926,038

PATENT SPECIFICATION

NO DRAWINGS

926,038

Date of Application and filing Complete Specification: Aug. 21, 1959.
No. 28757/59.
Application made in United States of America (No. 782,681) on Dec. 24, 1958.
Application made in United States of America (No. 804,576) on April 7, 1959.
Complete Specification Published: May 15, 1963.

804,567

Index at acceptance:—Class 2(3), C1J1A(1:3:4:5:6:9), C1J1C(2:3), C1Q(5:6B1:6C:7A:8A:8C), C1Q9(A:B:C:D1:D2:H:J), C1Q11(G:J), C2D43(C:F:S4).

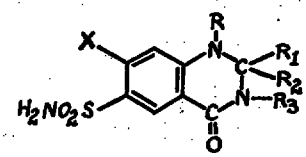
International Classification:—C07d.

COMPLETE SPECIFICATION

Sulphamoyl Quinazolinones

We, AMERICAN CYANAMID COMPANY, a corporation organized under the laws of the State of Maine, United States of America, of 30 Rockefeller Plaza, New York, New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:



...I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups, or R_1 and R_2 taken together are an oxygen atom, and X is halogen or an alkyl group or a trihalomethyl group.

The 1,2,3,4-tetrahydroquinazolinones of the present invention having a 7-halo or a 7-trihalomethyl and a 6-sulfamyl group are diuretics and have the advantage that they operate predominantly as chloruretic agents rather than as bicarbonate excretors. Because metabolic acidosis does not develop under these conditions, a much longer diuresis can be maintained. At the same time, the quinazolinones have low toxicity and do not have the highly undesirable properties of mercurial diuretics which were the classical chloruretic agents of the past.

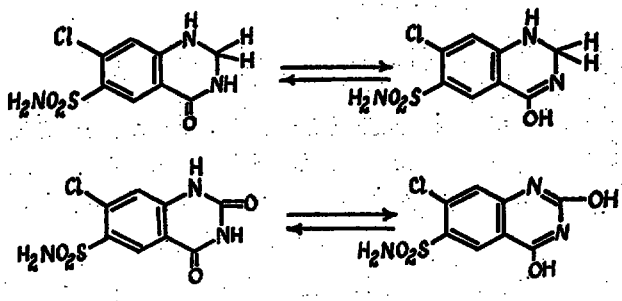
The 1,2,3,4-tetrahydroquinazolinones of the present invention having a 7-halo or a 7-trihalomethyl and a 6-sulfamyl group are particularly important and active as diuretics, and these reduced quinazolinones are of special advantage in causing only a mild kaluresis as a consequence of their use.

The quinazolinone compounds of the present invention having a 7-halo or a 7-trihalomethyl and a 6-sulfamyl group have the advantage that they excrete sodium and chloride ions rather than bicarbonate ions and therefore do not suffer the disadvantage of producing acidosis in patients taking these drugs.

Some of the intermediates of the present invention utilized in preparing the 7-halo (or 7-trihalomethyl) 6-sulfamyl quinazolinones also have diuretic activity.

Where the 1,2,3,4-tetrahydroquinazolinones of this invention have unlike substituents on the carbon atom in position 2 of the ring the compound is produced as the DL- racemate. These racemic mixtures may be resolved into their D and L isomers by well known methods, using optically active salts. It is to be expected that the D and L isomers thus isolated may have different orders of activities or different types of activity. The preferred compounds are the DL-racemic mixtures. The expense of separation makes the isolation of a particular D or L isomer undesirable.

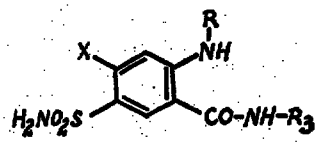
It should be noted that the 1,2,3,4-tetrahydroquinazolinones are capable of existing in tautomeric form. They are shown for typical members by the following equilibrium reactions:



For simplicity, in the examples and claims, the compounds have been set forth in their keto instead of their enol form.

In accordance with this invention there is provided a process for preparing 1,2,3,4-tetrahydroquinazolinones of the general formula I above which comprises:

(a) reacting an anthranilamide derivative of the general formula:



in an acidic medium with a carbonyl compound of the general formula:

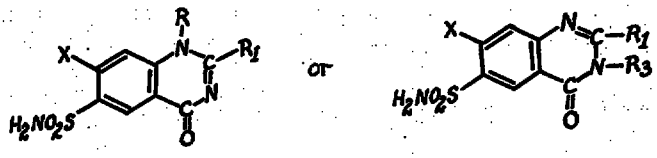
$$R_1—CO—R_2,$$

or with the corresponding acetal or ketal,

(b) and, if desired, alkylating in a manner known per se the resulting compounds in which R and/or R_3 are hydrogen.

Also, in accordance with this invention there is provided a process for preparing 1,2,3,4-tetrahydroquinazolinones of the general formula I above which comprises:

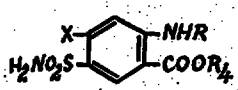
(a) hydrogenating a 6-sulfamyl-4-oxo-dihydroquinazolinone derivative of the general formula:



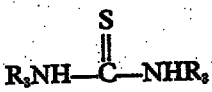
by means of an alkali metal boron hydride, if desired in the presence of aluminum chloride, and

(b) and, if desired, alkylating in a manner known per se the resulting compounds in which R and/or R_3 are hydrogen.

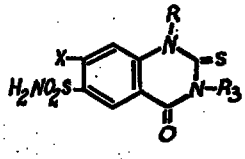
There is also provided in accordance with this invention a process for preparing 1,2,3,4-tetrahydroquinazolinones of the general formula I above which comprises condensing an anthranilic acid derivative of the following general formula:



with a thiourea of the following general formula:



to form a 2-thia-substituted quinazolinone of the following general formula:



which is then oxidized to the corresponding 2-oxo-1,2,3,4-tetrahydroquinazolinone, wherein R, R_3 and X are as hereinabove defined, and R_4 is hydrogen or is a hydrocarbon group, preferably a lower alkyl group containing up to 6 carbon atoms.

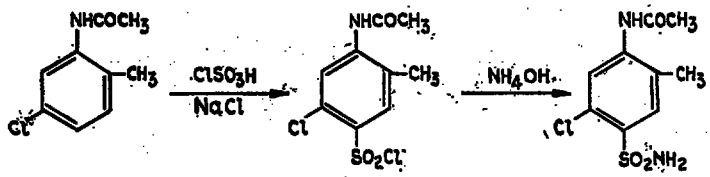
In Examples A to J there are indicated typical procedures for the preparation of some of the intermediates used in the process of this invention.

