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PATENT SPECIFICATION

NO DRAWINGS

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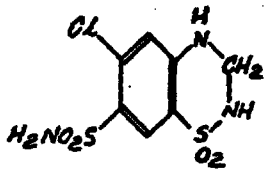
International Classification:—A61k. C07d.

COMPLETE SPECIFICATION

6-Chloro-7-Sulphamyl-3:4-Dihydro-1:2:4-Benzothiadiazine-1:1-Dioxide and its Salts and the preparation thereof

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basel, Switzerland, 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:—

The present invention provides 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide of the formula



and alkali metal salts thereof.

The above new compound has an excellent diuretic and natriuretic action, as is shown by comparative tests with the commercial product chlorothiazide (6 - chloro - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide). Tests of 6 hours' duration in dogs gave the following results, the new compound being given the designation SU 5879.

[*Price 3s. 6d.*]

Price 4s 6d

TABLE 1

SU 5879				Chlorthiazide		
Dose mg/kg oral	Urine ml/6 hrs.	Sodium mol equivalents 6 hrs.	Potassium mol equivalents 6 hrs.	Urine ml/6 hrs.	Sodium mol equivalents 6 hrs.	Potassium mol equivalents 6 hrs.
Control	51.9	8.84	3.19	51.9	8.84	3.19
0.02	61.5	10.28	3.78	—	—	—
0.04	67.59	11.16	5.29	—	—	—
0.08	77.91	13.53	4.34	48.83	9.68	3.75
0.16	83.85	14.76	4.89	55.5	9.21	3.31
0.31	105.11	19.34	6.25	87.75	15.16	4.33
0.63	117.41	24.24	5.91	96.17	17.59	4.22
1.25	126.33	25.45	6.99	96.58	19.87	5.82

Average values of experiments in 7 dogs.

From the above Table it is clear that the diuretic action of the new compound in dogs is substantially better than that of chlorothiazide.

In a further comparison of the diuretic action of the new compound with chlorothiazide, rats, which had received no food for 18 hours, were given sodium chloride solution of 0.2% strength in a quantity corresponding to 5% of their body weight. Immediately afterwards they were given orally one each of these compounds dissolved in 0.1 cc of dilute sodium hydroxide solution. The excreted urine was collected in graduated cylinders during the next three hours, its volume measured and calculated as a percentage of the intake of liquid. The concentrations of sodium and potassium were determined by flame-photometry and the total excretion of these electrolytes calculated for the 3-hour test period. The values put together in the Table below are average values of 8—12 rats per group.

TABLE 2

SU 5879				Chlorthiazide		
Dose mg/kg oral	Excretion of water in % of intake of liquid	Sodium mol equivalents 3 hrs × 100	Potassium mol equivalents 3 hrs × 100	Excretion of water in % of intake of liquid	Sodium mol equivalents 3 hrs × 100	Potassium mol equivalents 3 hrs × 100
Control	77	12.3	7.1	77	12.3	7.1
5.0	115	72.2	20.0	85	33.1	12.5
1.25	84	48.8	16.0	77	16.3	8.8
0.3	87	36.5	12.4	77	12.9	6.9
0.15	87	28.5	11.3	—	—	—
0.08	80	24.2	11.4	—	—	—

From the above it is clear that the new compound has a stronger action in rats than chlorothiazide.

The new compound has a strong diuretic and natriuretic action also when used in humans, whereas the excretion of potassium is not promoted to the same degree. In patients suffering from water and salt retention owing to heart, liver (cirrhosis) or kidney disease (nephrosis), the compound enhances water and salt excretion without any risk of too great a loss of potassium. The oral dose required to produce such an effect lies on an average between 25 and 100 mg a day. The new compound also reduces high blood pressure, particularly when it is administered together with another hyposensitive agent.

