96. *Synthesis of Sulphanilylguanidine.*

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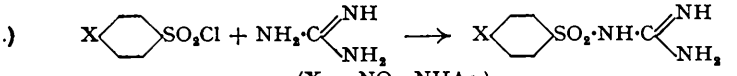
The synthesis of sulphanilylguanidine by four different reactions is described: (*a*) From *p*-acetamidobenzenesulphonamide and dicyandiamide; (*b*) from *p*-acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea by amidation, and hydrolysis at the acetamido group of the reaction product; (*c*) from sulphanilamide and *S*-methyl*iso*thiourea, or other related *iso*thioureas; (*d*) from sulphanilamide and guanidine.

p-Aminobenzenesulphonylguanidine (sulphanilylguanidine, sulphaguanidine) has attained importance as a chemotherapeutic agent, useful for treatment of certain pathogenic intestinal infections (Marshall *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163; 1941, **68**, 94; *Brit. Med. J.*, 1941, **497**, 514; *J. Amer. Med. Assoc.*, 1941, **117**, 326; Frisk, *Acta med. scand.*, 1941, **109**, 355). It was also required by us for the manufacture of the sulphanilamide derivative of 2-amino-4 : 6-dimethylpyrimidine (Rose and Swain, *J.*, in press). Its synthesis

has in consequence been extensively investigated in these laboratories during 1941—1942. Earlier publication has not been possible owing to war circumstances. Several routes have been examined in detail and we record here the main conclusions drawn from our researches.

Sulphanilylguanidine was first prepared in 1938 by Buttle and co-workers (*Biochem. J.*, 1938, **32**, 1101) by the interaction of dicyandiamide and sulphanilamide, but was mistakenly given the constitution 4-guanidinobenzenesulphonamide. Its true structure was revealed after the same substance had been prepared by Roblin *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2002) by the action of *p*-nitrobenzenesulphonyl chloride (I, X = NO_2) on guanidine, followed by reduction, and later analogously by Marshall *et al.* (*loc. cit.*) from *p*-acetamidobenzenesulphonyl chloride (I, X = NHAc) followed by hydrolysis at the acetamido group :

(A)

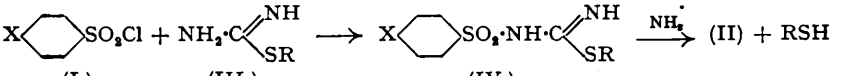


(I.) (II.)

(X = NO_2, NHAc.)

In addition to an examination of the above methods of synthesis, others, derived from existing reactions employed for guanidines in general, have been investigated as follows :

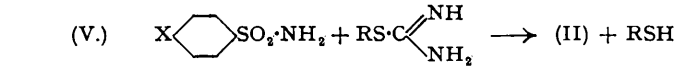
(B) Formation of a suitable benzenesulphonyl*iso*thiourea and conversion into the corresponding guanidine by ammonia with elimination of a thiol :



(I.) (III.) (IV.)

(X = NO_2, NHAc; R = Me, Et, Ph·CH_2.)

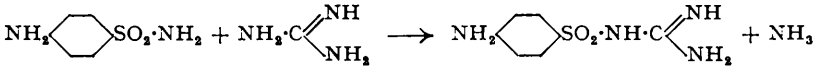
(C) Interaction of a suitably *p*-substituted benzenesulphonamide and an *iso*thiourea with elimination of a thiol :



(V.) (II.)

(X = NO_2, NH_2, NHAc; R = Me, Et, CH:CH·CH_2, HO[CH_2]$_2$, HO[CH_2]$_3$, [CH_2]$_2$·O·[CH_2]$_2$, C_6H_{11}, Ph·CH_2.)

(D) Interaction of sulphanilamide and guanidine with elimination of ammonia :



(British Spec. No. 571,780, describing a similar method of preparation, appeared whilst this paper was in preparation for press.)

