THE SYNTHESIS OF SOME p-SUBSTITUTED BENZENESULFONYL GUANIDINES

A Thesis

Presented to

The Faculty of the College of Pharmacy

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

Nickie Lee Nicholas

August 1966

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ABSTRACT

In view of the structural similarity of urea and guanidine combined with the fact that certain derivatives of sulfonylurea have been found to be active as oral hypogycemic agents, it seemed desirable to prepare several p-substituted benzenesulfonyl guanidines for further testing as hypoglycemic agents.

The synthesis of p-cyanobenzenesulfonyl cyclohexylguanidine was performed by direct condensation of equal molar quanities of p-cyanobenzenesulfonyl chloride with cyclohexylguanidine hydrochloride in an aqueous-acetone solution. Also p-cyanobenzenesulfonyl n-butylguanidine was synthesized by the same procedure.

The imino-ester hydrochloride was prepared from p-cyanobenzenesulfonyl cyclohexylguanidine by saturating a solution of the nitrile in ether and absolute ethanol at room temperature with dry hydrogen chloride.

The p-N-n-propyl carbamidino was then prepared from the imino-ester hydrochloride; i.e., N' - [(p-carbethoxyimino) benzenesulfonyl] cyclohexylguanidine hydrochloride.

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CHAPTER I

HISTORY AND INTRODUCTION

Following the isolation by Banting and Best in 1921 (1) of the pancreatic hormone insulin, for use in the treatment of diabetes mellitus, and the discovery that this hormone was ineffective when given by mouth, many attempts were made to prepare an orally active hypoglycemic agent. It was reported by Watanabe (2) in 1918 that guanidine bases were effective in depressing the blood sugar level. This led to the introduction of Synthalin A (decamethylenediguanidine) and Synthalin B (dodecamethylenediguanidine) in the early 1930's (3,4). In 1936 W. A. Broom (5) reported on the hypoglycemic activity of a number of amidine and guanidine derivatives. Interest in this field lagged until 1941 when Janbon et al. (6) reported that certain sulfonamide derivatives were mildly effective in producing hypoglycemia. This work was further confirmed in 1942 by Loubatieres (3) who found that the isopropylthiadiazole derivative of sulfanilamide showed definite hypoglycemic activity. He then synthesized amyl-, isoamyl-, and butyl derivatives of thiadiazole and found the butyl derivatives to be the most active. This led to the synthesis of Carbutamide (1-butyl-3-sulfanilylurea) by Franke and Fuchs (4) in 1954, and was followed by Tolbutamide [Orinase°, 1-butyl-3-(p-tolylsulfonyl)urea] and Chlorpropamide [Diabinase+, 1-propyl-3-(p-chlorophenylsulfonyl)urea] in 1957 and Phenformin (DBI++, N'-betaphenethylbiguanide

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°Manufactured by the Upjohn Company, Kalamazoo, Michigan.

+Manufactured by Pfizer Laboratories, New York, New York.

++Manufactured by U. S. Vitamin & Pharmaceutical Corp., New York, New York.

hydrochloride) and Metahexamide [1-cyclohexyl-3-(3-amino-4-methylphenylsulfonyl)urea] in 1958 (2). The search for hypoglycemic drugs was pushed in many directions. Acetohexamide [Dymelor°, 1-cyclohexyl-3-(p-acetylphenylsulfonyl)urea] was introduced in 1961 for testing as #U-14,812 (2), and was followed by Tolazamide [Tolinase+, 1-(hexahydro-1-azepinyl)-3-(p-tolylsulfonyl)urea] in 1961 as #U-17,835 (2).

Numerous digestive enzymes, vasodilators, antihistaminics, salicylates, estrogens, and plant extracts seemed to exhibit some hypoglycemic activity. Due to the low degree of activity as well as undesirable side effects such as gastro-intestinal and neurologic disturbances as well as hepatic changes these drugs were discarded (1,4,6). Tolbutamide, Chlorpropamide, Phenformin, Acetohexamide and Tolazamide, however, have proved to be very effective, and in addition were shown to possess a low degree of toxicity. As a result, these compounds are widely used today.