The ultra violet data in mμ units recorded in the Examples below are for solutions of the particular compound in 1/10N sodium hydroxide solutions.

In the following Examples where parts are indicated this is intended to mean parts by weight unless otherwise designated.

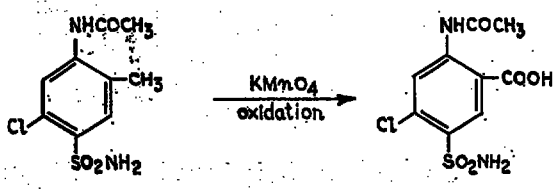
Preparation of Intermediates.

EXAMPLE A.
Preparation of 5-Chloro-4-Sulfamyl-N-Acetyltoluidine.



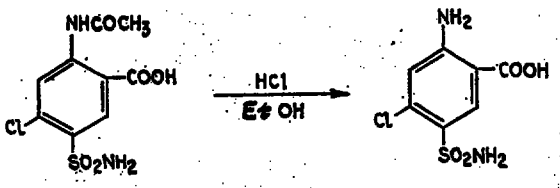
Seventeen parts of sodium chloride are gradually added to 100 parts of ice-cold chlorosulfonic acid. The reaction starts with the emission of HCl. Thereupon, 58 parts of N-acetyl-5-chlorotoluidine are gradually added to the chilled mixture. After the addition is complete, the reaction mixture is heated to from 90—100° C. until completion. The evolution of HCl continues during a good portion of this time. The mixture is then cooled and poured slowly onto 500 parts of ice with good agitation. A crude product is obtained which is filtered off and washed twice with 50 parts of ice water. To the damp cake resulting, 500 parts of an aqueous ammonia solution is added with stirring, the temperature being raised to from 90—100° C. After the reaction is complete, the mixture is cooled to room temperature and allowed to stand until precipitation is complete. The precipitate is then filtered off and the cake treated with 250 parts of 1N NaOH followed by filtration and decolorization of the filtrate with activated carbon. The filtrate is then acidified with concentrated hydrochloric acid and the sulfonamide compound precipitates out.

EXAMPLE B.
Preparation of 4-Chloro-5-Sulfamyl-N-Acetylanthranilic Acid.



Forty parts of the product of Example A are gradually added to a solution of 50 parts of potassium permanganate in 400 parts of warm water. The mixture is then heated to 90—100° C. until reaction is complete. During the reaction, a brown precipitate of MnO_2 is formed and this is filtered off and washed three times with 50 part portions of 1N NaOH. The combined filtrates and washings are decolorized with activated carbon and the resulting filtrate acidified to pH 2. A solid product precipitates which is 4-chloro-5-sulfamyl-N-acetylanthranilic acid.

EXAMPLE C.
Preparation of 4-Chloro-5-Sulfamylanthranilic Acid.



Ten parts of the product of Example B are dissolved in a warm mixture of 200 parts of HCl and 200 parts by volume of ethanol. The mixture is refluxed until reaction is complete, then cooled and evaporated to dryness under reduced pressure. The solid product obtained is then taken up with 200 parts of 1N NaOH, decolorized with activated carbon and the filtrate acidified to congo red. The product which separates out is 4-chloro-5-sulfamylanthranilic acid and if desired can be purified by recrystallization, although if it is to be used in the production of quinazolones, purification is not necessary.

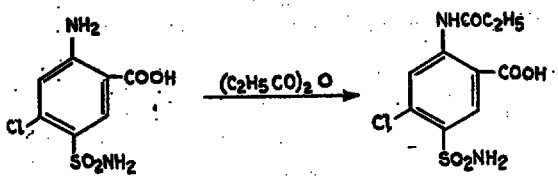
EXAMPLE D.
Alternate method of preparing 4-Chloro-5-Sulfamylanthranilic Acid.



Ten parts of the product of Example B are dispersed in 35 parts of 3N aqueous NaOH. The mixture is then refluxed until reaction is complete. The solution is clarified with activated carbon, filtered, and then the filtrate is cooled to 0° C. A sodium salt of 4-chloro-5-sulfamylanthranilic acid is produced.

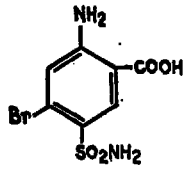
In order to produce the free acid, the sodium salt is acidified with aqueous mineral acid using congo red as an indicator. An off-white precipitate forms and is filtered and washed several times with small portions of ice water. Occluded sodium chloride is thereby removed but care should be taken to keep the washing with very small amounts of ice water, only sufficient to dissolve the sodium chloride, as the acid itself is somewhat soluble in water and large amounts of wash water would result in some loss of product.

EXAMPLE E.
Preparation of 4-Chloro-5-Sulfamyl-N-Propionylanthranilic Acid.



One part of the acid from Example C is heated with 50 parts of propionic anhydride at 90—100° C. until reaction is complete. The reaction mixture is then poured into 200 parts of ice water with stirring, the ice water being approximately half ice and half water. Two layers form, then merge and precipitate. Filtration is effected and the solid is washed with cold water, producing 4-chloro-5-sulfamyl-N-propionylanthranilic acid.

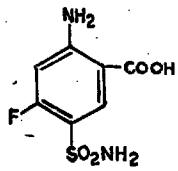
EXAMPLE F.
Preparation of 4-Bromo-5-Sulfamylanthranilic Acid.



The procedure of Example A is repeated replacing the N-acetyl-5-chlorotoluidine with a stoichiometrical equivalent of N-acetyl-5-bromotoluidine prepared by reacting 5-bromo-*o*-toluidine with acetic anhydride. 5-Bromo-4-sulfamyl-N-acetyltoluidine is obtained and is used in the process of Example B in the place of the corresponding chloro compound. However, instead of 40 parts, 47½ parts are used.

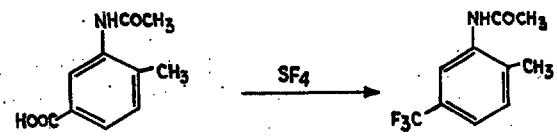
The acetyl product is then hydrolyzed as described in Example C to produce the 4-bromo-5-sulfamylanthranilic acid in the form of white crystals.

EXAMPLE G.
Preparation of 4-Fluoro-5-Sulfamylanthranilic Acid.



