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Structural Isomerism of Sulfanilylmethylaminoguanidine[1]

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Three of the possible nine structural isomers of sulfanilylmethylaminoguanidine have been synthesized. These isomers, 1-sulfanilyl-3-methyl-3-aminoguanidine (I), 1-sulfanilyl-1-methyl-3-aminoguanidine (II) and 1-sulfanilylamido-3-methylguanidine (III) have been shown to be distinct compounds and not tautomers by X-ray analysis, formation of chemical derivatives and by observation of other physical properties. On the basis of their modes of formation, formulas have been assigned to each compound. The reasons for the formation of each isomer have been discussed and logical explanations have been postulated.

Introduction

In a previous paper[3] the existence of structural isomerism of sulfanilyaminoguanidine was demonstrated. Definite structures were assigned to the three possible isomers and it was shown through X-ray analysis and chemical derivatives that these materials were not tautomers of each other.

A similar investigation was undertaken with sulfanilylmethylaminoguanidine where nine structural isomers are possible.[4] The present paper describes the preparation and properties of 1-sulfanilyl-3-methyl-3-aminoguanidine (I), 1-sulfanilyl-1-methyl-3-aminoguanidine (II) and 1-sulfanilylamido-3-methylguanidine (III). A partial synthesis of 1-sulfanilyl-3-methyl-1-aminoguanidine, 1-sulfanilylamido-1-methylguanidine and 1-(N^1-methylsulfanilylamido)-guanidine has been carried out and will be described in a later paper.

TABLE I

PROPERTIES OF THE THREE ISOMERS

Isomer	I	II	III
M.p. (uncor.), °C.	215–216	165–167	143–145 dec.
Density at 20°	1.46	1.36	1.31
Crystal system[a]	Monoclinic	Monoclinic	Orthorhombic
No. molecules/unit cell	4	8	4
Unit cell vol. (Å.)^3	1100	2390	1250
Molecular weight from X-ray data[b]	243	246	246

[a] X-Ray data obtained by Weissenberg moving film technique, see ref. 3. [b] Calcd. mol. wt., 243.

Discussion

Three sulfanilylmethylaminoguanidines have been prepared with the empirical and molecular formula $C_8H_{13}O_2N_5S$. The properties given in Table I demonstrate that these isomers are indeed different compounds and not tautomers of each other.

The conditions given have been selected to produce one distinct isomer. We were unable to isolate more than one isomer under the same conditions. Furthermore, if the conditions used in the Schotten–Baumann reaction were changed too drastically, poor yields were obtained. Mainly, the reduction of yield was caused by undue decomposition of the isothioureas and the isothiosemicarbazides, formation of the sulfonium salts and sometimes disulfanilylguanidine derivatives.

In those instances where more than one amino or imino nitrogen was present it was not possible to predict with certainty where condensation would occur with a sulfonyl chloride. The position of condensation was determined by the ability or failure of the material to form benzylidene derivative and the availability of hydrazine nitrogen as determined by the Jamieson method. The assigned structure of isomer I is supported by the formation of a benzylidene derivative, indicative of a primary hydrazine group. Furthermore, the presence of a $>N-NH_2$ grouping was substantiated by a qualitative Jamieson titration similar to that obtained for 1-sulfanilyl-1-aminoguanidine.[3] It is reasonable to assume that in methylhydrazine the nucleophilic center would be the nitrogen adjacent to the electron-donating methyl group. This assumption is supported by the fact that identical isomers were obtained when methylhydrazine was used in reactions of hydrazination and hydrazinolysis (reaction A-2 and A-3, respectively).

The preparation of isomer II through reaction B-1 is an unequivocal procedure for the establishment of the structure assigned. The formation of a benzylidene derivative indicates an available primary hydrazine grouping and the obtainment of a quantitative Jamieson titration designates that the hydrazine grouping to be $-NH-NH_2$.[3]

When N^4-acetylsulfanilyl chloride was added to a solution of S-methyl-N-methylisothiourea in a cold aqueous acetone solution containing sodium hydroxide, only N^4-acetylsulfanilylmethylcyanamide could be isolated. This unexpected reaction may have been caused by the excessive decomposition of the S-methylisothiourea in strong basic medium. However, when the S-allyl homolog was used with sodium carbonate as the alkaline medium, the expected product was obtained as shown in reaction B-2. The isolation of isomer II from both reactions B-3 and B-4 serves to indicate that the nucleophilic center of the substituted guanidines under these conditions was the nitrogen adjacent to the methyl group.