Reaction (A) was repeated with both *p*-acetamido- and *p*-nitro-benzenesulphonyl chloride; the former was found to give the higher yield (55%) at the condensation stage, which was carried out in aqueous acetone, or *iso*propyl alcohol in the presence of sodium hydroxide. Hydrolysis of the acetamido group with dilute hydrochloric acid effected conversion into sulphanilylguanidine in 80—90% yield.

Reaction (B) : The highest yields of (IV, X = NHAc, R = Me) (77%) were obtained in the first stage of the interaction with (I, X = NHAc) and (III, R = Me). Although the amidation took place in the absence of a solvent at high temperatures, a much more satisfactory conversion into the guanidine (II, X = NHAc) occurred at 110° by passing ammonia into a phenol solution of the *iso*thiourea (IV). Other substituents (R = Et, Ph·CH_2; X = NHAc) gave lower yields.

Reaction (C) : Although it is well known that alkyl guanidines can be made by treating a primary or secondary alkylamine with *S*-methyl*iso*thiourea sulphate with elimination of methylthiol, a similar reaction with a sulphonamido group, especially in the presence of a primary amino group in the same molecule, was not to be expected. However, we have found that such a reaction does take place under carefully controlled conditions. Thus when several *iso*thiourea salts were caused to react with the sodium salt of the sulphonamides (V), or with the free sulphonamides in the presence of an equivalent of alkali, the corresponding guanidines were formed and a thiol eliminated. *S*-Methyl*iso*thiourea sulphate was found to be the most suitable of the *iso*thiourea salts examined.

Reaction conditions have been most extensively examined where the reactants were sulphanilamide and *S*-methyl*iso*thiourea sulphate. Phenol was selected as solvent since it dissolves the sodio-sulphanilamide readily.

Optimum reaction temperature was 150—180°; below this range the yield fell rapidly. The sodio-sulphanilamide was either preformed or made *in situ* in phenol by adding sodium hydroxide or sodium carbonate. Various inorganic and organic bases were also used in the reaction. The order and method of mixing the reactants had a marked influence upon the yield. Continuous and smooth addition of the methyl*iso*thiourea sulphate during 3 hours to a solution of sodio-sulphanilamide in phenol at 160° gave the best yields. Rapid addition gave a diminished yield (5—7%), and addition over a period greater than 3 hours also decreased the yield. The actual course of the reaction has not been determined, but it is suggested that the free *iso*thiourea was first formed. This may then have reacted in one of two ways :

(1) Directly with the sulphonamide group as in C above.

(2) Through initial decomposition to cyanamide which then reacts with the sulphonamide group. A similar mechanism has been discussed for the synthesis of alkylated guanidines from alkylated *iso*thioureas and dialkylamines (cf. Schotte, Priewe, and Roescheisen, *Z. physiol. Chem.*, **1928**, **174**, 119; Lecher, *ibid.*, 1928, **176**, 43). In this event the cyanamide would undoubtedly also tend to polymerise, and it may be significant that minimal concentrations of *iso*thiourea and maximal concentrations of sulphanilamide have been shown to influence the reaction in favour of sulphanilylguanidine formation. Against this it was observed that cyanamide itself, when fused with sulphanilamide, gave only a 14% yield of sulphanilylguanidine, whilst other substances capable of liberating cyanamide on heating gave even lower yields.

Reaction (D) : Decomposition of the guanidine salt of sulphanilamide afforded the most facile method for the preparation of sulphanilylguanidine. α-Methyl- and αα-dimethyl-guanidine by a similar reaction yielded mainly sulphanilylguanidine, but α-phenylguanidine gave sulphanilylguanidine only as a by-product, with β-sulphanilyl-α-phenylguanidine as the main product.

Experimental.

(All melting points uncorrected.)

