NEW BENZENESULPHONYL SEMICARBAZIDES AND
A PROCESS FOR THEIR PREPARATION

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Following statement is a full description of this invention, including the best method of performing it known to us:

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This invention relates to benzenesulphonyl semicarbazides and to a process for their preparation.

The present invention provides a benzenesulphonyl semicarbazide of the general formula I:

\[ \text{HOOC} \quad \text{SO}_2 \quad \text{NH} \quad \text{CO} \quad \text{NH} \quad \text{Het} \quad (I) \]


The present invention also provides a salt, especially a physiologically tolerable salt, of a compound of the formula I with a base. As bases which provide physiologically tolerable salts there are, for example, alkali metal hydroxides, amines, for example propylamine, butylamine, diethylamine and diproylamino and amino-alcohols for example 1-amino-2-propanol, 2-amino-2-methyl-1-propanol and choline.

The present invention also provides a process for the preparation of a compound of the formula I which comprises reacting the compound of formula:

\[ \text{KOOC} \quad \text{SO}_2 \quad \text{NHK} \]

with a 4-4-diphenyl semicarbazide of the general formula II
wherein Het has the meanings given above, and, if desired, subsequently acidifying the product obtained to obtain the free acid.

A 4,4-diphenyl semicarbazide of the formula II may be prepared, for example, by the method described by J. M. McMANUS and C. F. GERBER in J. of Med. Chem. 9, 256 (1966) which comprises reacting a corresponding N-amino heterocycle (Het-NH$_2$) with diphenyl carbamoyl chloride.

An N-amino heterocycle may be prepared, for example, by the method described by J. B. WRIGHT and R.E. WILLETTE in J. Med. and Pharm. Chem., 5, 819 (1962) which comprises nitrosating the corresponding heterocycle and reducing the resulting N-nitroso derivative with lithium aluminium hydride.

The following Examples illustrate the invention. The parts are by weight and the melting points were determined on a Kofler block (K), or on a Kofler heater under a microscope (M.K.).
EXAMPLE 1

1-para-carboxybenzenesulphonyl-3-[3-azabicyclo (3,3,0) oct-3-yl] urea

32.1 parts of 1,1-diphenyl-3-[3-azabicyclo (3,3,0) oct-3-yl] urea were added to 27.7 parts of the dipotassium salt of para-carboxybenzenesulphonamide suspended in a mixture of 300 ml of dimethylformamide and 50 ml of water. The reaction mixture was heated on a steam-bath for 90 minutes and was then concentrated in vacuo. The resulting crude product was treated with 250 ml of water and 250 ml of ether. The aqueous layer was acidified to pH 3.5 with a normal aqueous solution of HCl. The precipitate formed was filtered and air-dried. Recrystallization from 92 ml of dimethyl formamide (D.M.F.) and 36 ml of water gave 17.5 parts of 1-para-carboxybenzenesulphonyl-3-[3-azabicyclo (3,3,0) oct-3-yl] urea, M.P. (K): 232 to 235°C, (M.K.): 136 to 191°C.

EXAMPLES 2 to 7

The following compounds were prepared by processes analogous to that described in Example 1.

2. 1-para-carboxybenzenesulphonyl-3-[3-azabicyclo (3,2,2) non-3-yl] urea, M.P. (K): 240°C, (M.K.): 181 to 182°C (D.M.F./H₂O), starting from 1,1-diphenyl-3-[3-azabicyclo (3,2,2) non-3-yl] urea and the dipotassium salt of para-carboxybenzenesulphonamide.

3. 1-para-carboxybenzenesulphonyl-3-[8-azabicyclo (4,3,0) non-3-en-8-yl]urea, M.P. (K): 242 to 246°C, (M.K.): 192 to 195°C. (D.M.F./H₂O), starting from 1,1-diphenyl-3-[2-aza-bicyclo (4,3,0) non-3-en-8-yl] urea and the dipotassium salt of para-carboxybenzenesulphonamide.

4. 1-para-carboxybenzenesulphonyl-3-[8-azabicyclo (4,3,0)
non-8-yl] urea, M.P. (K): 250°C, (M.K.): 190 to 192°C (D.M.F./H₂O), starting from 1,1-diphenyl-3-[8-azabicyclo (4,3,0) non-8-yl] urea and the dipotassium salt of para-carboxybenzenesulphonamide.

5. 1-para-carboxybenzenesulphonyl-3-[3-azabicyclo (3,2,0) hept-3-yl] urea, M.P. (K): 252 to 253°C, (M.K.): 194 to 199°C. (D.M.F./H₂O), starting from 1,1-diphenyl-3-[3-azabicyclo (3,2,0) hept-3-yl] urea and the di-potassium salt of para-carboxybenzenesulphonamide.