The assigned structure of isomer III is substantiated by its failure to form a benzylidene derivative, indicating the absence of a primary hydrazine group. A negative Jamieson titration indicates the grouping S–N–N–C to be present similar to that found in sulfanilylamidoguanidine.[3]

In reaction C-1, sulfanilylthiosemicarbazide gave no benzylidene derivative and the subsequent reactions of methylation and aminolysis can only give a

(1) Abstracted from part of the thesis submitted by Albert H. Greer to the Graduate Faculty in partial fulfillment of the Ph.D. degree in Chemistry, 1949.

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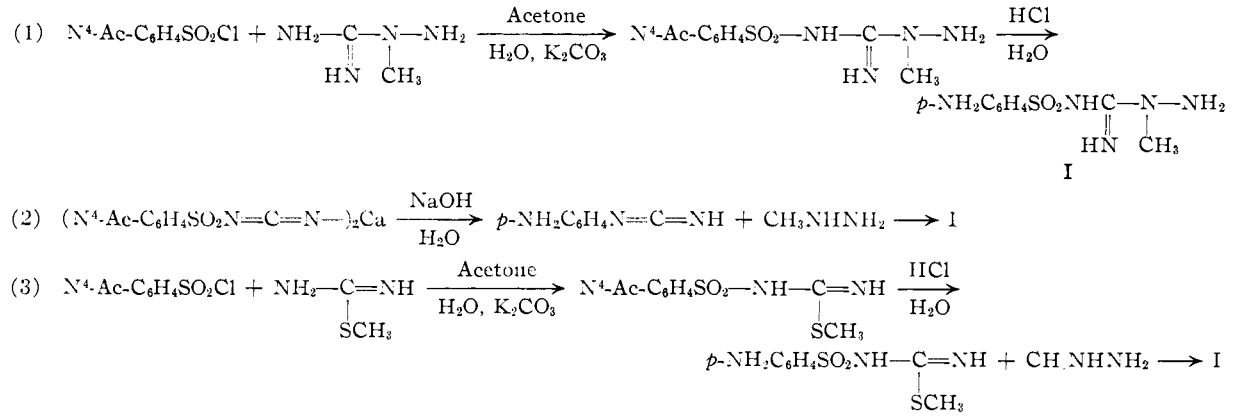
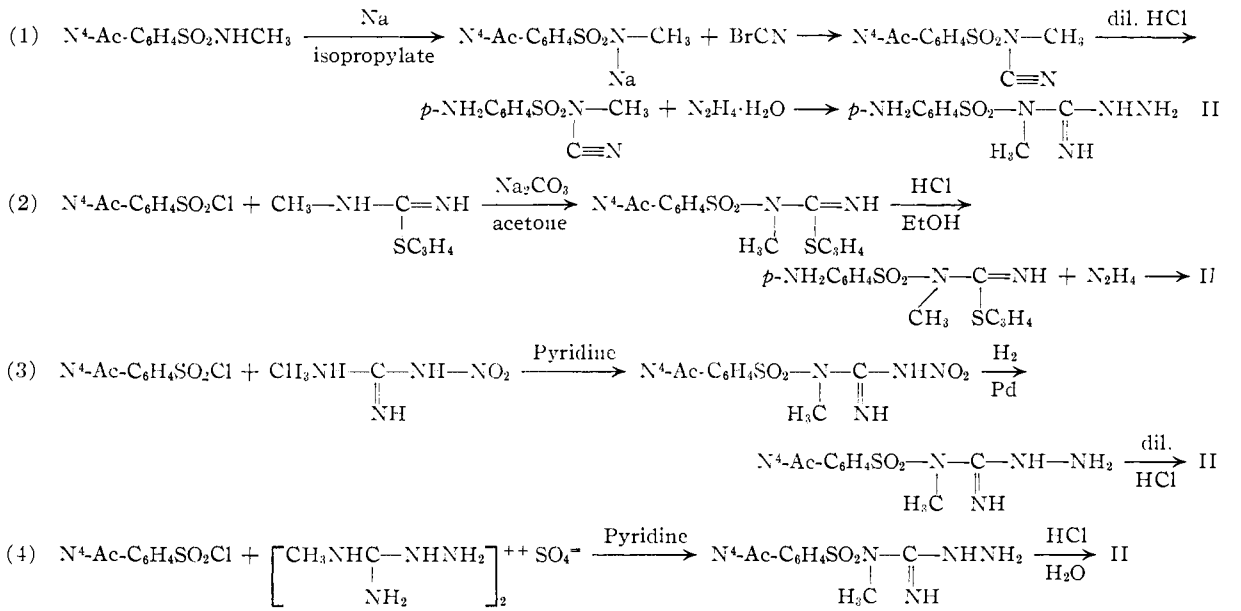
(3) A. H. Greer, J. Kertesz and G. B. L. Smith, THIS JOURNAL, **71**, 3005 (1949).