Reaction between p-*Acetamidobenzenesulphonamide and Dicyandiamide.*—*p*-Acetamidobenzenesulphonamide (53·5 g., 0·8 mol.) and dicyandiamide (26·3 g., 1 mol.) were intimately mixed by grinding and the mixture stirred and heated to 200° in an oil-bath until a vigorous reaction set in (15 minutes). When the initial reaction had subsided heating was continued for 1 hour. The product was cooled to 70° and digested with a solution of sodium hydroxide (11·5 g. in 20 c.c. of water), cooled rapidly to below 15° by addition of ice, and allowed to stand for 3 hours. The crude *p*-acetamidobenzenesulphonylguanidine was filtered, resuspended in cold water (100 c.c.), and again filtered and washed with cold water. Yield 22·0 g., m. p. 240°. Recrystallisation from hot water with charcoal treatment gave colourless crystalline *p*-acetamidobenzenesulphonylguanidine (19·8 g.; 36%), m. p. 254—255° (Marshall *et al.*, *loc. cit.*, give m. p. 264·5—267·5°, softens at 261°). A repetition of the method of Buttle *et al.* (*loc. cit.*) employing sulphanilamide and dicyandiamide gave a 5—10% yield of sulphanilylguanidine, m. p. 183—185° (Roblin *et al.*, *loc. cit.*, give m. p. 189—190°).

Reaction B. p-*Acetamidobenzenesulphonyl*-S-*methyliso*thiourea (IV, X = NHAc, R = Me).—The method of preparation described by Cox (*J. Org. Chem.*, 1942, **7**, 307) was employed with slight modifications. *p*-Acetamidobenzenesulphonyl chloride (Marshall *et al.*, *loc. cit.*) prepared immediately before use by interaction of acetanilide with chlorosulphonic acid and used as a wet paste (2800 g. of 46·7% ≡ 1308 g. of 100%) was added to a mixture of ice (2500 g.), and acetone (2500 c.c.) and stirred to a thin cream. *S*-Methyl*iso*thiourea sulphate (780 g.) was added and the mixture stirred for 10 minutes. Sodium hydroxide solution (456 g. in 4 l. of water) at 0° was added during 1½ hours with rapid stirring. The temperature rose to 6—7° and was maintained at this by addition of ice. The reaction mixture was stirred for 1½ hours and filtered, and the solid was washed with water and dried in a vacuum at 60—80° (yield : 1370 g.; 85%). It had m. p. 225—226°, and was sufficiently pure for the next stage. Cox (*loc. cit.*) gives m. p. 230—232°.

Conversion into p-*Acetamidobenzenesulphonylguanidine* (II, X = NHAc).—(a) *In phenol.* The above product (1350 g.) was added to a stirred melt of phenol (2400 g.) heated in an oil-bath maintained at 110°. Ammonia gas was passed into the mixture with continuous stirring for 12 hours. The suspension slowly formed a solution which later deposited a crystalline solid. The effluent gases finally gave no coloration (or only a faint yellow) with lead acetate paper. The reaction mixture was cooled to 100° and poured into a well-stirred solution of sodium hydroxide (1040 g. in 2 l. of water) mixed with ice (6000 g.). After stirring for ½ hour the solid was filtered off, washed with cold water (20 l.) until the filtrate was no longer alkaline, and dried. Yield 810 g. (67%), m. p. 248—251°. The product was used in the next stage without further purification. From *p*-nitrobenzenesulphonyl-*S*-methyl*iso*thiourea or the corresponding ethyl derivative no guanidine reaction product was obtained even though the reaction temperature was varied. *p*-Acetamidobenzenesulphonyl-*S*-ethyl*iso*thiourea under similar conditions yielded only 15—18% of the corresponding guanidine at reaction temperatures of 140—170°. At 110° unchanged *iso*thiourea only was isolated.

(b) *In absence of a solvent.* *p*-Acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea (10 g.) was heated to 245—250° (oil bath temperature) and dry ammonia passed into the molten mass for 30 minutes, by which time frothing had ceased and the effluent gases gave no discoloration with wet lead acetate paper. The fused mass was heated with water (50 c.c.) until granular, cooled, made alkaline by addition of concentrated sodium hydroxide solution, and the insoluble solid filtered off. Acetylsulphanilylguanidine (4·8 g., 54%), m. p. 245—250°, was obtained. Acidification of the alkaline filtrate yielded *p*-acetamidobenzenesulphonamide (2·5 g.) identified by mixed m. p. with an authentic specimen. Amidation of *p*-acetamidobenzenesulphonyl-*S*-benzyl*iso*thiourea under similar conditions at 180—200° gave a 40% yield of acetylsulphanilylguanidine.

