Experimental

Methyl and Ethyl Carbazates.—These esters were prepared in about 90% yields from 85% hydrazine hydrate and dimethyl and diethyl carbonates, respectively, by the procedure of Diels.[3]

Preparation of the Carbomethoxy- and Carboethoxyhydrazones.—Approximately 1 g. of the aldehyde or ketone was dissolved in 3–4 ml. of alcohol and sufficient water was added to cause a faint turbidity. This was removed by means of a few drops of alcohol, and then 3 drops of acetic acid and 1 g. of the carbazate were added. The mixture was shaken and allowed to stand for a few minutes. If crystallization did not result, the reaction mixture was heated to reflux for one hour and cooled. The precipitate was removed by filtration, weighed and crystallized. In those cases where a solid was not obtained readily, the reaction was carried out without the addition of water, and after refluxing for one hour, the solvent was evaporated and the residue recrystallized.

In practically all of the condensations, the yields of the derivatives were high. The products were purified by recrystallization from dilute alcohol or a mixture of benzene and petroleum ether.

(3) O. Diels, *Ber.*, **47**, 2183 (1914).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI

Streptohydrazid

BY FRANK C. PENNINGTON, PETER A. GUERCIO AND I. A. SOLOMONS

RECEIVED JANUARY 19, 1953

Previous investigators[1] have demonstrated the condensation of streptomycin with a wide variety of amino compounds. Since isoniazid and streptomycin are both used in the chemotherapy of tuberculosis and have been proposed for combined therapy,[2] it was of interest to prepare and characterize an analogous condensation product, Streptohydrazid.[3]

The condensation of streptomycin with isoniazid was found to occur readily, and it was possible to isolate Streptohydrazid sulfate and hydrochloride as white crystalline products. Whereas isoniazid exhibits an absorption maximum in water at 262 mμ (ε 4,360), Streptohydrazid absorbs at 260 mμ (ε 14,700). The latter value was obtained in the presence of a large molar excess of streptomycin to prevent hydrolysis. It was found that by utilizing the difference in absorption at 260 mμ the extent of reaction could be estimated. It was also observed that in concentrated aqueous solutions Streptohydrazid hydrolyzes very little, but in very dilute solution it dissociates into its component parts.

In tuberculosis protection studies in animals Streptohydrazid has been found at least as effective as combined therapy utilizing streptomycin and isoniazid.[2]

Streptomyclideneisonicotinylhydrazine Trihydrochloride.—A mixture of 30 g. of streptomycin hydrochloride and 6 g. of isoniazid in 300 ml. of absolute methanol was boiled under reflux for 15 minutes. The solution was allowed to stand several days in a refrigerator, and large crystals slowly formed. The supernatant solution was decanted and the product filtered, washed with cold methanol and dried; yield 19.0 g. (54%), decomposes *ca.* 200°.

The infrared spectrum exhibits broad strong absorption at 1650 cm.$^{-1}$ and at longer wave lengths is very similar to isoniazid. Weak absorption is evident near 1350, 1300, 1210, 1140, 1110, 1060 and 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{47}N_{10}O_{12}Cl_3$: C, 40.03; H, 5.85; N, 17.29; Cl, 13.13. Found: C, 39.94; H, 5.90; N, 17.23; Cl, 13.18.

Streptomycylideneisonicotinylhydrazine Sesquisulfate.—Streptomycin trihydrochloride calcium chloride double salt (50 g.) assaying about 660 mcg. per mg., was dissolved in 160 ml. of water containing 8.5 g. of isoniazid. Over a period of 0.5 hour, 85 ml. of methanolic triethylamine sulfate solution (1.98 *M* in $SO_4^=$, *p*H 5) was introduced with stirring, followed by the addition of 255 ml. of methanol during the succeeding hour. The precipitated $CaSO_4$ was collected and washed with a mixture of one part methanolic triethylamine sulfate solution, two parts of water, and three parts of methanol.

Methanol (about 100 ml.) was added until a haze persisted and the mixture was then allowed to crystallize. Methanol (2000 ml.) was added dropwise with stirring and the white crystalline product was collected, washed with methanol, and dried *in vacuo;* yield 36.0 g. (75%), decomposes *ca.* 230°.

Anal. Calcd. for $C_{27}H_{44}N_{10}O_{12}\cdot 3/2H_2SO_4$: C, 38.25; H, 5.59; N, 16.52; S, 5.67. Found: C, 38.04; H, 5.74; N, 16.22; S, 5.63.

Streptohydrazid trihydrochloride and sesquisulfate are extremely soluble in water. The former is partially soluble in methanol, whereas the latter is insoluble. Both salts are insoluble in less polar solvents.

RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
BROOKLYN 6, N. Y.

Hypotensive Agents. III.[1] Dialkylaminoalkyl Pyrrolidine Derivatives[2a,b]

BY LEONARD M. RICE, CHARLES H. GROGAN AND E. EMMET REID[3]

RECEIVED DECEMBER 19, 1952

In the course of a continuing study of potential hypotensive compounds we investigated the reduction of various N-dialkylaminoalkyl succinimides. The various substituted succinimides were obtained in good yields by the reaction of equimolecular amounts of the appropriate dialkylaminoalkylamine with succinic anhydride. After the exothermic reaction had subsided, the resulting mixture was heated at 160–170° for two hours to complete the reaction. Ohki[4] had prepared this type of imide and studied its electrolytic reduction. He isolated the corresponding pyrrolidone by this means.

The reduction of N-phenylsuccinimide to yield N-phenylpyrrolidine with lithium aluminum hydride has been reported by Spitzmueller.[5] Wojcik and Atkins[6] obtained N-amylpyrrolidine by reduction of amylsuccinimide by means of copper chromite catalyst in excellent yields. In our past experi-

(1) W. A. Winsten, C. I. Jarowski, F. X. Murphy and W. A. Lazier, THIS JOURNAL, **72**, 3969 (1950).

(2) G. L. Hobby and T. F. Lenert, "The Action of Isoniazid and Streptomycin Alone and in Combination," Annual Meeting Public Health Association, Cleveland, Ohio, October 24, 1952.

(3) Chas. Pfizer and Co., Inc., trade name for streptomyclideneisonicotinylhydrazine.

(1) For the first paper in this series see L. M. Rice, A. Popovici, M. Rubin, C. F. Geschickter and E. E. Reid, THIS JOURNAL, **74**, 3025 (1952).

(2) (a) Supported (in part) by a research grant from the Geschickter Fund for Medical Research, Inc. (b) Presented at the Meeting of the American Chemical Society at Atlantic City, N. J., Sept., 1952.

(3) Professor Emeritus, Johns Hopkins University, Baltimore, Md.

(4) Sadao Ohki, *J. Pharm. Soc. Japan*, **70**, 92 (1950).

(5) Weldon G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 492.

(6) B. Wojcik and H. Adkins, THIS JOURNAL, **56**, 2419 (1934).