(4) A. H. Greer and G. B. L. Smith, *ibid.*, **72**, 874 (1950). The synthesis of 1-methylaminoguanidine was described recently by W. G. Finnegan, R. A. Henry and G. B. L. Smith, *ibid.*, **74**, 2981 (1952).

A. 1-Sulfanilyl-3-methyl-3-aminoguanidine (I)



B. 1-Sulfanilyl-1-methyl-3-aminoguanidine (II)



C. 1-Sulfanilamido-3-methylguanidine (III)

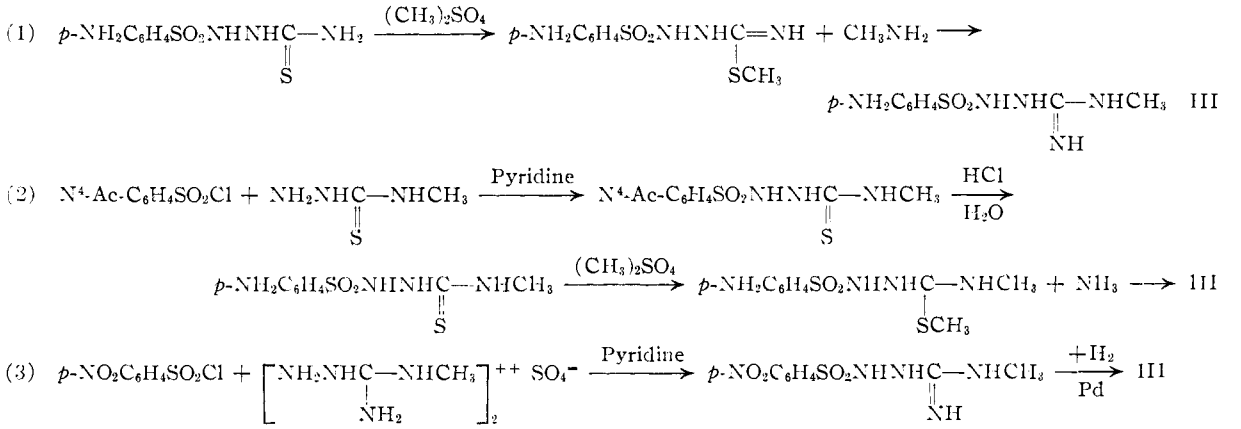


Fig. 1.—Preparation of sulfanilylmethylaminoguanidines.

material with no available primary hydrazine group. The reaction of acetylsulfanilyl chloride and 4-methylthiosemicarbazide (reaction C-2) may give three possible isomers. However, isomer III was the only isolable product after S-methylation and aminolysis. In all probability the acidic nature of the C=S group may reduce the basicity of the amido nitrogens and thus their ability to act as nucleophilic centers.

In all of the previously described reactions, either N^4-acetylsulfanilyl chloride or *p*-nitrobenzenesulfonyl chloride could be used interchangeably as the

TABLE II

INTERMEDIATES OBTAINED BY SIMILAR REACTIONS

Compound	M.p., °C.	Empirical formula	Sulfur, % Calcd.	Found
p-NO_2—C_6H_4—SO_2NH—C(=HN)—N(CH_3)—NH_2[a]	256–260	$C_8H_{11}N_5O_4S$	11.70	11.50
p-NO_2—C_6H_4—SO_2NH—C(=HN)—N(CH_3)—N=CHC_6H_5	198–200	$C_{15}H_{17}N_5O_2S$	9.60	9.30
p-NO_2—C_6H_4—SO_2N(CH_3)—C(=NH)—$NHNO_2$[b]	153–155	$C_8H_9N_5O_6S$	10.50	10.50
p-$NH_2C_6H_4SO_2$—N(CH_3)—C(=NH)—$NHNO_2$[c]	140–142	$C_8H_{11}N_5O_4S$	11.60	11.20
p-$NO_2C_6H_4SO_2N$(CH_3)—C(=NH)—$NHNH_2$[d]	209–210	$C_8H_{11}N_5O_4S$	11.60	11.90
N^4—$AcC_6H_4SO_2NHNHC$(=NH)—SCH_3[e]	173–175 dec.	$C_{10}H_{14}N_4O_3S_2$	21.20	20.90
p-$NH_2C_6H_4SO_2NHNH$—C(=NH)—SCH_3[e]	150–153 dec.	$C_8H_{12}N_4O_2S_2$	24.60	24.80
NH_2NH—C(SCH_3·HI)—NH—CH_3	160–163 dec.	$C_3H_9N_3S$·HI	S, 12.95 I, 51.40	13.02 51.32
N^4—$AcC_6H_4SO_2NHNH$—C(SCH_3·HI)—$NHCH_3$[f]	208–210 dec.	$C_{11}H_{12}N_4O_3S_2$·HI	S, 6.88	6.80

