series. When applied to this series of imides the yields were 90-95%. Phillips⁷ had reported that the reaction of ethanolamine with succinic anhydride yielded no imide but only the bis-amide under any of the conditions that he employed. We have prepared diethylaminoethylpyrrolidine by the reaction of β -diethylaminoethyl chloride and pyrrolidine and found that the product obtained was identical with that produced by the reduction of diethylaminoethylsuccinimide.

The various imides prepared and the corresponding pyrrolidine reduction products are listed in Tables I and II, respectively. When tested on dogs for hypotensive activity the dimethiodides of these dialkylaminoalkyl pyrrolidines were found to possess a moderate hypotensive effect.

Experimental

General Procedure for the Preparation and Reduction of Dialkylaminoalkyl Succinimides.—To 0.3 mole of succinic anhydride was slowly added with cooling 0.3 mole of the appropriate dialkylaminoalkyl amine. When the reaction had subsided the mixture was heated in an oil-bath at 175° for two hours. After the product had cooled to room temperature it was fractionated in vacuum to yield the imide as a colorless oil or low melting solid.

The imide (50 g.) was dissolved in twice its volume of anhydrous ether and slowly added with stirring to a solution of 19 g. of lithium aluminum hydride in 1 liter of anhydrous ether. The rate of addition was such as to cause gentle refluxing. After all the imide had been added the reaction mixture was allowed to stand overnight. Decomposition was effected by the slow addition of water and the mixture stirred an additional hour. The suspension was filtered, dried over sodium sulfate, and the ether stripped off. The products were obtained by vacuum distillation as colorless liquids.

The hydrochlorides were prepared in the usual way by means of alcoholic hydrogen chloride.

The dimethiodides were made in the usual manner by adding methyl iodide to an alcohol solution of the amine.

Diethylaminoethylpyrrolidine was obtained in the usual way by reaction of diethylaminoethyl chloride (0.2 mole)

with pyrrolidine (0.4 mole) in benzene solution. The boiling point of the base and melting point of the hydrochloride corresponded to those of the product obtained by reduction. A mixed melting point of the hydrochloride gave no depression.

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Isolation of Fructose from Beef Serum¹

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RECEIVED SEPTEMBER 12, 1952

The isolation of additional amounts of the recently reported TPS (*Treponema pallidum* survival) factor,² for the purpose of chemical investigations necessitated the processing of considerable quantities (approximately 100 liters) of beef serum. In order to isolate the TPS factor, protein is removed from the serum by means of tungstic acid, the factor is adsorbed from the protein-free filtrate on charcoal (Darco G-60) and eluted with acetone; the acetone-soluble material after having been extracted with ether, is condensed with acetone in the presence of sulfuric acid. The isopropylidene derivative of the TPS factor which is ether-soluble is now precipitated from ether with petroleum ether (b.p. 30-60°) and recrystallized from ethyl acetate.² The material soluble in ether-petroleum ether from individual lots of serum (in all approximately 100 liters) was pooled and concentrated to dryness. The thick brown sirup which resulted gave a strong positive test for carbohydrate by the conventional Molisch and Anthrone³ tests. It was thought to be of interest particularly in view of the major role played by carbohydrates in metabolism, to attempt to separate, and identify

(1) Supported by a grant from the Whitehall Foundation, New York, N. Y.

(2) F. A. H. Rice and Robert A. Nelson, Jr., *J. Biol. Chem.*, **191**, 35 (1951).

(3) R. Dreywood, *Ind. Eng. Chem., Anal. Ed.*, **18**, 499 (1946); L. Sattler and F. W. Zerban, *THIS JOURNAL*, **72**, 3814 (1950).

if possible, these carbohydrates. Chromatographic adsorption⁴ on a silicic acid⁵-Celite⁶ mixture led to the isolation of 15 mg. of a compound (m.p. 97°, $[\alpha]_D -32.9^\circ$ Me₂CO ca. 0.2) which analyzed for C₁₂H₂₀O₆; the physical constants are those of diisopropylidene- β -D-fructose.⁷ The compound showed no depression of melting point when mixed with an authentic sample of diisopropylidene-D-fructose.

Although fructose has been shown to be a normal constituent of seminal plasma⁸ it does not appear to have been isolated heretofore from blood.

It should be noted that the procedure used in the isolation of the fructose prevents even speculation as to the normal concentration of this sugar in blood, or to the form in which it occurs since the acid used in acetonation may have hydrolyzed a fructose derivative.