The invention also provides pharmaceutical preparations which comprise the new compound or an alkali metal salt thereof in admixture or conjunction with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral, e.g. oral, or parenteral administration. For making up the preparations there are used substances that do not react with the new compound, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol or any other known carriers for medicaments. The pharmaceutical preparations may be made up, for example, as tablets, dragees, capsules or in liquid form as solutions, suspensions, or emulsions. They may also be sterilised and/or contain auxiliary substances, such as preserving agents, stabilising agents, wetting agents or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances, for example, hypotensive agents, and Rauwolfia, or Veratrum alkaloids, for example reserpine, rescinnamine, deserpidine, germine or protoveratrine, synthetic hypotensive compounds, for example, hydralazine or ganglionic blockers, for example, chlorisondamine.

The invention also provides a process for the manufacture of new compound and alkali metal salts thereof, wherein 5 - chloro - 2:4 - disulphamyl - aniline or an alkali metal salt thereof or a salt thereof with an acid is reacted with formaldehyde in approximately molar equivalent quantities of the reactants, and, if desired, the compound so obtained, when in the form of an alkali metal salt, is converted into the free compound or, when in the form of the free compound, is converted into an alkali metal salt thereof.

The reaction with formaldehyde is preferably carried out in the presence of an acid, such as a mineral acid, for example, a hydrohalic acid, for instance, hydrochloric acid or hydrobromic acid, or sulphuric acid, which may be in anhydrous form. The formaldehyde can be used in the form of a polymer or reactive functional derivatives, such as paraformaldehyde, trioxane or hexamethylene tetramine, or of an acetal, for example, dimethoxy-methane or diethoxy-methane. The reaction may be performed in the absence or, preferably, presence of a solvent, such as an ether, for example, para-dioxane or diethylene glycol dimethyl ether, or of a formamide, for example, dimethyl formamide. It may be carried out at room temperature or an elevated temperature and under normal or increased pressure or in the presence of an inert gas, such as nitrogen.

Depending on the reaction conditions, the new compound is obtained in free form or in alkali metal salt can be converted into the the form of its alkali metal salts. A resulting free compound for example by reaction with an aqueous acid agent, such as mineral acid, for example, a hydrohalic acid, for instance hydrochloric acid or sulphuric acid. A free compound can be converted into an alkali metal salt, by treatment, for example, with an alkali metal hydroxide, such as sodium or potassium hydroxide, in a solvent, such as an alkanol, for example, methanol or ethanol, or in water and evaporating the solvent, or by reacting the free compound in an ether, such as para-dioxane or dimethyleneglycol dimethyl ether, with an alkali metal hydride or amide, for example, sodium or potassium hydride or amide.

The following Examples illustrate the invention:—

EXAMPLE 1.

A mixture of 2.9 grams of 5 - chloro - 2:4 - disulphamylaniline in 15 cc of anhydrous diethyleneglycol dimethyl ether, 0.5 cc of an ethyl acetate solution containing 109.5 grams of hydrogen chloride per 1000 cc and 0.33 gram of paraformaldehyde is heated to 80—90°C and maintained at that temperature for 1 hour. The resulting mixture is cooled to room temperature and concentrated to one third of its volume under reduced pressure, diluted with water, then allowed to crystallise. The product is filtered off and recrystallized from water, to yield the desired 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 266—268°C.

By replacing paraformaldehyde by 0.84 gram of 1:1 - dimethoxymethane and proceeding as above, the same compound is obtained.

The sodium salt may be prepared by evaporating the solution of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in an equimolar amount of aqueous sodium hydroxide.

EXAMPLE 2.

A mixture of 2.9 grams of 5 - chloro - 2:4 - disulphamyl - aniline in 15 cc of diethylene - glycol dimethyl ether, 0.8 cc of a 37% aqueous solution of formaldehyde (0.3

gram of formaldehyde) and 0.5 cc of a saturated solution of hydrogen chloride in ethyl acetate is heated for one hour to 80—90°C. After concentration under reduced pressure and addition of water the 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide crystallises and is recrystallised from water, m.p. 271—275°C.

EXAMPLE 3.