[a] By reaction A-1. [b] By reaction B-3. [c] Obtained by reduction of previous compd. with hydrogen and Raney nickel. [d] By reaction B-4. [e] Obtained by treating acetylsulfanilylthiosemicarbazide with methyl iodide or with the sulfanilyl derivative for the latter compd. [f] Obtained by treating 1-N^4-acetylsulfanilyl-4-methylthiosemicarbazide with methyl iodide.

starting material to produce the same sulfanilylmethylaminoguanidine with the proper materials. When *p*-nitrobenzenesulfonyl chloride was condensed with 1-methyl-3-aminoguanidine sulfate in pyridine the expected condensate was not obtained. After reduction of the nitro group the material was found to be isomer III and not isomer II (reaction C-3). When the methylaminoguanidine iodide salt was used the reaction was similar to reaction B-4. No definite explanation can be given for this abnormal behavior.

In the course of this investigation, it was found that great difficulty was encountered in the successful amination or aminolysis of an intermediate that contained a *p*-nitro group. The order of ease of reactivity was found to be $NH_2 >> NHCOCH_3 > NO_2$. This relationship is coincidental with the decrease in basicity of the substituent group and its subsequent decreasing effect in inductive neutralization of the acidic sulfonyl group.

Experimental

1-Sulfanilyl-3-methyl-3-aminoguanidine (I). Reaction A-1.—A mixture of 15.0 g. (0.11 mole) of 1-methyl-1-aminoguanidine sulfate[4] and 23.3 g. (0.10 mole) of N^4-acetylsulfanilyl chloride was added for 30 minutes to a stirred suspension of 30.0 g. (0.23 mole) of anhydrous potassium carbonate in 100 ml. of acetone and 30 ml. of water. The temperature was kept at 10–15° with an ice-bath. When the addition was complete, the ice-bath was removed and the milky, white suspension was stirred for three additional hours at room temperature. The product was filtered from solution, washed with water and dilute acetic acid. Repeated washings with water were made and the material air-dried. The product was crystallized from a large quantity of hot water to afford 18.0 g. (65%) of fine white crystals, m.p. 249–251°.

Anal. Calcd. for $C_{10}H_{15}N_5O_3S$: S, 11.00. Found: S, 11.25.

Twenty grams (0.07 mole) of the above material was heated with 137 ml. of a 10% hydrochloric acid solution for 30 minutes in a boiling water-bath, then 30 ml. of water and 5 g. of decolorizing charcoal added to the solution and heating continued for ten additional minutes. The solution was filtered while hot, the filtrate chilled in an ice-bath and a 40% solution of potassium hydroxide in water was added to bring the *p*H to 5. A white precipitate formed which was collected on a filter, washed with water and crystallized from hot water to give 10 g. (59%) of I as white needles, m.p. 215–216°.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: S, 13.20. Found: S, 13.10.

Reaction A-2.—Sixty-five grams (0.25 mole) of calcium N^4-acetylsulfanilylcyanamide[5] was heated under reflux for 30 minutes in 300 ml. of a 10% solution of sodium hydroxide in water. Five grams of decolorizing charcoal was added and the mixture was heated for five additional minutes and then filtered. The filtrate was cooled and made slightly acidic with dilute hydrochloric acid to precipitate a heavy white material. This material was redissolved in sodium hydroxide solution and reprecipitated with acid. The product, sulfanilylcyanamide (yield, 65%) was collected on a filter, washed with water and air-dried, m.p. 290–295° dec.

Anal. Calcd. for $C_7H_7N_3O_2S$: S, 16.2. Found: S, 16.0.

To a solution of 19.7 g. (0.10 mole) of sulfanilylcyanamide in 100 ml. of dry isopropyl alcohol was added 10 g. (0.22 mole) of anhydrous methylhydrazine. The solution was heated under reflux for 24 hours, decolorizing charcoal added, the solution filtered and the filtrate evaporated to nearly 20 ml. on a steam-bath. The concentrate was cooled and I precipitated with the addition of cold water. The product was recrystallized from hot water to give 8.0 g. (40.5%), m.p. 215–218°. A mixed melting point determination with a sample of I from reaction A-1 gave no depression.