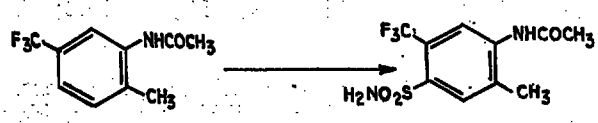
The procedure of Example A is repeated replacing the N-acetyl-5-chlorotoluidine with a stoichiometrical equivalent of N-acetyl-5-fluorotoluidine prepared by reacting 4-fluoro-*o*-toluidine with acetic anhydride. 5-Fluoro-4-sulfamyl-N-acetyltoluidine is obtained and is used in the oxidation process of Example B in the place of the corresponding chloro compound. The acetyl product is then hydrolyzed as described in Example C to produce 4-fluoro-5-sulfamylanthranilic acid in the form of white crystals.

EXAMPLE H.
N-Acetyl-5-Trifluoromethyl-Toluidine.



The reaction of 10 parts of N-acetyl-5-carboxytoluidine with an excess of sulfur tetrafluoride at 120—150° C. in a sealed tube according to the method of Smith, et. al., J.A.C.S. *81*, 3165 (1959) gives N-acetyl-5-trifluoromethyltoluidine as the main product.

EXAMPLE I.
Preparation of 4-Sulfamyl-5-Trifluoromethyl-N-Acetyltoluidine.



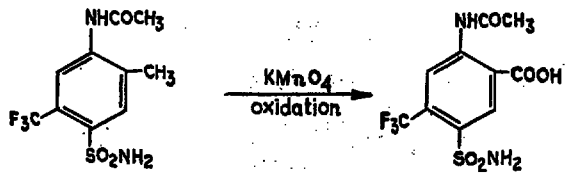
By replacing the N-acetyl-5-chlorotoluidine of Example A with 50 parts of N-acetyl-5-trifluoromethyltoluidine, the product is 4-sulfamyl-5-trifluoromethyl-N-acetyltoluidine.

PATENT OFFICE 16

Cap A

EXAMPLE J.

Preparation of 5-Sulfamyl-4-Trifluoromethyl-N-acetylanthranilic Acid.



By replacing the 5-chloro-4-sulfamyl-N-acetyltoluidine of Example B with 40 parts of 4-sulfamyl-5-trifluoromethyl-N-acetyltoluidine, the product is 4-sulfamyl-5-trifluoromethyl-N-acetylanthranilic acid.

Preparation of Final Products.

EXAMPLE 1.

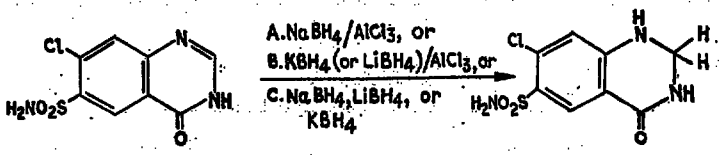
Preparation of 7-Chloro-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.

I. Preparation of intermediate 7-Chloro-6-Sulfamyl-4-Quinazolinone.

Five parts of the acid obtained from Example C or Example D are added to 5 parts of formamide and the mixture heated with stirring to 170—175° C. until reaction is complete. A light brown solution results which is cooled and taken up in 10 parts of methanol. The methanol solution is then poured into 100 parts of water. This results in crystals and an oily layer. After separation, the oil is triturated with methanol to form additional crystals and all of the crystals are recovered by filtration. Greater purity is obtained by dissolving in 1N aqueous NaOH, clarifying with activated carbon and reprecipitating with acid. By this method, crystals that are only slightly off-white color are obtained and constitute a high quality of 7-chloro-6-sulfamyl-4-quinazolinone. M.p. 310—315° C.

Analysis Calc'd: C, 37.0; H, 2.31; N, 16.2; S, 12.3; Cl, 13.7.
Found: C, 37.1; H, 2.60; N, 15.8; S, 12.4; Cl, 13.6.
λmax. 295 mμ.

II. Final Product.



(A) 103 Parts of aluminum chloride were added to 25,000 parts by volume of diethylene glycol dimethyl ether while cooling in an ice bath. The mixture was then stirred with warming and 200 parts of 7-chloro-6-sulfamyl-4-quinazolinone added. A solution of 140 parts of sodium borohydride in 7000 parts of dry diethylene glycol dimethyl ether was then added gradually. An orange mixture resulted which was kept at 85° C. until the reaction was complete. The reaction mixture was then cooled to approximately 0° C. and 4000 parts of water slowly added. Dilute HCl was then added to form a strongly acidic clear solution which was evaporated to dryness. The solid was triturated with cold water to yield 90 parts of a solid which on recrystallization from 50% aqueous acetone gave pale yellow crystals. M.p. 256—8° C.

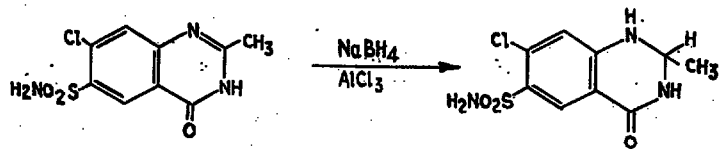
Analysis Calc'd: C, 36.7; H, 3.06; N, 16.1; S, 12.3; Cl, 13.6.
Found: C, 37.2; H, 3.30; N, 16.2; S, 12.2; Cl, 14.3.
λmax. 265.

(B) The preparation is carried out as described in (A) above except that instead of sodium borohydride, 140 parts of potassium (or lithium) borohydride are used.

(C) The preparation is carried out as described in (A) or (B) above, except that $AlCl_3$ is not used, and the reduced product is isolated.

EXAMPLE 2.

Preparation of 7-Chloro-2-Methyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



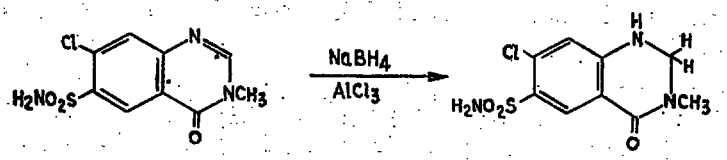
The procedure of Example 1 was repeated except that a corresponding amount of 7-chloro-2-methyl-6-sulfamyl-4-quinazolinone was used for the 7-chloro-6-sulfamyl-4-quinazolinone. The crude product obtained was stirred with aqueous sodium bicarbonate solution, filtered off and the solid dissolved in 1N aqueous NaOH and reprecipitated with dilute hydrochloric acid. As before, recrystallization from 50% aqueous acetone and 50% ethanol resulted in a well crystallized product. M.p. 285° C.