Rather encouraging clinical trials pertaining to Phenformin would indicate that guanidine derivatives may be effective as therapeutic agents in the management of diabetes. Phenformin may be effective in juvenile diabetes, whereas the other oral agents are effective only in maturity onset diabetes (1,4,5).

There has been no definite proof as to the mode(s) of action of the various hypoglycemic agents. Considering the actions of the sulphonylureas, one concludes that at present it is impossible to limit the mode of action to one simple biochemical or physico-chemical principle (1,3,11).

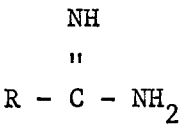
°Manufactured by Eli Lilly and Company, Indianapolis, Indiana.

+Manufactured by the Upjohn Company, Kalamazoo, Michigan.

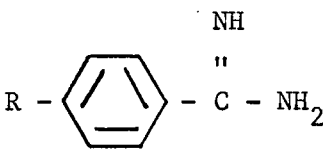
The compounds exhibiting oral hypoglycemic activity may be grouped on the basis of their chemical configurations as follows:

A. Amidine Class of Compounds

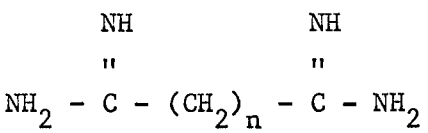
1. Monoamidines (alkyl)



2. Benzamidines (aryl)

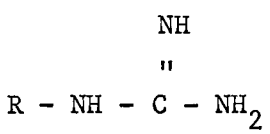


3. Diamidines (alkyl)

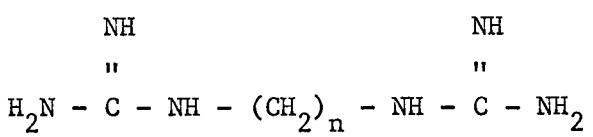


B. Guanidine Class of Compounds

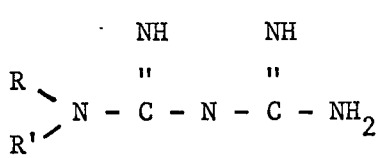
1. Monoguanidines



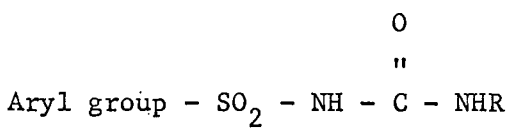
2. Diguanidines



3. Biguanidines (diguanides)

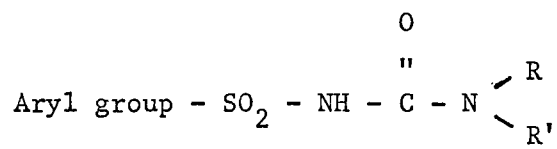


C. Sulfonylurea Class of Compounds



Due to liver damage and untoward reactions, the amidine class of compounds has not been used clinically. In the guanidine class of compounds, Phenformin, a biguanidine type, has proved to be an effective agent possessing only mild side effects when used in the treatment of diabetes (2,5,13,14).

A summary (2,15) of the research work done on the sulfonylurea derivatives with respect to their effectiveness as hypoglycemic agents led to the following generalizations based on Tolbutamide activity as a reference:



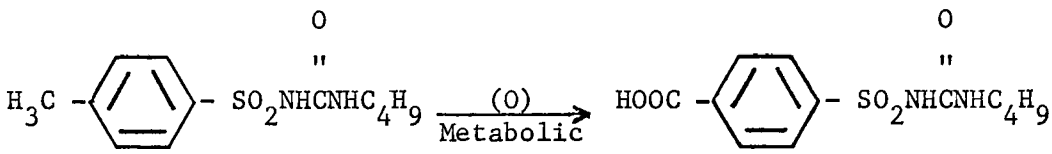
a. When R was hydrogen and R' (alkyl) was equal to 3-4 carbons, peak activity of (+3 to +4) occurred; was branched 3-5 carbons, activity of (+2 to +4) was observed; and was cyclic 5-7 carbons, activity of (+3 to +4) was found.

b. When R and R' were alkyl groups, moderate activity of (+2 to +3) occurred.

c. When R was hydrogen and R' was an aryl group, an activity of (+2 to +3) was observed.