Reaction A-3.—A solution of 13.8 g. (0.09 mole) of methylhydrazine sulfate in 10 ml. of ice-water was neutralized to congo red paper with a measured volume of a 40% solution of potassium hydroxide and then an equal volume of the potassium hydroxide solution added. The hydrazine solution was added to a suspension of 7.6 g. (0.03 mole) of sul-

(5) E. Leitsch and E. Gnasky, *Can. J. of Research*, 139 (1945).

fanilyl-S-methylisothiourea[6] in 10 ml. of water and the mixture heated under reflux for three hours until no further evolution of methyl mercaptan was detected. The solution was evaporated on a steam-bath to one-half of its original volume and cooled. A white crystalline material separated and was removed by filtration and washed with a large volume of cold water. The material was twice recrystallized from boiling water to yield 4 g. (61%) of I, m.p. 215–216°.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: N, 28.81; S, 13.2. Found: N, 28.79; S, 13.0.

A mixed melting point determination with a sample obtained from reaction A-1 gave no depression.

A benzylidene derivative of I was prepared by dissolving 1.0 g. (0.004 mole) in 100 ml. of water containing two drops of glacial acetic acid and adding 0.4 ml. of benzaldehyde. The mixture was warmed for two minutes at 45° whereupon a white precipitate formed. The material was filtered and crystallized from 30% aqueous ethyl alcohol to yield 1.2 g. of product, m.p. 188–190°.

Anal. Calcd. for $C_{15}H_{17}N_5O_2S$: S, 9.6. Found: S, 9.3.

1-Sulfanilyl-1-methyl-3-aminoguanidine (II). Reaction B-1.—N^4-Acetylsulfanilylmethylamide, m.p. 185–189°,[7] 17.4 g. (0.075 mole), was partially dissolved in 300 ml. of warm anhydrous isopropyl alcohol and there was added at one time, 0.01 mole of sodium isopropylate dissolved in 100 ml. of hot isopropyl alcohol. The remaining undissolved material entered into solution with the formation of the amide sodium salt which precipitated upon cooling. The mixture was refrigerated overnight, filtered and the residue washed with cold ether. The amorphous material weighed 10 g. (55%). Additional material (5.0 g.) was obtained by evaporating the filtrate and washings to a small volume and adding cold ether. The total yield was 80% and the product did not melt below 320°.

Anal. Calcd. for $C_9H_{11}N_2O_2SNa$: S, 12.8. Found: S, 12.5.

In a flask, 8.0 g. (0.075 mole) of freshly prepared cyanogen bromide[8] was dissolved in 175 ml. of dry isopropyl alcohol, and 18.6 g. (0.075 mole) of dry sodium N^4-acetylsulfanilylmethylamide was added with vigorous stirring. The flask was stoppered and shaken for 30 minutes, heat was evolved, the material turned deep pink in color and grew very bulky in volume. The mixture was gently heated on a water-bath for one hour and the solvent evaporated on a steam-bath. The residue was cooled and transferred to a flask, 100 ml. of water added and the flask stoppered and shaken for five minutes. At first, nearly complete solution took place, but then with continued shaking a heavy white precipitate formed. After cooling overnight, the material was collected, washed with a 5% aqueous solution of sodium hydroxide and then with water and air-dried. The crude N^4-acetylsulfanilylmethylcyanamide was recrystallized from 80% ethyl alcohol in water to yield a pure product that weighed 12 g. (63%), m.p. 179–182°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: S, 12.7. Found: S, 12.9.[9]

Four grams (0.016 mole) of the above material was heated for one hour with 50 ml. of a 15% aqueous hydrochloric acid in a boiling water-bath. Decolorizing charcoal was added and the solution was filtered, the filtrate cooled and neutralized with a 10% aqueous solution of sodium hydroxide whereupon a fine white precipitate formed. The product was filtered from solution, washed with water and air-dried to produce 2 g. (60%) of sulfanilylmethylcyanamide, m.p. 119–122°.

Anal. Calcd. for $C_8H_9N_3O_2S$: S, 15.1. Found: S, 14.7.

Four grams (0.02 mole) of sulfanilylmethylcyanamide was heated under reflux for 30 hours with 2.4 ml. (0.04 mole) of 85% hydrazine hydrate solution dissolved in 40 ml. of isopropyl alcohol and containing a few crystals of sodium bisulfite. The initial red color of the solution turned to straw yellow at the end of the reflux period. A mass of white crystals was obtained at the end of the reaction. The material was filtered and the mother liquor was evaporated *in vacuo* to one-half its volume and then 25 ml. of water added to precipitate an additional crop of crystals. The product was crystallized from 50% aqueous ethyl alcohol and then from water to yield 3.0 g. (65%) of II, m.p. 165–168°.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: S, 13.15. Found: S, 12.90.