Analysis Calc'd: C, 39.2; H, 3.63; N, 15.3; S, 11.7; Cl, 12.9.
Found: C, 39.1; H, 3.60; N, 15.1; S, 11.8; Cl, 12.7.
λmax. 265.

The 7-chloro-2-methyl-6-sulfamyl-4-quinazolinone can be prepared by condensing urethane with 2-carboxy-5-chloro-4-sulfamylacetanilide.

EXAMPLE 3.

Preparation of 7-Chloro-3-Methyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The procedure of Example 1 was repeated replacing the 7-chloro-6-sulfamyl-4-quinazolinone with an equivalent amount of the 3-methyl derivative.

A good yield of plate crystals was obtained on recrystallization from 50% acetone. M.p. 257—9° C.

Analysis Calc'd: C, 39.2; H, 3.63; N, 15.3; S, 11.7; Cl, 12.9.
Found: C, 39.1; H, 3.76; N, 15.4; S, 11.5; Cl, 12.9.
λmax. 265.

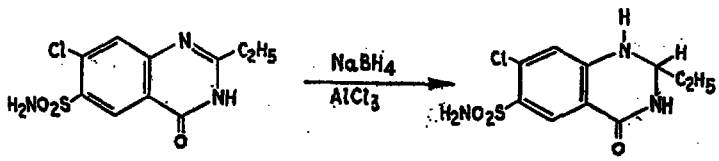
The 3-methyl derivative is prepared as follows:

One part of the acid from Example C is heated with an equal part of N-methylformamide at 175—180° C. until reaction is complete. The reaction product is then cooled and triturated with 5 parts of methanol followed by filtration producing off-white crystals. The crystals are stirred with 5 parts of 10% aqueous sodium bicarbonate to remove traces of starting material and again filtered off. The solid is then dissolved in 5 parts of 1N aqueous sodium hydroxide, clarified with activated carbon and precipitated with mineral acid. The precipitate is 7-chloro-3-methyl-6-sulfamyl-4-quinazolinone. M.p. 238—40° C.

Analysis Calc'd: (including one mole water):
C, 37.0; H, 3.42; N, 14.4; S, 11.0; Cl, 12.2.
Found: C, 36.7; H, 3.38; N, 14.1; S, 11.5; Cl, 13.6.
λmax. 285.

EXAMPLE 4.

Preparation of 7-Chloro-2-Ethyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The procedure of Example 1 was repeated replacing the 7-chloro-6-sulfamyl-4-quinazolinone with the 2-ethyl derivative. Fibrous crystals were obtained by recrystallization from 50% acetone. M.p. 248—250° C.

Analysis Calc'd: C, 41.4; H, 4.15; N, 14.5; S, 11.1; Cl, 12.3.
Found: C, 41.0; H, 4.52; N, 14.3; S, 11.1; Cl, 12.4.

λmax. 270.

The 2-ethyl derivative is prepared as follows:

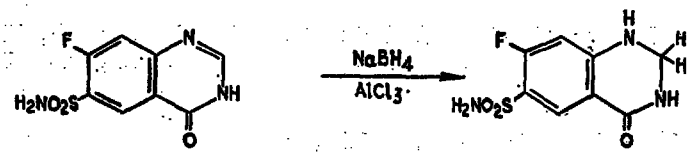
Five parts of the product of Example E and an equal weight of urethane are ground together and heated at 190° C. until reaction is complete which can be determined by cessation of the evolution of carbon dioxide from the fused material. The reaction mixture is then cooled and stirred with 50 parts of 10% aqueous sodium bicarbonate solution to remove any unreacted starting material. This is followed by filtration producing a crude, tan colored residue. The product is then purified by solution in 1N aqueous sodium hydroxide, decolorizing with activated carbon and acidification with concentrated hydrochloric acid to give a white solid precipitate which is filtered off, washed with water and dried. It is 7-chloro-2-ethyl-6-sulfamyl-4-quinazolinone. M.p. >250° C.

Analysis Calc'd: (including $\frac{1}{2}$ mole of water):
C, 40.5; H, 3.71; N, 14.1; S, 10.8; Cl, 12.0.
Found: C, 40.0; H, 3.98; N, 13.7; S, 10.7; Cl, 13.0.

λmax. 295.

EXAMPLE 5.

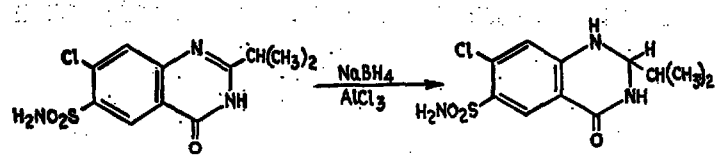
Preparation of 7-Fluoro-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The process of Example 1 is repeated replacing 7-chloro-6-sulfamyl-4-quinazolinone with the corresponding 7-fluoro-6-sulfamyl-4-quinazolinone, which was prepared by the procedure of Example 1 except that 5 parts of the product of Example D were replaced with 4 parts of the product of Example G. 7-Fluoro-6-sulfamyl-4-quinazolinone is obtained as colorless crystals.

EXAMPLE 6.

Preparation of 7-Chloro-2-Isopropyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The procedure of Example 1 was repeated replacing 7-chloro-6-sulfamyl-4-quinazolinone with the 2-isopropyl derivative. The fibrous crystals were obtained in good yield by recrystallization from 50% acetone. M.p. 296—9° C.

Analysis Calc'd: (this includes ½ mole of water):

C, 42.2; H, 4.79; N, 13.4; S, 10.3; Cl, 11.4.
Found: C, 42.1; H, 4.64; N, 13.2; S, 10.2; Cl, 11.5.

λmax. 285.

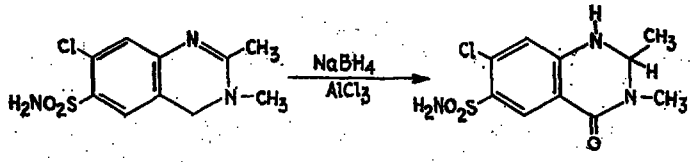
The 7-chloro-2-isopropyl-6-sulfamyl-4-quinazolinone is prepared from isobutyramide and the acid of Example C or D. M.p. 280° C.

Analysis Calc'd: C, 43.8; H, 3.98; N, 13.9; S, 10.6; Cl, 11.8.
Found: C, 43.9; H, 4.18; N, 14.2; S, 10.3; Cl, 12.1.