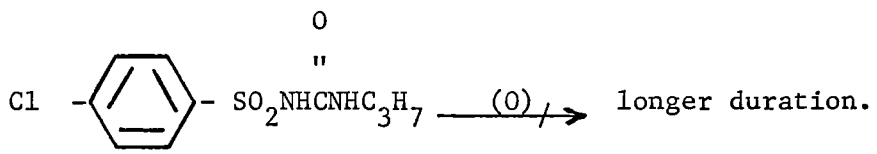
d. In any modification of the urea portion, most changes led to loss of activity, but weak activity was retained in thioureas and carbamates.

e. Variations in the aryl portion showed that para-substitution yielded compounds with maximal activity and duration, that unsubstituted phenyl derivatives were less active, that ortho-substituted and disubstituted phenyl compounds were still less active, and that heterocyclic substitution for aryl was moderately active. The most effective para-substitution group was halogen.



Tolbutamide

inactive metabolite of short duration.



longer duration.

Chlorpropamide

Since guanidines may be converted to urea, the rate depending upon the pH (16) and temperature (17) conditions, one may suggest that the sulfonylguanidine derivatives may act similarly to those of sulfonylurea. This thesis will be concerned primarily with the synthesis of some p-substituted benzenesulfonyl derivatives of cyclohexylguanidine and n-butylguanidine as their hydrochloride salts.

CHAPTER II

I. INTRODUCTION

The procedures employed in the synthesis of some para-substituted benzenesulfonyl guanidine derivatives were similar to those used by Montgomery (19).

An oil was obtained when using the calcium cyanamide fusion procedure by Gagnon et al. (20,21) in preparing n-butylguanidine nitrate and cyclohexylguanidine nitrate. Crystals of cyclohexylguanidine hydrochloride were obtained by fusion of cyanoguanidine (dicyandiamide) with the amine hydrochloride according to Werner and Bell (22) and others (23-26). From IR data some di- and tri-substituted guanidines were also evident, but upon fractional recrystallization the mono-substituted cyclohexylguanidine hydrochloride was obtained in 40-60 percent yields. When recrystallizing from water the di- and tri-substituted guanidines presented less problems of contamination as opposed to using ethanol and water for recrystallization. The di- and tri-substituted guanidines predominated when fusing more than 10 grams of cyanoguanidine with 33.6 grams of cyclohexylamine hydrochloride.

Contrary to Montgomery (19), p-cyanobenzenesulfonyl chloride was prepared by maintaining the molten reaction mixture, consisting of p-sulfonamidobenzoic acid and phosphorus pentachloride, at 195-205^{o}C. under vacuum until distillation of the phosphorus oxychloride was completed (27-29).

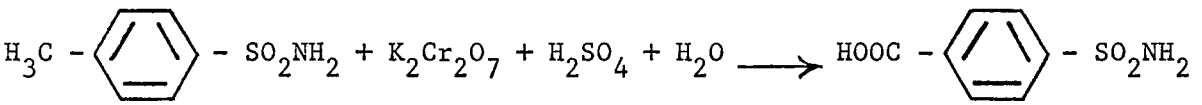
When employing the procedure of Werner and Bell (22) in making n-butylguanidine hydrochloride, a syrup was obtained. According to the

procedure of Paden and MacLean (30) in which the butylamine hydrochloride was reacted with cyanamide, the syrup obtained was converted to the free base and then to butylguanidine bicarbonate. The syrup from the cyanoguanidine fusion of butylamine hydrochloride was condensed with p-cyanobenzenesulfonyl chloride, but no crystals of p-cyanobenzenesulfonyl butylguanidine could be obtained.