A mixture of 2.9 grams of 5-chloro - 2:4 - disulphamyl - aniline, 0.3 gram of para - formaldehyde and 15 cc of diethylene glycol dimethyl ether is heated for one hour at 80—90°C. The reaction mixture is concentrated under reduced pressure, water is added, whereupon 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide crystallises slowly. It is filtered off and recrystallized from water. In a mixed melting point test with the product obtained as described in Example 1 the mixed products begin to melt at 263°C.

EXAMPLE 4.

A mixture of 5.9 grams of 5 - chloro - 2:4 - disulphamyl - aniline in 40 cc of ethanol of 90% strength containing about 100 mg of solid sodium hydroxide, is treated with 1.6 cc of aqueous formaldehyde of 37% strength and heated for one hour on a steam bath. After cooling and neutralising with 2N-aqueous hydrochloric acid, 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide crystallises out. It is recrystallised from water and melts at 272—275°C.

The mother liquors are concentrated and water is added, whereupon a second portion of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is obtained. After recrystallisation from water it melts at 272—275°C. A mixed melting point test with the product obtained as described in Example 1 shows no depression.

Instead of ethanol other lower alkanols, such as methanol, propanol, isopropanol or n-butanol may be used as solvent. Other alkali metal hydroxide, such as lithium or potassium hydroxide, or other basic condensing agents may also be used.

EXAMPLE 5.

From 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzo - thiadiazine - 1:1 - dioxide capsules which contain 0.05 grams of active substance can be prepared, for example, by the following method (for 1000 capsules):

6-chloro-7-sulphamyl-3:4-dihydro-1:2:4-benzothiadiazine-1:1-dioxide	50.0 g
Corn starch	17.5 g
Magnesium stearate	3.5 g
Lactose	279.0 g

The mixture is sifted through a 20 mesh screen and mixed well for 20 minutes. Empty capsules (No. 2 hard gelatine) are filled with 0.35 gram of this mixture.

Tablets for oral administration can be prepared as follows (for 1000 tablets):

6-chloro-7-sulphamyl-3:4-dihydro-1:2:4-benzothiadiazine-1:1-dioxide	50.0 g
Lactose	124.0 g
Polyethyleneglycol 6000	8.0 g
Tragacanth	4.0 g
Sugar	3.0 g
Talc	10.0 g
Magnesium stearate	1.0 g
Distilled water and ethanol	

The active substance, tragacanth, lactose, sugar, talc and magnesium stearate are mixed for 20 minutes and passed through a 20 mesh sieve. The polyethylene glycol is dissolved in a mixture of 15 cc of water and 50 cc of ethanol, the mixed powders are wetted with this solution, the moist mass is passed through a 10 mesh sieve and then dried at 38°C in circulating air until the moisture content amounts to only about 2—3%. The granulate is broken on a 16 mesh sieve and compressed into tablets of 0.2 gram weight.

WHAT WE CLAIM IS:—

1. 6 - Chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzo-thiadiazine - 1:1 - dioxide.

2. An alkali metal salt of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

3. The sodium salt of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

4. A pharmaceutical preparation which comprises 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine or an alkali metal salt thereof, in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

5. A pharmaceutical preparation having substantially the composition given in Example 5 herein.

6. A process for the manufacture of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzo - thiadiazine - 1:1 - dioxide and alkali metal salts thereof, wherein 5 - chloro - 2:4 - disulphamyl - aniline or an alkali metal salt thereof or a salt thereof with an acid is reacted with formaldehyde in approximately molar equivalent proportions of the reactants and, if desired, the compound so obtained, when in the form of an alkali metal salt, is converted into the free compound or, when in the form of the free compound, is converted into an alkali metal salt thereof.