λmax. 295 mμ.

EXAMPLE 7.

Preparation of 7-Chloro-2,3-Dimethyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The procedure of Example 1 was repeated replacing 7-chloro-6-sulfamyl-4-quinazolinone with the 2,3-dimethyl derivative. A good yield of plate crystals was obtained by recrystallization from 50% acetone. M.p. 233—5° C.

Analysis Calc'd: C, 41.4; H, 4.14; N, 14.5; S, 11.1; Cl, 12.3.
Found: C, 41.8; H, 4.42; N, 14.2; S, 11.0; Cl, 12.2.

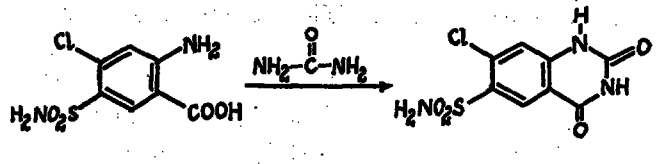
λmax. 265.

The 2,3-dimethyl derivative was prepared as follows:

Five hundred parts of the product of Example D and an equal amount of N-methylacetamide are heated at 195—200° C. until reaction is complete. The mixture is then cooled and the resulting solid triturated with methanol and 10 volumes of water added. An oil forms and on standing at low temperatures crystallizes. The solids are separated by filtration and are then stirred with 10% aqueous sodium bicarbonate and the solid recovered by filtration in the form of light yellow crystals which are further purified by dissolving in aqueous 1N sodium hydroxide solution, clarifying with activated carbon and precipitated by the addition of mineral acid. The product is 7-chloro-2,3-dimethyl-6-sulfamyl-4-quinazolinone. M.p. 245°.

EXAMPLE 8.

Preparation of 7-Chloro-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



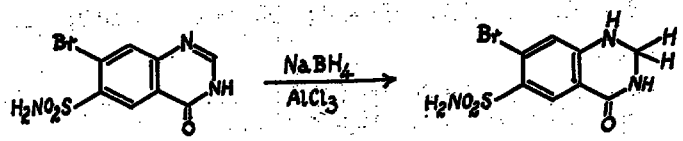
One part of 4-chloro-5-sulfamyl anthranilic acid was heated with 1 part of urea at 180° C. until reaction was complete as evidenced by cessation of evolution of ammonia. The mixture was then cooled, the unreacted starting material was dissolved in 10% aqueous sodium bicarbonate solution, filtered and the remaining solid recrystallized by dissolving in alkali, clarifying with decolorizing carbon and precipitation by acidification. M.p. 275° C.

Analysis Calc'd: C, 33.8; H, 2.45; N, 14.9; S, 11.2.
Found: C, 33.7; H, 2.89; N, 15.4; S, 11.4.

λmax. 265.

EXAMPLE 9.

Preparation of 7-Bromo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.

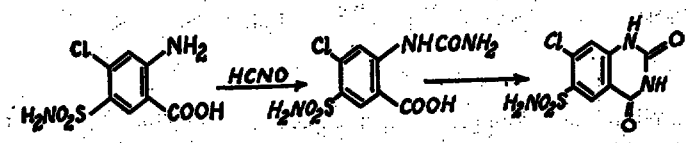


The process of Example 1 is repeated replacing 7-chloro-6-sulfamyl-4-quinazolinone with the corresponding 7-bromo-6-sulfamyl-4-quinazolinone. The product is obtained as a colorless solid on crystallization from aqueous acetone.

The 7-bromo-6-sulfamyl-4-quinazolinone is prepared according to the preparation of Example 1(I), replacing the product of Example C by the product of Example F.

EXAMPLE 10.

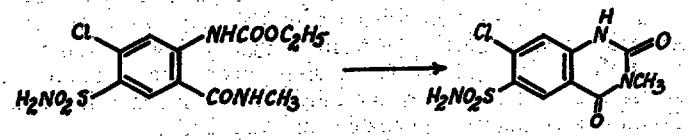
Preparation of 7-Chloro-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



An aqueous solution of ten parts of 4-chloro-5-sulfamylanthranilic acid in an excess of cyanic acid is heated at 35° C. until the reaction is complete. The formed ureido intermediate is then heated at reflux in aqueous sodium hydroxide solution to give 7-chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone, m.p. 275° C.

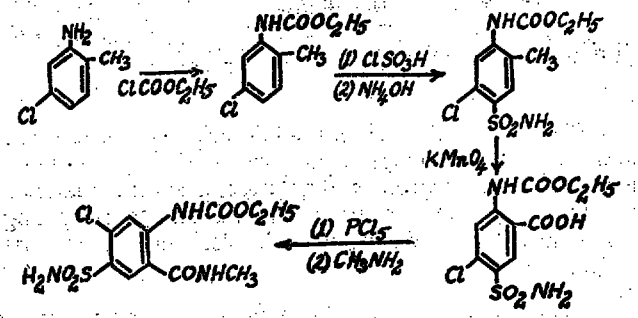
EXAMPLE 11.

Preparation of 7-Chloro-3-Methyl-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



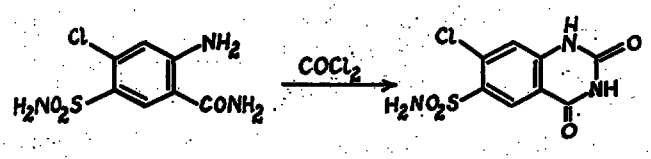
A. Twenty five parts of N-methyl-2-carboethoxyamino-4-chloro-5-sulfamylbenzamide are heated at 170—190° C. until evolution of ethanol is complete. The formed product is crystallized from aqueous acetone as a colorless, high-melting solid.

B. The intermediate N-methyl-2-carboethoxyamino-4-chloro-5-sulfamylbenzamide is prepared in accordance with the following reaction sequence:



The conditions for the conversion to the 4-chloro-5-sulfamyl-N-carboethoxyanthranilic acid are substantially identical to those for the preparation of the 4-chloro-5-sulfamyl-N-acetylanthranilic acid (Examples A and B).

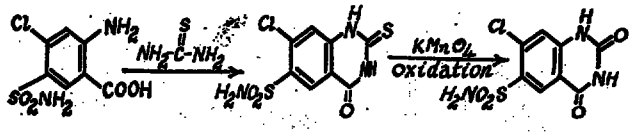
EXAMPLE 12.
Preparation of 7-Chloro-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



A. Fifteen parts of 4-chloro-5-sulfamyl-anthranilamide are dissolved in dilute hydrochloric acid and phosgene gas is bubbled through the solution at room temperature for 1—2 hours. The formed product, which precipitates out, is filtered off and crystallized from aqueous alcohol to give 7-chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone as colorless crystals, m.p. 275° C.