In the condensation reaction of p-cyanobenzenesulfonyl chloride with cyclohexylguanidine hydrochloride, the pH of 8-9 had to be maintained throughout the reaction (19,31-34). A light brown gummy mass resulted, and several solvents were tried in order to obtain white crystals. Aqueous ethanol proved to be the best solvent for recrystallization of the gummy mass. The first collection of crystals from the warm solution had a melting point of 190-195°C. with an IR very close to that of the desired product which appeared in the second collection with a melting point of 144-150°C.

II. SYNTHETIC METHODS

Preparation of p-sulfonamidobenzoic acid (p-sulfamylbenzoic acid) (28,19) according to the following reaction:



p-toluenesulfonamide

p-sulfonamido-benzoic acid m.p. 280-282°C.

A four liter beaker fitted with a mechanical stirrer was placed on a hot plate and the following were added in the order listed: (1) 960 mls. water; (2) 390 gms. potassium dichromate; (3) 320 mls. concentrated sulfuric acid, added slowly; and (4) 136 gms. p-toluenesulfonamide. The solution was gradually heated to boiling while being continually stirred. The temperature was carefully controlled and the reaction mixture allowed to react for two hours. Upon cooling to room temperature, one liter of ice was added and the precipitate thus formed was collected. The precipitate was washed on the filter with cold water until the filtrate appeared clear. After recrystallization of the p-sulfamylbenzoic acid from 1500-2000 mls. of water and drying in an oven at 50-80°C., crystals were obtained in 75-85 percent yields with a melting point* of 280-282°C. Montgomery (19) reported 275-278°C. as the melting point of p-sulfonamidobenzoic acid.

Preparation of p-cyanobenzenesulfonyl chloride (27,19) according to the following reaction:

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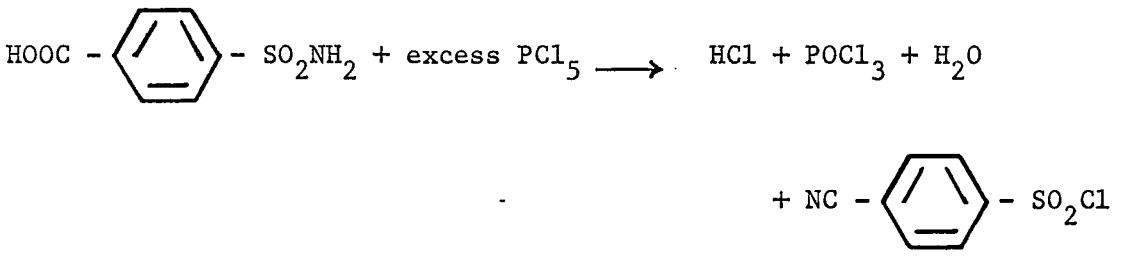
*The melting points reported in this paper are uncorrected.



p-Sulfonamidobenzoic acid

p-Cyanobenzenesulfonyl chloride
m.p. 110°C.