7. 1-para-carboxybenzenesulphonyl-3-(1,2,3,4-tetrahydroisoquinol-2-yl) urea, M.P. (M.K.): 228 to 230°C, (D.M.F./H₂O), starting from 1,1-diphenyl-3-(1,2,3,4-tetrahydroisoquinol-2-yl) urea and the dipotassium salt of para-carboxybenzenesulphonamide.

The compounds of the present invention possess valuable pharmacological and therapeutic properties, especially microcirculation-improving, fibrinolytic- and platelet-adhesiveness and aggregation-decreasing properties.

Their toxicity is very weak and the LD₅₀ in mice by the oral route is from 1 to >3 g/kg.

The activity on the microcirculation was studied by the method described by French (c.f. Brit. J. Exp. Path. 45, 467, 1964) on the mesocaecum of the rat. It was observed that the compounds of the invention delay the appearance and the growth of the mural thrombus and decrease the formation of the platelet-thrombus on the wounded wall. The active dose in this
The fibrinolytic activity was studied by the method described by von Kaulla (c.f. Am. J. Clin. Path. 29, 104 (1959)). By administering perorally to rats from 10 to 100 mg/kg of a compound of the invention, a decrease of from 16 to 50% of the euglobulin lysis time was observed 30 to 90 minutes after administration.

Inhibition of the platelet stickiness was studied by the method described by E. W. Salzmann (c.f. J. Lab. Clin. Med. 62, 724 (1923) on rats and rabbits. From 10 to 50 mg/kg of a compound of the invention administered perorally decreases the platelet adhesiveness by from 30 to 72%.

The effect of the compounds of the invention on the platelet aggregation was studied by the photometric technique of Born and O'Brien, modified by Sinakos and Caen (c.f. Rev. Fr. E. Clin. Biol., 11, 538-31, 1966). A concentration of from 100 to 1000 μg/ml of a compound of the invention inhibits by from 27 to 71% the platelet aggregation provoked by adenosine diphosphate in the rabbit's plasma.

It is to be noted that the compounds of the invention were tested for hypoglycemic activity and surprisingly they were found to be found devoid of any action on the blood sugar level.

The low toxicity and the here-above described pharmacological properties of the compounds of the invention render them suitable for use in therapy, especially in the prevention and treatment of thromboembolic diseases and arteriosclerosis.

The present invention also provides a pharmaceutical preparation which contains as an active ingredient a compound of general formula I or a physiologically tolerable salt.
thereof, in admixture or conjunction with a pharmaceutically acceptable carrier, for example distilled water, glucose, lactose, talc, starch, magnesium, stearate or cocoa butter. The pharmaceutical preparations may be in the form of tablets, dragees, capsules, suppositories or solutions, and may be administered by an oral, rectal or parenteral route at doses of, for example, from 50 to 500 mg, 1 to 5 times a day. A pharmaceutical preparation is preferably in dosage unit form and contains, for example, from 50 to 500 mg of the active ingredient per dosage unit.

There is also provided a pack comprising a pharmaceutical preparation of the invention together with instructions, the instructions requiring that it be administered orally, rectally or parenterally, preferably in doses of from 50 to 500 mg, 1 to 5 times a day, especially for the prevention or treatment of thromboembolic diseases or arteriosclerosis.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the general formula I:

\[
\text{HOOC} - \overset{\text{SO}_2}{\text{O}} - \text{NH} - \text{CO} - \text{NH} - \text{Het}
\] (I)


2. 1-para-carboxybenzenesulphonyl-3-[3-aza-bicyclo(3,3,0)oct-3-yl]urea.

3. 1-para-carboxybenzenesulphonyl-3-[8-aza-bicyclo(4,3,0)non-3-en-8-yl]urea.

4. 1-para-carboxybenzenesulphonyl-3-(2-isindolinyl)urea.

5. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a compound of formula:

\[
\text{KOOC} - \overset{\text{SO}_2}{\text{O}} - \text{NHK}
\]

with a 4,4-diphenyl semicarbazide of the general formula II:

\[
\text{Het} - \text{NH} - \overset{\text{C}}{\text{N}} - \overset{\text{C}_6\text{H}_5}{\text{C}_6\text{H}_5} \quad \text{(II)}
\]
wherein Het has the meanings given in claim 1.

6. A process as claimed in claim 5 carried out substantiably as described in any one of the Examples herein.

7. A compound as claimed in claim 1 which has been prepared by a process as claimed in claim 5 or claim 6.

8. A salt of a compound as claimed in any one of claims 1 to 4 and 7 with a base.

9. A salt as claimed in claim 8 which is physiologically tolerable.

10. A pharmaceutical preparation which contains as an active ingredient a compound as claimed in any of claims 1 to 4, 7 and 9 in admixture or conjunction with a pharmaceutically acceptable carrier.

11. A pharmaceutical preparation as claimed in claim 10 which is in dosage unit form and contains within the range of from 50 - 500 mg of the active ingredient per dosage unit.

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