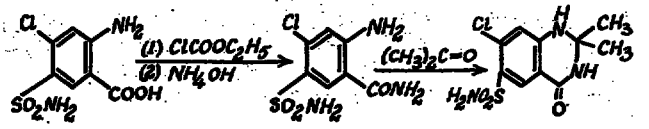
B. The intermediate 4-chloro-5-sulfamyl-anthranilamide is prepared from 4-chloro-5-sulfamylanthranilic acid (Example C) by treatment first with a chloroformic acid ester, preferably ethyl chloroformate, in the presence of a tertiary amine at a low temperature of less than about 15° C. and preferably at 0 to −10° C. and the product formed is then treated with ammonium hydroxide. 4-Chloro-5-sulfamyl-anthranilamide melts at 282—284° C.

EXAMPLE 13.
Preparation of 7-Chloro-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



Ten parts of 4-chloro-5-sulfamylanthranilic acid, and 10 parts of thiourea are fused at 185—190° for 3 hours. After cooling the crude 2-thio compound is oxidized with excess permanganate in neutral solution to form the desired 7-chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone. Recrystallized from aqueous ethanol, the product has a melting point of 275° C.

EXAMPLE 14.
Preparation of 7-Chloro-2,2-Dimethyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.

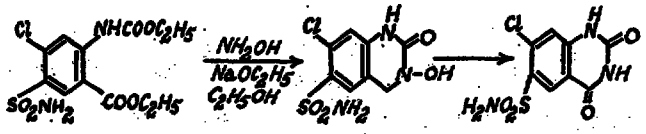


Three parts of 4-chloro-5-sulfamyl anthranilic acid in 30 parts of dimethylformamide are treated with 3 parts of triethylamine. To the ice-cold, well-stirred solution are added 3 parts of ethyl chlorocarbonate. After 10 minutes, 24 parts of concentrated aqueous ammonia are added, and the mixture is warmed to 80° C. on a steam bath. The solution is concentrated *in vacuo* to a thick syrup and 60 parts of water are added. White crystals of 2-carbamyl-5-chloro-4-sulfamylaniline are filtered off and recrystallized from aqueous alcohol.

The 2-carbamyl-5-chloro-4-sulfamylaniline is dissolved in 60 parts of diethyleneglycol dimethyl ether, an excess of acetone is added and then 4 parts of concentrated hydrochloric acid is added. After refluxing for 3 hours, the solution is stripped to dryness and the resulting solid is dissolved in base and reprecipitated by mineral acid. White crystals of 7-chloro-2,2-dimethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone are formed.

EXAMPLE 15.

Preparation of 7-Chloro-2-Oxo-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



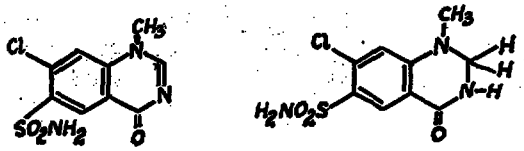
A. 20 Parts of ethyl 2-carbethoxyamino-4-chloro-5-sulfamylbenzoate and 10 parts of hydroxylamine, in 50 parts of ethanol containing 10 parts of sodium ethoxide, are refluxed for 3 hours. After cooling, the solution is concentrated to dryness and the crude solid is reduced with an excess of sodium amalgam to yield 7-chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone. Recrystallization gives the product, m.p. 275° C.

B. The intermediate ethyl 2-carbethoxyamino-4-chloro-5-sulfamylbenzoate is prepared from 4-chloro-5-sulfamyl-N-carbethoxyanthranilic acid by refluxing in ethyl alcohol for a period of four hours, during which time HCl gas is bubbled through the solution. After refluxing is over, the reaction mixture is heated to 50° C. *in vacuo* to remove the excess hydrochloric acid and alcohol, and the crude dried residue is then usable in the further reaction.

4-Chloro-5-sulfamyl-N-carbethoxy-anthranilic acid is prepared according to the sequence shown in part B of Example 11.

EXAMPLE 16.

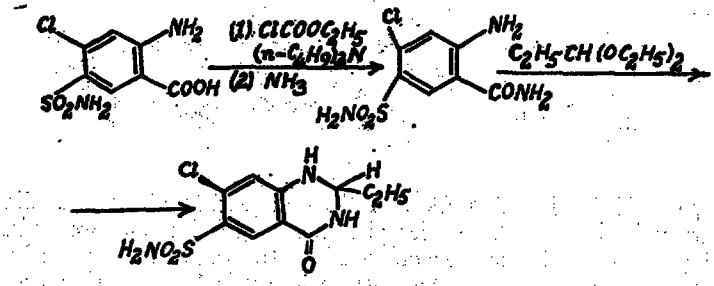
Preparation of 7-Chloro-1-Methyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The reduction procedures of Example 1 parts A, B, or C are carried out, except that 7-chloro-6-sulfamyl-4-quinazolinone is replaced by 7-chloro-1-methyl-6-sulfamyl-4-quinazolinone. There is obtained as a result of the reduction 7-chloro-1-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.

EXAMPLE 17.

Preparation of 2-Ethyl-7-Chloro-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.

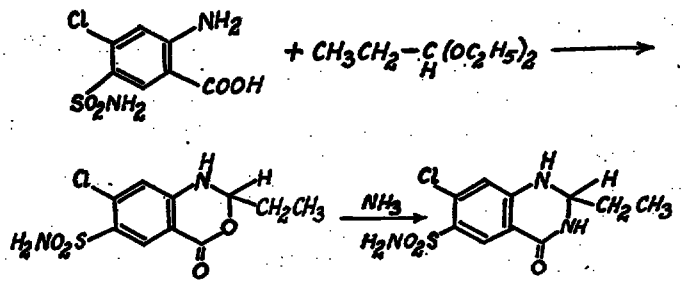


A. Two parts of 4-chloro-5-sulfamylanthranilic acid and 2 parts of tri-n-butylamine are dissolved in 100 parts of dry tetrahydrofurane and the solution is cooled to −5° C. in an ice-alcohol bath. One part of ethyl chlorocarbonate is then added all at once with stirring. After 10 minutes at this temperature, an excess of liquid NH_3 is added and the mixture is warmed briefly to about 60° C. and then concentrated *in vacuo* to give a solid residue. This is washed with dilute $NaHCO_3$ and with H_2O and air dried to give 4-chloro-5-sulfamylanthranilamide.