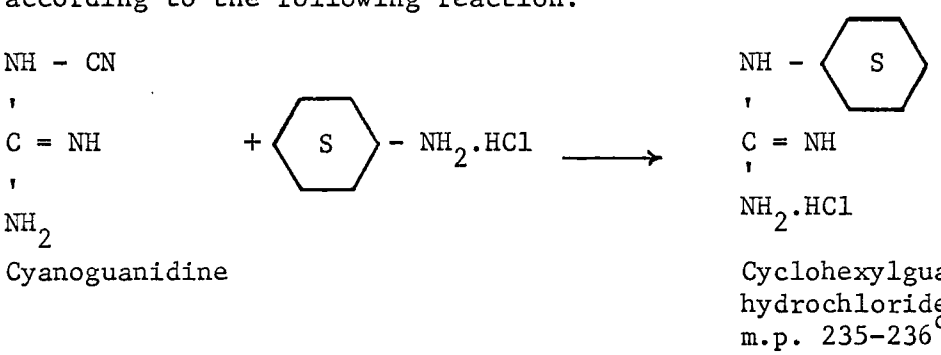
In a mortar, 123 gms. of p-sulfamylbenzoic acid was mixed intimately with 255.8 gms. of phosphorus pentachloride. The mixture was placed in a two necked liter flask fitted with a thermometer and a condenser for distillation. The temperature was raised slowly to 200-205°C. until no more HCl fumes and phosphorus oxychloride distilled over. A vacuum was applied slowly and the temperature maintained at 190-195°C. until nothing further distilled over. The molten mass was poured into a dry mortar and allowed to cool under the hood. At this point the solid mass was placed in a desiccator and left in a refrigerator overnight. The brown solid mass was washed with 400-600 mls. of ice water, dried with suction, and then placed in a vacuum desiccator over phosphorus pentoxide for 24 hours. Cyclohexane was used to recrystallize the crude product. A dark brown residue remained after decanting the hot cyclohexane. Light yellow needles of p-cyanobenzenesulfonyl chloride were collected. Yields varied from 50-75 percent after recrystallization.

In preparation of cyclohexylamine hydrochloride (20), dilute hydrochloric acid (6 N., 51.6 mls. concentrated hydrochloric acid and 48.4 mls. water) was treated with an excess of cyclohexylamine (80 mls. cyclohexylamine/100 mls. dilute hydrochloric acid). The solution was

evaporated and the crystals of cyclohexylamine hydrochloride collected. The melting points varied from 204-205° and 210-211°C., and yields varied from 80-91 percent.

In preparation of n-butylamine hydrochloride (20), dilute hydrochloric acid (6 N.) was treated slowly with an excess of n-butylamine (68 mls. n-butylamine/100 mls. dilute hydrochloric acid). The solution was evaporated and the crystals of n-butylamine hydrochloride were collected. The melting point 204-207°C. was obtained after drying in a vacuum oven at 60-80°C., and yields varied from 50-75 percent.

Preparation of cyclohexylguanidine hydrochloride (22,23-26) according to the following reaction:

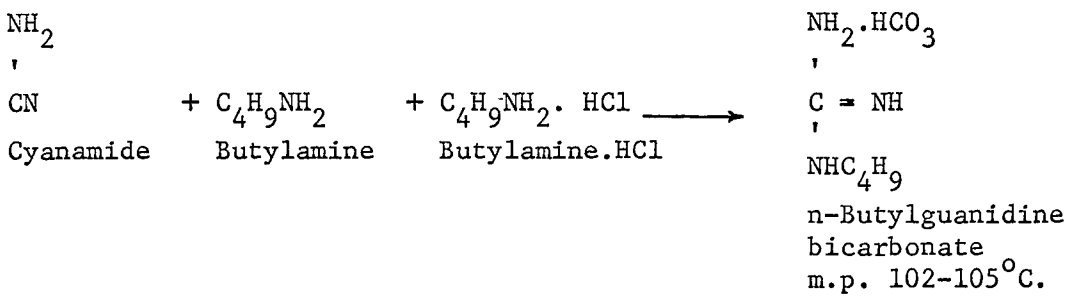


Cyanoguanidine

Cyclohexylguanidine hydrochloride m.p. 235-236°C.