Hydrolysis to sulphanilylguanidine. The *p*-acetamidobenzenesulphonylguanidine obtained from the above reaction (a) was added to hydrochloric acid (3040 c.c., 1·28N) and stirred at 94—95°. After 30 minutes all the solid had dissolved; decolorising charcoal was then added, and the solution stirred at 90—94° for 10 minutes and filtered. The clear filtrate at 75° was poured into a well stirred solution of sodium hydroxide (258 g. in 2 l. of water) mixed with ice (4500 g.). After stirring for ½ hour the sulphanilylguanidine was filtered off, washed with water (*ca.* 5 l.), and dried at 60°. Yield 620 g. (91·3%), m. p. 188—189° (decomp.) (Roblin *et al.*, *loc. cit.*, give m. p. 189—190°).

Reaction C. Reaction between Sulphanilamide (*Sodium Salt*) *and* S-*Methyliso*thiourea *Sulphate in Phenol.*—Sodium hydroxide (80 g. flake) was added with stirring to phenol (500 g.) heated at 60—80° in an oil-bath. When the reaction was complete (*ca.* 10 minutes) the mixture was heated to 150—160° and sulphanilamide (344 g.) added. Methyl*iso*thiourea sulphate (278 g.) was then added continuously during 3 hours with the temperature maintained at 160°. The hot reaction mixture was poured into water (2 l.) and heated to 45°. Concentrated hydrochloric acid (295 g.) was added, the mixture stirred until solution was complete, and xylene (200 g.) run in with vigorous agitation. The upper xylene–phenol layer was separated after standing and the lower aqueous layer treated at 45—50° with charcoal (10 g.) and filtered. The filtrate at 40° was made alkaline by addition of sodium hydroxide solution (approx. 170 g. in 400 c.c. of water). The resulting suspension was cooled to 25° and the solid filtered off. The filter cake was washed thoroughly with water, suspended in water (2·5 l.) at 90°, and cooled to 25°, and the crude sulphanilylguanidine was filtered off, washed, and dried. Yield 216 g. (50%), m. p. 182—185°. One crystallisation from water (2·5 l.) raised the m. p. to 189—190°. Sulphanilamide (35 g.) was recovered from the aqueous extract of the crude reaction mixture.

Similar reaction conditions employing *p*-acetamidobenzenesulphonamide gave a somewhat higher yield of the acetyl derivative of sulphanilylguanidine (55—60%), but from *p*-nitrobenzenesulphonamide a greatly reduced yield (2—10%) of guanidine derivative resulted. Likewise replacement of methyl*iso*thiourea sulphate by other *iso*thiourea salts caused

considerable and varying falls in yield, *viz.*, ethyl*iso*thiourea sulphate (10%), allyl*iso*thiourea hydrochloride (9—10%), β-hydroxyethyl*iso*thiourea hydrochloride (1—2%), γ-hydroxypropyl*iso*thiourea hydrochloride (2—3%), *cyclo*hexyl-*iso*thiourea hydrobromide (40—50%), benzyl*iso*thiourea hydrochloride (30%), bis-(β-*S*-*iso*thiocarbamidoethyl) ether dihydrochloride (10—12%). Cyanamide in place of the *iso*thiourea gave a 14% yield of sulphanilylguanidine, whilst nitrosoguanidine, thiourea with lead oxide, and *O*-methyl- or *O*-ethyl-urea gave yields varying from 4 to 10%. Calcium cyanamide, urea, thiourea, or ammonium thiocyanate gave products from which no sulphanilylguanidine could be isolated.