Identical treatment of N^4-acetylsulfanilylmethylcyanamide with hydrazine hydrate gave a 35% yield of 1-(N^4-acetylsulfanilyl)-1-methyl-3-aminoguanidine, m.p. 195–198°.

Anal. Calcd. for $C_{10}H_{15}N_5O_3S$: S, 11.2. Found: S, 10.9.

The material was deacetylated according to procedures described in this paper to yield II.

Reaction B-2.—Methylthiourea,[10] 16.0 g. (0.18 mole), was treated with 22.0 g. (0.183 mole) of allyl bromide in 30 ml. of ethyl alcohol and the mixture heated under reflux on a water-bath. The solvent was removed under slightly reduced pressure leaving 35 g. of crude S-allyl-N-methylisothiourea bromide in the form of a light yellow sirup. Into 200 ml. of acetone containing 5.3 g. of anhydrous sodium carbonate, 10.6 g. (0.051 mole) of the above bromide salt was dissolved and then 11.7 g. (0.05 mole) of recrystallized N^4-acetylsulfanilyl chloride was added at one time. The mixture was stirred for one hour and then heated under reflux for an additional four hours. The insoluble inorganic material was removed by filtration and the solvent removed *in vacuo*. The residue remained as a non-crystallizable oil. The oil was mixed with 12 ml. of a 4% ethanolic hydrochloric acid solution and heated under reflux for one hour. The solvent was evaporated and the residue dissolved in a small volume of ethyl alcohol. Dilute aqueous ammonia was added until a *p*H of 5 was attained whereupon the bromide salt of 1-sulfanilyl-S-allyl-N-methylisothiourea, m.p. 150–152°, was precipitated and was crystallized from ethyl alcohol.

Anal. Calcd. for $C_{11}H_{15}O_2N_3S_2Br$: S, 17.5. Found: S, 17.3.

The above material, 3.3 g. (0.01 mole), and 1.8 ml. (0.03 mole) of 85% hydrazine hydrate solution was added at the same time to 4 ml. of water. An exothermic reaction set in and two layers appeared. The mixture was allowed to stand for 24 hours and then heated under reflux for one hour. The allyl mercaptan was removed by ether extraction and the aqueous layer was diluted with water to precipitate II. The product was filtered, crystallized from water and air-dried to yield pure II weighing 2 g. (82%), m.p. 166–168°. Mixed melting point determination with a representative sample of II from reaction B-1 gave no depression.[11]

Reaction B-3.—Thirty grams (0.26 mole) of methylnitroguanidine[12] was dissolved in 160 ml. of dry pyridine and cooled to 10° with an ice-bath and then 58 g. (0.25 mole) of recrystallized N^4-acetylsulfanilyl chloride was added with stirring for 30 minutes. When addition was complete, the mixture was heated at 65° for two hours. The mixture was then cooled and an equal volume of water added. The solution was neutralized with concentrated hydrochloric acid and the solvent removed *in vacuo* at 40°. The oily residue was acidified with concd. hydrochloric acid, a 1:1 mixture of isopropyl alcohol–ethyl ether added and the entire mixture refrigerated overnight. The precipitated material was dried in an Abderhalden oven and then recrystallized three times from 90% ethyl alcohol to yield 28 g. (34%) of 1-(N^4-acetylsulfanilyl)-1-methyl-3-nitroguanidine, m.p. 163–165° dec.

Anal. Calcd. for $C_{10}H_{13}N_5O_5S$: S, 10.15. Found: S, 10.33.

(6) E. H. Cox, *J. Org. Chem.*, **7**, 307 (1942).

(7) B. Post, M.S. Thesis, Polytechnic Inst. of Brooklyn, 1949.

(8) H. Hartman and E. Dreger, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

(9) N^4-Acetylsulfanilylmethylcyanamide also was obtained in a 40% yield by direct condensation of methyl cyanamide and N^4-acetylsulfanilyl chloride in dry pyridine.

(10) M. Moore and F. Crossley, *Org. Syntheses*, **21**, 81 (1941).