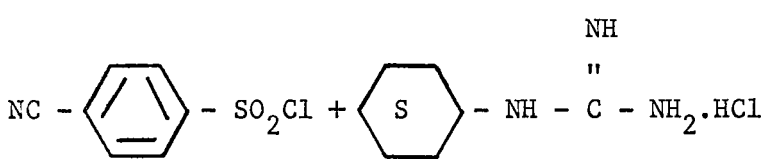
Cyanoguanidine, 10 gms., was mixed intimately with 33.62 gms. of cyclohexylamine hydrochloride and placed in a 500 ml. Erlenmeyer flask. A thermometer was placed inside the flask and used as a stirrer also. The reaction mixture was heated on an oil bath at 170-180°C. for three hours. After cooling, the solid reaction product was recrystallized twice from 300-400 mls. of boiling water. Yields varied from 30-60 percent after two recrystallizations. Charles Braun (23) reported the melting point of cyclohexylguanidine hydrochloride as 224-226°C., and Bannard et al. (24) reported the melting point as 228-229°C. After several recrystallizations a melting point of 235-236°C. was obtained.

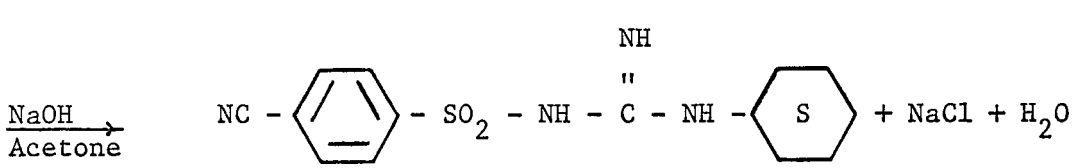
Preparation of n-butylguanidine bicarbonate (30) according to the following reaction:



In a liter beaker fitted with a mechanical stirrer, the following were added: 100 gms. of butylamine hydrochloride, 7 gms. of butylamine, and 63 gms. of water. The mixture was heated to 100°C., and 283 gms. of 23 percent cyanamide solution was added over 3 hours and 30 minutes. The mixture was heated 15 minutes longer and evaporated to a syrup on a steam bath. The n-butylguanidine hydrochloride was converted to the free base by the addition of 360 mls. of 10 percent sodium hydroxide. Carbon dioxide was bubbled into the solution containing the n-butylguanidine to form the n-butylguanidine bicarbonate with a melting point of 102-105°C., after drying in an oven at 80°C. for 24 hours.

Preparation of p-cyanobenzenesulfonyl cyclohexylguanidine (19,31-34) according to the following reaction:





p-Cyanobenzenesulfonyl cyclohexylguanidine
m.p. 159-159.5°C.

A mixture of 44.42 gms. of cyclohexylguanidine hydrochloride suspended in 200 mls. of acetone was stirred and cooled to 0-10°C. A cold solution of 25 gms. of sodium hydroxide in 55 mls. of water was added until a pH* of 8-9 was obtained. Immediately the addition of a solution of 50.4 gms. of p-cyanobenzenesulfonyl chloride in 188 mls. of acetone was begun dropwise. The mixture was stirred, temperature maintained at 5-10°C., and pH maintained at 8-9. After the addition of p-cyanobenzenesulfonyl chloride was completed, stirring was continued for two hours while the sides of the beaker were washed with 650 mls. of acetone. The precipitate from the reaction was removed by filtration, and the acetonic filtrate was adjusted to pH 6 with acetic acid. The acidified filtrate was evaporated to dryness with an air jet, and the resulting light brown gummy mass was washed with a small amount of cold water to remove the excess acetic acid present. After drying the mass as much as possible by filtration, aqueous ethanol was used to recrystallize the final product. The crystals obtained were slightly soluble in cold ethanol, soluble in hot ethanol, insoluble in cold or hot water, and very slightly soluble in ether. After five recrystallizations, the melting point was 159-159.5°C.

Analysis for $C_{14}H_{18}N_4O_2S$. Calculated: C, 54.88; H, 5.92; N, 18.29. Found: C, 54.73; H, 6.16; N, 17.52.