The reaction was also carried out in dichlorobenzene, and in ethylene glycol, in place of phenol, using sulphanilamide in the presence of sodium carbonate. Ammonium carbonate, sodium acetate, zinc hydroxide, or aluminium hydroxide used in place of sodium carbonate gave much reduced yields, whilst with pyridine, piperidine, quinoline, triethanolamine, or 2-aminopyridine little or no sulphanilylguanidine was obtained, although with *p*-nitrobenzenesulphonamide as reactant the last two bases gave *ca.* 10% of *p*-nitrobenzenesulphonylguanidine.

Reaction D. Reaction between Sulphanilamide and Guanidine.—Sodium hydroxide (64 g.) was dissolved in hot methyl alcohol (370 c.c.). Guanidine nitrate (196 g.) was added, and the mixture stirred for 15 minutes at 50—65°, and then cooled to 20°. The separated sodium nitrate was filtered off and washed with methyl alcohol (2 lots of 50 c.c.). The combined filtrates were stirred at 50—55° and sulphanilamide (276 g.) added. Methyl alcohol (375 c.c.) was removed by distillation from an oil-bath and *cyclo*hexanol (48 g.) then added. The oil-bath temperature was raised to 180—190° and distillation continued. Reaction commenced with evolution of ammonia when the internal temperature reached 145°. The internal temperature was then kept at 150—160° for 2 hours. The reaction mixture was poured into hydrochloric acid (1·8 l., 1·5N.), the sulphanilylguanidine precipitated by the gradual addition of sodium hydroxide solution, and the suspension cooled and filtered. The crude solid was recrystallised from water (1600 c.c.) to give sulphanilylguanidine (216 g., 63%), m. p. 188—190°.

A similar yield was obtained with guanidine carbonate in place of the guanidine solution prepared from sodium methoxide and guanidine nitrate. α-Methylguanidine and αα-dimethylguanidine (Clarke and Phillips, *J. Amer. Chem. Soc.*, 1923, **45**, 1755) in similar reactions yielded crude sulphanilylguanidine in 50% and 38% yields respectively.

Reaction between Sulphanilamide and Phenylguanidine Carbonate.—A mixture of sulphanilamide (175 g.), phenylguanidine carbonate (166 g.) (Smith, *J. Amer. Chem. Soc.*, 1927, **51**, 476) and *cyclo*hexanol (50 c.c.) was heated slowly to 160°, and maintained at 160° for 3 hours. The mixture was poured into dilute hydrochloric acid (1150 c.c. 1·75N), and filtered from insoluble matter. The filtrate was made alkaline with sodium hydroxide solution and the precipitate filtered off and digested with water (1 l.) at 90°. The undissolved solid (A) (96 g., m. p. 195—200°) was filtered off. The filtrate on cooling deposited crystalline solid (55 g., m. p. 172—177°) which after several crystallisations from water gave pure sulphanilylguanidine, m. p. 189—190°, undepressed in admixture with an authentic specimen.

(A) Repeated recrystallisation from ethanol gave β-sulphanilyl-α-phenylguanidine, m. p. 208—209° (Found: C, 53·95; H, 4·55; N, 19·2; *M*, by nitrite titre, 289. $C_{13}H_{14}O_2N_4S$ requires C, 53·6; H, 4·8; N, 19·35%; *M*, 290). No depression in m. p. was observed in admixture with a specimen prepared either by interaction of sulphanilamide and *N*-phenyl-*S*-methyl*iso*thiourea sulphate (cf. method C) or by the method of Winnek *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1683), who, however, give the m. p. as 230—231°. It is significant that this m. p. is identical with that of the acetyl derivative of β-sulphanilyl-α-phenylguanidine prepared by any of the above methods. Also, the maximum blood concentration following oral administration of 5 mg./20 g. mouse was found to be 17·1 mg.-% for our specimens of β-sulphanilyl-α-phenylguanidine, whereas Winnek *et al.* found only 1·6 mg.-% in mice after administration of twice the above dose. (We are indebted to Dr. Spinks for the blood level determinations.)

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