(11) When S-methyl-N-methylisothiourea sulfate, m.p. 150–152°, was treated with acetylsulfanilyl chloride in a sodium carbonate-acetone mixture no reaction occurred. However, when sodium hydroxide was substituted for sodium carbonate, methyl mercaptan was given off and the isolated material was found to be N^4-acetylsulfanilylmethyl cyanamide. In order to show that this material was identical with the product obtained in reaction B-1 the material was deacetylated with acid to give sulfanilylmethylcyanamide, m.p. 118–120°, which when treated with hydrazine hydrate gave II.

(12) T. L. Davis and A. J. Abrams, *Proc. Am. Acad. Arts and Sci.*, **61**, 437 (1926).

Twenty-one grams of the above product (0.067 mole) was suspended in 100 ml. of water and reduced at 25° with hydrogen in the presence of 0.5 g. of 5% palladium-on-charcoal at 50 p.s.i. for 10 hours when adsorption of hydrogen ceased. The catalyst was removed and the filtrate concentrated *in vacuo* to yield a material which when crystallized from boiling water gave 15 g. (81%) of 1-(N^4-acetylsulfanilyl)-1-methyl-3-aminoguanidine, m.p. 193–195°.

Anal. Calcd. for $C_{10}H_{15}N_5O_3S$: S, 11.20. Found: S, 11.00.

This material, 28 g. (0.1 mole), was heated under reflux for one hour with 100 ml. of 1:1 10% hydrochloric acid solution and ethanol. Decolorizing charcoal was added and the solution filtered. The filtrate was cooled, and the *p*H of the solution was adjusted to 5–6 with 40% aqueous sodium hydroxide. The crude II which had settled out was filtered, washed with cold water and crystallized from hot water to yield pure II weighing 16 g. (66%), m.p. 165–167°. A mixed melting point determination with a representative sample from reaction B-1 gave no depression.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: S, 13.18; N, 28.80; N_2H_4 (hydrazine), 13.18. Found: S, 13.18; N, 28.65; N_2H_4 (hydrazine), 13.10.

One gram of II (0.004 mole) was suspended in 20 ml. of ethyl alcohol and the mixture heated under reflux until complete solution took place. One drop of concentrated hydrochloric acid was added followed by 0.4 ml. of benzaldehyde and the solution heated under reflux for one hour. A yellow precipitate settled out. This material was filtered, washed with alcohol and water to yield 1.2 g. of the benzylidene derivative of II, m.p. 278–280° dec.

Anal. Calcd. for $C_{15}H_{15}N_5O_2S$: S, 9.65. Found: S, 9.75.

Reaction B-4.—1-Methyl-3-aminoguanidine sulfate,[18] 18 g. (0.13 mole), was dissolved in 160 ml. of dry pyridine and cooled to 10°. During 30 minutes, 39 g. (0.17 mole) of N^4-acetylsulfanilyl chloride was added at 10–15°. The mixture was heated on a steam-bath for two hours, cooled, neutralized with dilute hydrochloric acid and the solution evaporated *in vacuo*. The residue was extracted with ethyl alcohol, acidified with hydrochloric acid and refrigerated overnight. A white crystalline material was removed by filtration, and crystallized from ethyl alcohol to give 16 g. (43%) of 1-(N^4-acetylsulfanilyl)-1-methyl-3-aminoguanidine, m.p. 190–192°.

Anal. Calcd. for $C_{10}H_{15}N_5O_3S$: S, 11.20. Found: S, 11.09.

Six grams (0.02 mole) of the above product and 75 ml. of a 5% ethanolic hydrochloric acid solution was heated under reflux for two hours. The solvent was evaporated, hot water added to dissolve the residue and the cooled solution treated with dilute aqueous ammonia to precipitate crude II. Recrystallization from boiling water afforded 4 g. (80%) of pure II, m.p. 165–167°. A mixed melting point determination with a representative sample obtained from reaction B-1 gave no depression.

1-Sulfanilylamido-3-methylguanidine (III). Reaction C-1.—Eleven grams (0.044 mole) of sulfanilylthiosemicarbazide was suspended in 20 ml. of water and 3.0 ml. of dimethyl sulfate. The mixture was heated under reflux for two hours, neutralized with 40% aqueous sodium hydroxide and 7.5 ml. (0.06 mole) of a 25% aqueous solution of methylamine added. The deep red colored solution was heated under reflux until no further methyl mercaptan was evolved. The solution was evaporated on a steam-bath and the residual oil mixed with 50 ml. of a 1:1 mixture of ethyl alcohol and ethyl ether and refrigerated overnight. A crude dark brown material was isolated and recrystallized several times from a minimum amount of hot water to yield 3 g. (28%) of III, m.p. 143–144° dec.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: S, 13.15; N, 28.80. Found: S, 13.15; N, 28.72.