Preparation of p-cyanobenzenesulfonyl n-butylguanidine (19,31-34) according to the following reaction:

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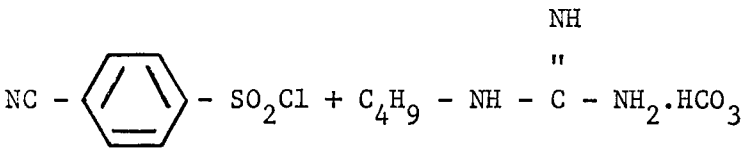
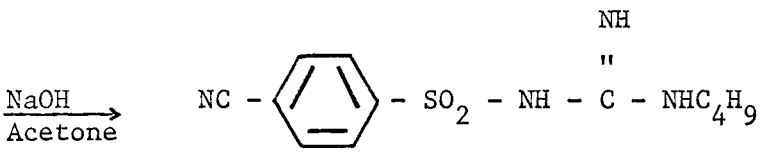
*Hydrion pH papers were employed to determine the pH.



p-Cyanobenzenesulfonyl chloride — n-Butylguanidine bicarbonate



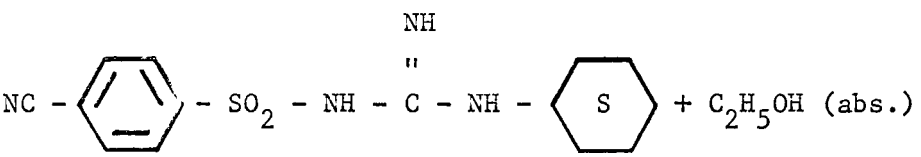
p-Cyanobenzenesulfonyl n-butylguanidine
m.p. 94-95°C.

A mixture of 44.0 gms. of n-butylguanidine bicarbonate suspended in 112 mls. of acetone was stirred and cooled to 0-10°C. The pH of the suspension was above 8, therefore, the addition of a solution of 50.4 gms. of p-cyanobenzenesulfonyl chloride in 188 mls. of acetone was begun dropwise. The mixture was stirred, temperature maintained at 5-10°C., and the pH maintained at 8-9 with a solution of 25 gms. of sodium hydroxide in 55 mls. of water. After the addition of p-cyanobenzenesulfonyl chloride was completed, stirring was continued for two hours while the sides of the beaker were washed with 750 mls. of acetone. The precipitate from the reaction was removed by filtration, and the acetonic filtrate was adjusted to pH 6 with acetic acid. The acidified filtrate was evaporated to dryness with an air jet, and the crystals washed with a small amount of cold water to remove excess acetic acid. After drying the mass as much as possible by filtration, hot water was used to recrystallize the final product. The crude product was slightly soluble in hot water, soluble in cold ethanol, very slightly soluble in cold dioxane, slightly soluble in hot dioxane, very slightly soluble in hot ether, insoluble in cyclohexane, insoluble in cold chloroform, and soluble in hot chloroform.

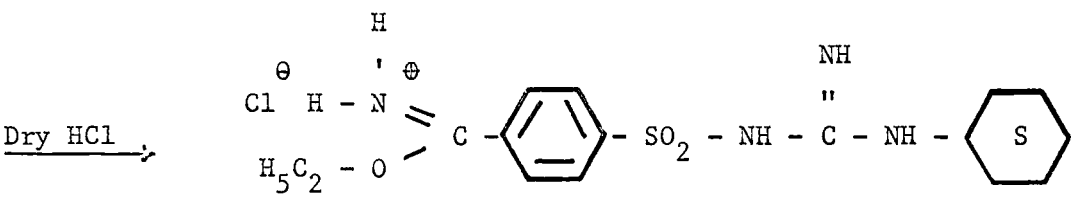
The recrystallized p-cyanobenzenesulfonyl butylguanidine was dried at 40°C. in a vacuum oven for 24 hours.

Analysis for $C_{12}H_{16}N_4O_2S$. Calculated: C, 51.41; H, 5.75; N, 19.98. Found: C, 51.20; H, 5.92; N, 19.48.