B. A mixture of 5 parts of the product from A, 2 parts of propionacetal and 50 parts of diethylene glycol dimethylether containing 1 part of dissolved HCl gas is heated on the steam bath with stirring for 1—2 hrs. The reaction mixture is then concentrated to dryness *in vacuo* and the solid residue is recrystallized from aqueous acetone to give 2-ethyl-7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone, m.p. 248—250° C.

EXAMPLE 18.

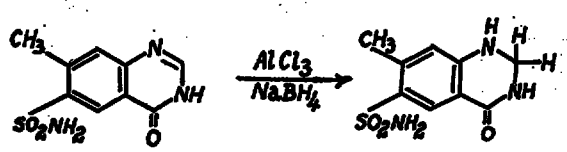
Preparation of 7-Chloro-2-Ethyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



One part of 4-chloro-5-sulfamylanthranilic acid, one part of propionaldehyde diethylacetal and 0.5 parts of concentrated hydrochloric acid are dissolved in 60 parts of diethyleneglycol dimethyl ether. The mixture is then heated on a steam bath for 1 to 3 hours. The resulting solution is cooled and an excess of concentrated ammonium hydroxide is added and refluxing continued for 3 to 4 hours. The resulting mixture is taken to dryness *in vacuo* and the solid residue washed with water. The final product is purified by dissolving in dilute sodium hydroxide and reprecipitated by mineral acid. On washing with water and air drying the product is obtained, m.p. 248—250° C.

EXAMPLE 19.

7-Methyl-6-Sulfamyl-1,2,3,4-Tetrahydro-4-Quinazolinone.



The procedure of Example 1 was repeated except that a corresponding amount of 7-methyl-6-sulfamyl-4-quinazolinone was used for 7-chloro-6-sulfamyl-4-quinazolinone. The product was worked up in the same manner.

The results of an extensive diuretic evaluation programme upon the compounds of this invention are set out below in order that a *bona fide* showing of the compounds as diuretics may be made.

Many different criteria or standards exist for the evaluation of diuretics. For example, total salt excretion, rapidity, low toxicity and freedom from side effects, are all important. Since a screening programme is directed to developing compounds which will assume possible commercial therapeutic importance, some rather generally accepted criteria (assuming, of course, low toxicity and freedom from side effects have been assured by preliminary screening) have been settled on. They are, in order of their relative importance, relatively low excretion of potassium ion, diuresis at low mg/kg. dose levels and a favorable chloride ion excretion. While, admittedly, a high rate of chloride ion excretion is important in treating the edema that frequently accompanies ~~cardivascular~~ cardiovascular episodes, its value is greatly exaggerated if one neglects the extreme importance of low potassium ion excretion during diuretic therapy. For example, it is well known that extreme potassium depletion can result in side effects, sometimes culminating in shock or even death. For this reason, rather than high chloride excretion *per se*, it is much more important that a clinically successful diuretic causes a low potassium ion excretion coupled with a relatively high chloride ion excretion rate. The ratio of chloride ion excretion to potassium ion excretion affords a figure which is useful to indicate the efficacy of a diuretic.

The second most important characteristic of a clinically useful diuretic is the ability of a diuretic to function at low mg/kg. dose levels. Unfortunately, because of the pressure to market drugs, there has been a tendency to overlook the need for a diuretic to function at low dose levels.

When maximum effective doses of diuretics are employed, the diuretics having a relatively weak potency induce a lesser degree of chloride excretion and a greater incidence of untoward reactions than when more potent diuretics are administered. For

this reason diuretics are preferred having activity below 10 mg/kg. In the screening programme the compounds which were deficient in or barely marginally active in the above qualities, have been dropped from further consideration and less data are available on them than on the compounds disclosed in this specification.

Using the method of J. M. Little and C. Cooper, Jr. Fed. Proc. *9*; 296, 1950, dogs were given 35 ml/kg. water by gavage, deprived of food and water, catheterized 16 hours later, and given an additional 25 mg/kg of water plus a gelatin capsule of test compound. The animals were then returned to their metabolism cages and 24 hours later total urine volume was collected and analyzed.

Sodium and potassium concentrations were determined by flame photometry in a Baird-Atomic DB4 using the direct method. Chloride was measured by mercurimetric titration, as noted by O. Schales and S. S. Schales, J. Biol. Chem. *140*; 879, 1941.

In determining 95% confidence limits in Table I below, the standard deviation was estimated by a procedure based on the range of observations as noted by G. W. Snedecor, Statistical Methods, 5th Ed., Ames, Iowa State College Press, 1956, p. 38. For testing the significance of differences, the conventional "Student's" t-test was employed. The procedure outlined by Snedecor was used for analysis of variance.

In Table II the so-called cross-over method was used, as originally suggested by Youden (Youden Square), see Cocharan & Cox, Ch. 13, Exptl. Designs, 2nd Ed., 1957.

Both the statistical methods used in Tables I and II will give the same order of results.

TABLE I

Compound	No. of Dogs	Dose mg/kg.	Avg. % Change from Control in 0—24 hr. Cl^-	Avg. % Change from Control in 0—24 hr. K^+	Avg. % Change from Control in 0—24 hr. Cl^-/K^+
6-quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo	4	1	243	62	3.92
	4	5	212	24	8.90
	3	20	192	63	3.04
6-quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-4-oxo	3	1	169	52	3.25
	2	20	340	144	2.36
6-quinazolinesulfonamide, 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo	6	1	251	101	2.50
	5	5	291	32	9.13
	4	25	309	137	2.25

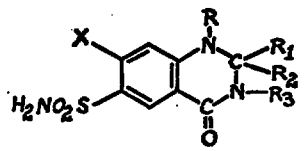
TABLE II

Compound	Oral Dose mg/kg.	Avg. % Change from Control in 0—24 hr. Electrolyte Concentration Cl^-	Avg. % Change from Control in 0—24 hr. Electrolyte Concentration K^+	Avg. % Change from Control in 0—24 hr. Electrolyte Concentration Cl^-/K^+
6-quinazolinesulfonamide, 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo	1	215	101	2.12
	5	291	32	9.10
	25	309	137	2.26
6-quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo	1	49	22	2.23
	5	212	24	8.83
	25	237	56	4.23
6-quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-4-oxo	1	150	9	16.67
	5	360	58	6.21
	25	369	250	1.48

Based on the above data obtained in dogs, the compounds of the invention showed effectiveness as diuretics, and particularly high effectiveness at dosages of less than 10 mg/kg. body weight.