Reaction C-2.—In the preparation of 1-(N^4-acetylsulfanilyl)-4-methylthiosemicarbazide, Roth and Degering[14] used N^4-acetylsulfanilyl hydrazide and methyl isothiocyanate with no reported yield. The following procedure is a direct one-step preparation of this compound.

Twenty grams (0.19 mole) of 4-methylthiosemicarbazide[15] was suspended in 146 ml. of dry pyridine and the mixture cooled to 10° with an ice-bath. During 30 minutes, 49 g. (0.21 mole) of N^4-acetylsulfanilyl chloride was added at 10–15°. The solution was then heated to 60–65° for one hour on a steam-bath, cooled and poured into a liter of 10% aqueous hydrochloric acid. The precipitate that formed was filtered, washed with water and dissolved in cold dilute sodium hydroxide solution. Decolorizing charcoal was added and the mixture stirred in the cold for 30 minutes and then filtered. The filtrate was neutralized with cold dilute aqueous hydrochloric acid and the precipitate that formed was collected on a filter, washed with water and air-dried to yield 45 g. (79%) of 1-(N^4-acetylsulfanilyl)-4-methylthiosemicarbazide, m.p. 225–227° dec. No benzylidene derivative could be formed.

Twenty-two grams (0.073 mole) of the above product and 210 ml. of a 15% aqueous hydrochloric acid solution were heated on a boiling water-bath for one hour. Five grams of decolorizing charcoal and 20 ml. of water were added and the heating continued for an additional ten minutes. The mixture was filtered and the filtrate chilled. When the *p*H of the solution was adjusted to 6 with 40% aqueous sodium hydroxide solution, 1-sulfanilyl-4-methylthiosemicarbazide settled out. The material was filtered, washed with water and air-dried to yield 15 g. (79%) with a melting point of 242–245° dec.

Anal. Calcd. for $C_8H_{12}N_4O_2S_2$: S, 24.60. Found: S, 24.83.

In an all-glass apparatus fitted with a reflux condenser were placed 16.5 g. (0.064 mole) of the above material, 30 ml. of water and 32 ml. of dimethyl sulfate. The mixture was heated under reflux for two hours when complete solution took place. The solution was cooled and neutralized with a 40% aqueous sodium hydroxide solution. The solution was transferred to a 100-ml. two-necked ground-glass flask fitted with a condenser and a capillary tube. Concentrated ammonia solution, 5.4 ml. (0.08 mole), was added and the solution boiled under reflux for two hours under slightly reduced pressure. An additional 2 ml. of concentrated ammonia solution was added after the first hour. The solution was concentrated *in vacuo* on a steam-bath to a thick oil, 10 ml. of water added and the mixture warmed until incipient crystallization. Eight grams (55%) of III was obtained; m.p. 142–143° dec. A mixed melting point determination with a representative sample obtained from reaction C-1 gave no depression.

Reaction C-3.—Fourteen grams (0.15 mole) of 1-methyl-3-aminoguanidine sulfate was dissolved in 125 ml. of dry pyridine, cooled to 10° and 29 g. (0.13 mole) of *p*-nitrobenzenesulfonyl chloride added for 30 minutes with stirring at 10–15°. The mixture was heated for two hours on a steam-bath and the solution evaporated *in vacuo* to a residual oil. Approximately 250 ml. of water was added, and a yellow material settled out which was filtered, washed with dilute hydrochloric acid solution followed with several washings with water and air-dried. The material was recrystallized from boiling water, decolorized with charcoal to yield 15 g. (55%) of pale yellow crystals of 1-(*p*-nitrobenzenesulfonylamido)-3-methylguanidine, m.p. 155–158°.

Anal. Calcd. for $C_8H_{11}N_5O_4S$: S, 11.70. Found: S, 11.43.

The above product, 10 g. (0.037 mole), was dissolved in 100 ml. of ethyl alcohol and reduced with hydrogen in the presence of 0.5 g. of 5% palladium-on-charcoal at room temperature at 50 p.s.i. After 90 minutes no further adsorption of hydrogen took place. The mixture was filtered and the solvent evaporated *in vacuo* at 30°. The solid residue was recrystallized from hot water and yielded upon cooling 5 g. (56%) of III, m.p. 143–144° dec. A mixed melting point determination with samples obtained from the previous two methods gave no depression. No benzylidene derivative could be obtained.

Anal. Calcd. for $C_8H_{13}N_5O_2S$: S, 13.15; N, 28.80. Found: S, 13.42; N, 28.87.

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