Preparation of N' - [(p-carbethoxyimino) benzenesulfonyl] cyclohexylguanidine hydrochloride (19,35,36) according to the following reaction:



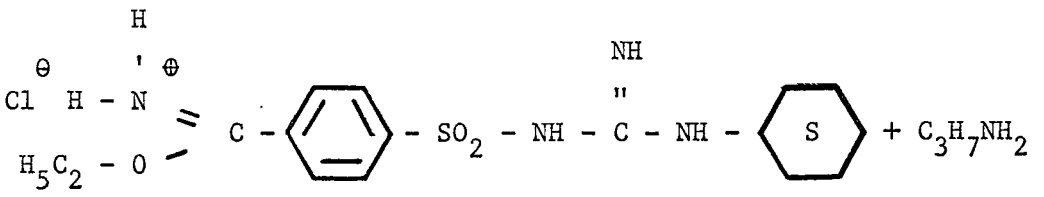
p-Cyanobenzenesulfonyl cyclohexylguanidine
in anhydrous ether



N' -[(p-Carbethoxyimino) benzenesulfonyl]
cyclohexylguanidine hydrochloride

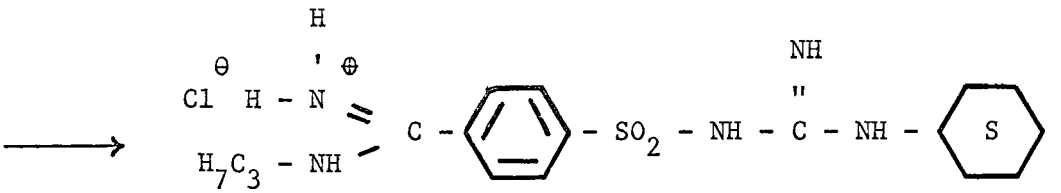
Ten grams of p-cyanobenzenesulfonyl cyclohexylguanidine was suspended in 200 mls. of anhydrous ether and 4 mls. of absolute ethanol. The solution was saturated with anhydrous hydrogen chloride. The reaction mixture was stirred at room temperature for 36 hours, and the final product was then collected. The imino-ester hydrochloride was stored over phosphorus pentoxide until used for the preparation of the amidines.

Preparation of N' - [N-n-propyl (p-carbamidino) benzenesulfonyl] cyclohexylguanidine hydrochloride (19,37,38) according to the following reaction:



N' - [(p-Carbethoxyimino) benzenesulfonyl] cyclohexylguanidine.HCl

n-Propylamine



N' - [N-n-Propyl (p-carbamidino) benzenesulfonyl] cyclohexylguanidine.HCl
m.p. 112-113°C.

Three grams of N' - [(p-carbethoxyimino) benzenesulfonyl] cyclohexylguanidine hydrochloride was added to a solution of absolute ethanol containing 0.8 mls. of n-propylamine. The solution was adjusted to pH 7 with n-propylamine, and the reaction mixture allowed to remain at room temperature for 24 hours. The solvent was then removed by vacuum, and the residue treated with 150 mls. of anhydrous ether. The crystals thus formed were collected and recrystallized from methanol. The product obtained was slightly soluble in hot water, very soluble in hot ethanol, and slightly soluble in hot dioxane.

Analysis of $C_{17}H_{28}ClN_5O_2S$. Calculated: C, 50.80; H, 7.02; N, 17.42. Found: C, 50.88; H, 7.04; N, 17.21.

CHAPTER III

CONCLUSION

Cyclohexylguanidine hydrochloride was condensed directly with an equal molar quantity of p-cyanobenzenesulfonyl chloride to yield p-cyanobenzenesulfonyl cyclohexylguanidine.

The direct condensation of n-butylguanidine bicarbonate with an equal molar quantity of p-cyanobenzenesulfonyl chloride yielded p-cyanobenzenesulfonyl butylguanidine.

The imino-ester hydrochloride was then prepared from p-cyanobenzenesulfonyl cyclohexylguanidine.

The p-N-n-propyl carbamidino was then prepared from the imino-ester hydrochloride referred to above; i.e., N' - [(p-carbethoxyimino) benzenesulfonyl] cyclohexylguanidine hydrochloride.

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