WHAT WE CLAIM IS:—

1. 4-Oxo-6-sulfamyl-1,2,3,4-~~tetrahydroquinabolinone~~ tetrahydroquinazolinone derivatives of the general formula:

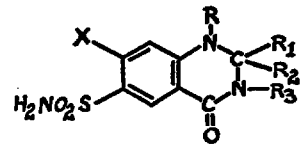


...I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups, or R_1 and R_2 taken together are an oxygen atom, and X is halogen or an alkyl group or a trihalomethyl group.

2. 7-Chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
3. 7-Chloro-2-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
4. 7-Chloro-3-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
5. 7-Chloro-2-ethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
6. 7-Fluoro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
7. 7-Chloro-2-isopropyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
8. 7-Chloro-2,3-dimethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
9. 7-Bromo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
10. 7-Chloro-2,2-dimethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
11. 7-Chloro-1-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
12. 7-Methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
13. 7-Chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
14. 7-Chloro-3-methyl-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.

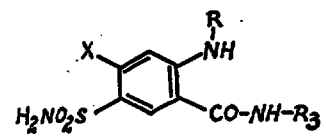
15. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:



...I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups, and X is halogen or an alkyl group or a trihalomethyl group, which comprises

(a) reacting an anthranilamide derivative of the general formula:



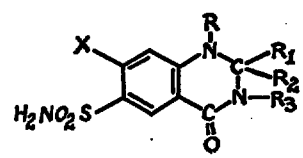
in an acidic medium with a carbonyl compound of the general formula:

$$R_1—CO—R_2,$$

or with the corresponding acetal or ketal,

(b) and, if desired, alkylating in a manner known per se the resulting compounds in which R and/or R_3 are hydrogen.

16. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:

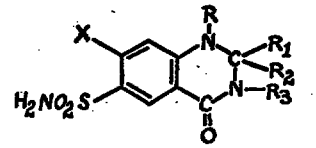


...I

Based on the above data obtained in dogs, the compounds of the invention showed effectiveness as diuretics, and particularly high effectiveness at dosages of less than 10 mg/kg. body weight.

WHAT WE CLAIM IS:—

1. 4-Oxo-6-sulfamyl-1,2,3,4-~~tetrahydroquinabolinone~~ tetrahydroquinazolinone derivatives of the general formula:

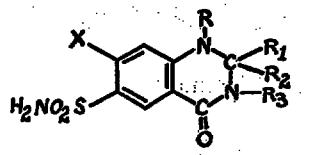


... I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups, or R_1 and R_2 taken together are an oxygen atom, and X is halogen or an alkyl group or a trihalomethyl group.

2. 7-Chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
3. 7-Chloro-2-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
4. 7-Chloro-3-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
5. 7-Chloro-2-ethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
6. 7-Fluoro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
7. 7-Chloro-2-isopropyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
8. 7-Chloro-2,3-dimethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
9. 7-Bromo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
10. 7-Chloro-2,2-dimethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
11. 7-Chloro-1-methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
12. 7-Methyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
13. 7-Chloro-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.
14. 7-Chloro-3-methyl-2-oxo-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone.

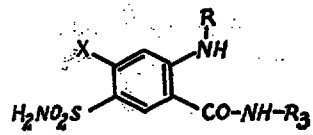
15. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:



... I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups, and X is halogen or an alkyl group or a trihalomethyl group, which comprises

(a) reacting an anthranilamide derivative of the general formula:



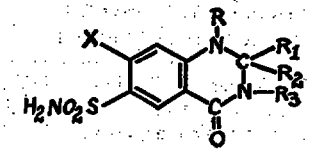
in an acidic medium with a carbonyl compound of the general formula:

$$R_1—CO—R_2,$$

or with the corresponding acetal or ketal,

(b) and, if desired, alkylating in a manner known per se the resulting compounds in which R and/or R_3 are hydrogen.

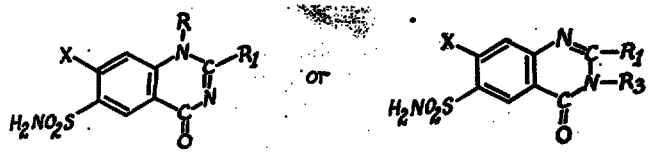
16. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:



... I

in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 are hydrogen or alkyl radicals containing up to 6 carbon atoms or aralkyl groups and X is halogen or an alkyl group or a trihalomethyl group, which comprises:

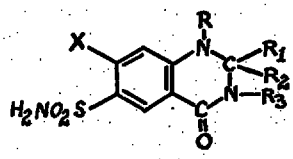
(a) hydrogenating a 6-sulfamyl-4-oxo-dihydroquinazolinone derivative of the general formula:



by means of an alkali metal boron hydride, if desired in the presence of aluminum chloride, and

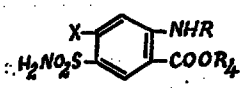
(b) if desired, alkylating in a manner known per se the resulting compounds in which R and/or R_3 are hydrogen.

17. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinone derivatives of the general formula:

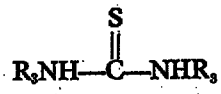


... I

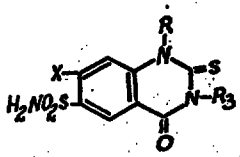
in which R and R_3 are hydrogen or alkyl radicals containing up to 6 carbon atoms, R_1 and R_2 taken together represent an oxygen atom and X is halogen or an alkyl group or a trihalomethyl group, which comprises condensing an anthranilic acid derivative of the following general formula:



with a thiourea of the following general formula:



to form a 2-thia-substituted quinazolinone of the following general formula:



which is then oxidized to the corresponding 2-oxo-1,2,3,4-tetrahydroquinazolinone, wherein R, R_3 and X are as hereinabove defined, and R_4 is hydrogen or is a hydrocarbon group, preferably a lower alkyl group containing up to 6 carbon atoms.

18. A process for preparing 4-oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinones of formula I substantially as herein described.

19. 4-Oxo-6-sulfamyl-1,2,3,4-tetrahydroquinazolinones whenever prepared by the process substantially as described herein.

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Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1963. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

THE PATENT OFFICE 21 NOV 1963

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