7. A process as claimed in claim 6, wherein the formaldehyde is used in the form of a polymer thereof.

8. A process as claimed in claim 6, wherein paraformaldehyde is used.

9. A process as claimed in claim 6 wherein the formaldehyde is used in the form of hexamethylene tetramine.

10. A process as claimed in claim 6, wherein an acetal of formaldehyde is used.

11. A process as claimed in claim 10, wherein dimethoxy-methane is used.

12. A process as claimed in claim 10, wherein diethoxy-methane is used.

13. A process as claimed in any one of claims 6 to 12, wherein the reaction between 5 - chloro - 2:4 - disulphamyl - aniline and formaldehyde is carried out in the presence of an acid.

14. A process as claimed in claim 12, wherein the said reaction is carried out in the presence of hydrochloric acid.

15. A process for the manufacture of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, conducted substantially as described in any one of Examples 1—4 herein.

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ERRATA

SPECIFICATION NO. 847,064

Page 3, line 41, *after* "agents," ~~*delete* "and"~~.

Page 3, line 46, *for* "chlorisodamine" *read* "chlorisondamine"

Page 3, *for* "line 81" *read* "line 82"

Page 3, *and for* "line 82" *read* "line 81"

Page 4, line 46, *for* "n —" *read* "n —"

Page 4, line 62, *for* "gram" *read* "grams"

THE PATENT OFFICE,
10th January, 1961

DS 84016/1(19)/8533 200 12/60 PL

The active substance, tragacanth, lactose, sugar, talc and magnesium stearate are mixed for 20 minutes and passed through a 20 mesh sieve. The polyethylene glycol is dissolved in a mixture of 15 cc of water and 50 cc of ethanol, the mixed powders are wetted with this solution, the moist mass is passed through a 10 mesh sieve and then dried at 38°C in circulating air until the moisture content amounts to only about 2—3%. The granulate is broken on a 16 mesh sieve and compressed into tablets of 0.2 gram weight.

WHAT WE CLAIM IS:—

1. 6 - Chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzo-thiadiazine - 1:1 - dioxide.

2. An alkali metal salt of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

3. The sodium salt of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

4. A pharmaceutical preparation which comprises 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine or an alkali metal salt thereof, in admixture or conjunction with a pharmaceutical carrier suitable for enteral or parenteral administration.

5. A pharmaceutical preparation having substantially the composition given in Example 5 herein.

6. A process for the manufacture of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzo - thiadiazine - 1:1 - dioxide and alkali metal salts thereof, wherein 5 - chloro - 2:4 - disulphamyl - aniline or an alkali metal salt thereof or a salt thereof with an acid is reacted with formaldehyde in approximately molar equivalent proportions of the reactants and, if desired, the compound so obtained, when in the form of an alkali metal salt, is converted into the free compound or, when in the form of the free compound, is converted into an alkali metal salt thereof.

7. A process as claimed in claim 6, wherein the formaldehyde is used in the form of a polymer thereof.

8. A process as claimed in claim 6, wherein paraformaldehyde is used.

9. A process as claimed in claim 6 wherein the formaldehyde is used in the form of hexamethylene tetramine.

10. A process as claimed in claim 6, wherein an acetal of formaldehyde is used.

11. A process as claimed in claim 10, wherein dimethoxy-methane is used.

12. A process as claimed in claim 10, wherein diethoxy-methane is used.

13. A process as claimed in any one of claims 6 to 12, wherein the reaction between 5 - chloro - 2:4 - disulphamyl - aniline and formaldehyde is carried out in the presence of an acid.

14. A process as claimed in claim 12, wherein the said reaction is carried out in the presence of hydrochloric acid.

15. A process for the manufacture of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, conducted substantially as described in any one of Examples 1—4 herein.

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ERRATA

SPECIFICATION NO. 847,064

Page 3, line 41, ~~after "agents," delete "and"~~ FOR "AND" READ "SUCH"

Page 3, line 46, *for* "chlorisodamine" *read* "chlorisondamine"

Page 3, *for* "line 81" *read* "line 82"

Page 3, *and for* "line 82" *read* "line 81"

Page 4, line 46, *for* "n —" *read* "*n* —"

Page 4, line 82, *for* "gram" *read* "grams"

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