Experimental

The sirup obtained by concentrating the ether-petroleum ether soluble material (as indicated above²) was thoroughly extracted with petroleum ether (b.p. 30-60°) and the petroleum ether soluble material concentrated to dryness under reduced pressure at room temperature. The material was then separated into two fractions in the following manner: the sirup was dissolved in 10 ml. of benzene and filtered through a column (16 cm. \times 2 cm.) packed with a mixture of silicic acid and Celite (3:1 by weight). The column was then washed with 150 ml. of benzene, extracted and the entire column eluted with acetone (250 ml.). The acetone eluate (representing the material adsorbed from benzene solution by silicic acid-Celite) was concentrated to dryness under reduced pressure at room temperature, redissolved in benzene and rechromatographed under the same conditions with the exception that in place of the benzene wash the column was developed with 100 ml. of benzene containing 1% (by volume) of *t*-butyl alcohol. The column was extruded and streaked with alkaline permanganate.⁹ The zone at approximately the center of the column was cut and eluted with acetone, concentrated to dryness under reduced pressure at room temperature. The material crystallized after standing several days at 4°. After recrystallization from petroleum ether (b.p. 30-60°) the compound melted at 95-96°, $[\alpha]_D -32.9^\circ$ (Me₂CO ca. 0.2).

Anal. Calcd. for C₁₂H₂₀O₆: C, 55.43; H, 7.74. Found: C, 55.45; H, 7.53.

The compound showed no depression of melting point when mixed with an authentic sample of diisopropylidene-fructose.

(4) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, *ibid.*, **67**, 527 (1945).

(5) Baker and Adamson, Silicic Acid Powder (Reagent) Lot No. 6123.

(6) No. 535 obtained from Johns-Manville, New York.

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Reactions of Toluic Acids with Sulfur. I. Stilbenedicarboxylic Acids

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RECEIVED NOVEMBER 1, 1952

Previous methods for the preparation of 4,4'-stilbenedicarboxylic acid have involved a number of steps, such as conversion of stilbene to the dibro-

midate, to the dinitrile, and finally to the diester,¹ or by the decarboxylation of more complex acids.² The preparation of 3,3'-stilbenedicarboxylic acid does not appear to have been reported. We have found that a shorter, more economical route to both these acids is provided by the reaction of the corresponding toluic acid with sulfur. Spectroscopic evidence indicates that the 4,4'-stilbenedicarboxylic acid thus formed is the *trans* isomer. The reaction of sulfur with amine and hydroxyl-substituted aromatic compounds leads to attachment of sulfur to the aromatic ring, but the dehydrodimerizing action of sulfur has been demonstrated in the conversion of toluene to stilbene and tetraphenylthiophene, of *m*- and *p*-xylenes to the corresponding dimethylstilbenes,³ and in the dehydropolymerization of 4-picoline.⁴ The mechanism of some of these reactions has been discussed.⁵ Previously reported dehydrodimerization reactions, however, do not involve compounds containing reactive functional groups such as the carboxyl group.

With *p*-toluic acid, 50-70% yields of 4,4'-stilbenedicarboxylic acid are obtained by reaction with sulfur. Other products are hydrogen sulfide, a large amount of a sulfur-containing acid of higher molecular weight, believed to be tetra-(*p*-carboxyphenyl)-thiophene, and a small amount of an unidentified compound of lower molecular weight. Sulfur reacts with *m*-toluic acid to give lower yields of 3,3'-stilbenedicarboxylic acid, but no stilbene derivatives were obtained from the reaction of sulfur with *o*-toluic acid under the conditions studied.

Several variables of the reaction of sulfur with *p*-toluic acid to yield 4,4'-stilbenedicarboxylic acid were investigated, and the optimum reaction conditions are shown in Table I. The rate of reaction increases rapidly with temperature, but the yield decreases simultaneously. Impurities in the toluic acid prolong the reaction time, and increased reaction time decreases the yield. The higher the toluic acid:sulfur ratio, the higher is the yield, based on *p*-toluic acid reacted. More than 90% of the theoretical amount of sulfur cannot be used in the absence of solvent, or the reaction mixture solidifies before the reaction is complete.

Experimental

Materials.—The isomeric toluic acids were made by the air oxidation of the corresponding xylenes, using a soluble cobalt salt catalyst, and purified by filtering and washing the residue with xylene, followed by distillation through a 90-cm. glass helices-packed column. Isomer content was determined by ultraviolet spectrography. Sublimed flowers of sulfur, U.S.P., were used.

Reaction of *p*-Toluic Acid with Sulfur.—A mixture of *p*-toluic acid and sulfur was heated in a three-neck flask equipped with an air-cooled condenser, stirrer and thermometer. At reaction temperature, the mixture darkened and hydrogen sulfide was evolved. After partial reaction had occurred, a yellow solid, consisting largely of 4,4'-stilbenedicarboxylic acid, began to separate. The threshold tem-

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