

PATENT SPECIFICATION

NO DRAWINGS

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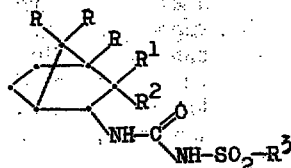
COMPLETE SPECIFICATION

Novel Sulphonamides and a Process for the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, 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 relates to novel sulphonamides and a process for the manufacture thereof. More particularly, the invention is concerned with novel sulphonyl-urea derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The novel sulphonyl-urea derivatives provided by the invention are compounds of the general formula



(1)

20 wherein R stands for a hydrogen atom or a methyl group, R¹ stands for a hydrogen atom and R² stands for a hydroxy group or R¹ and R² together stand for an oxo or ketal-

[Price 4s. 6d.]

25 ised oxo group and R³ stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benzamidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom, and salts thereof with pharmaceutically acceptable bases.

It will be appreciated that the term "lower alkyl" is used in the foregoing description and in the accompanying claims to mean a straight-chain or branched-chain alkyl group containing from 1 to 7 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl). The term "lower alkoxy" is used to mean lower-alkyl ether groups in which the lower-alkyl moiety has the foregoing meaning. The term "halogen" denotes bromine, iodine and chlorine with chlorine being preferred. The term "acylamino" denotes an aliphatic or aromatic acyl residue such as acetamino or benzylamino. The term "diacylamino" denotes, for example, phthalamido. A preferred substituted-benzamidoethylphenyl group is an alkoxy-halo-benzamidoethylphenyl group, especially the β -(2-methoxy-5-chloro-benzamido)-ethylphenyl group. The term "aryl" denotes a group such as phenyl or tolyl. Examples of 5- or 6-membered nitrogen-containing heterocyclic groups linked through nitrogen are piperidino and pyrrolidino.

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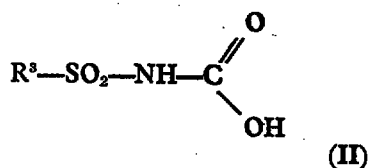
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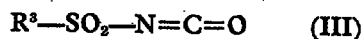
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An interesting class of novel sulphonyl-urea derivatives provided by the invention comprises those compounds of formula I in which R^3 stands for a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group. The preferred novel sulphonyl-urea derivatives provided by the invention are those in which R stands for a methyl group. Also preferred are those novel sulphonyl-urea derivatives in which R^1 stands for a hydrogen atom and R^2 stands for a hydroxy group or R^1 and R^2 together stand for an oxo group.

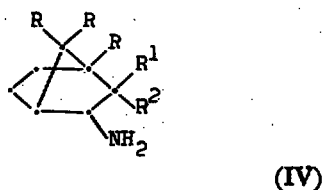
According to the process provided by the invention, the novel sulphonyl-urea derivatives are manufactured either (a) by reacting a reactive derivative of a sulphonylcarbamic acid of the general formula



or a sulphonylisocyanate of the general formula



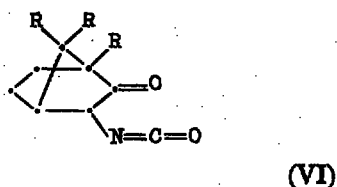
with a bicyclic amine of the general formula



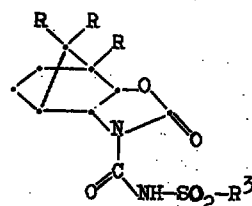
or (b) by reacting a salt of the amide of a sulphonic acid of the general formula



with a bicyclic isocyanate of the general formula

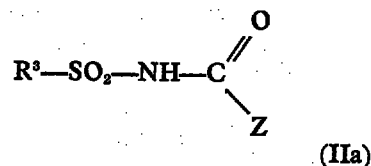


or a ketal thereof or (c) by treating an N-substituted oxazolidinone of the general



with an alkali-metal hydroxide and, if desired, reducing the ring-located keto group if present in the reaction product of embodiment (a) or (b) and separating the isomers obtained thereby or, if desired, oxidising any product which carries a hydroxy group or, if desired, saponifying any product which carries a ketalised oxo group and, also if desired, converting any product into a salt with a pharmaceutically acceptable base; in the foregoing formulae R , R^1 , R^2 and R^3 have the significance given earlier.

Thus, in accordance with one embodiment of the present process [embodiment (a)], the novel sulphonyl-urea derivatives can be manufactured by reacting a reactive derivative of a sulphonylcarbamic acid of formula II or a sulphonylisocyanate of formula III with a bicyclic amine of formula IV. The preferred reactive derivatives of a sulphonylcarbamic acid which can be used in this embodiment are those having the general formula



wherein R^3 has the significance given earlier and Z stands for a lower-alkoxy, aryloxy, lower-alkylthio, arylthio, imidazolyl-(1) or 3,5-di(lower alkyl)-pyrazolyl-(1) group. A preferred 3,5-di(lower alkyl)-pyrazolyl-(1) group is the 3,5-dimethyl-pyrazolyl-(1) group. Further, the substituent R^3 in the reactive derivative of the sulphonylcarbamic acid or the sulphonylisocyanate is suitably a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

According to one aspect of the foregoing embodiment a reactive derivative of formula IIa in which Z stands for the imidazolyl-(1) group (prepared *in situ*) is reacted with a bicyclic amine of formula IV. Conveniently, the corresponding sulphonamide or preferably



formula

an alkali-metal salt thereof is reacted with carbonyl-diimidazole in a suitable anhydrous organic solvent which is inert towards carbonyl compounds and which does not contain hydroxy groups and the sulphonylcarbamate acid imidazolid which is formed is then allowed to react *in situ* with a bicyclic amine of formula IV. Suitable organic solvents for this reaction are, for example, N,N-dimethyl-formamide, hydrocarbons such as benzene and halogenated hydrocarbons such as chloroform.

According to another embodiment of the present process [embodiment (b)], the novel sulphonyl-urea derivatives aforesaid are manufactured by reacting a salt of the amide of a sulphonic acid of formula V with a bicyclic isocyanate of formula VI or with a ketal thereof. A salt formed between the amide of a sulphonic acid and a strong base (for example, an alkali-metal salt such as the sodium salt) is conveniently used. Organic solvents of the type mentioned earlier which are inert towards the reactants can suitably be used in this embodiment. Examples of ketals which can be used in one aspect of this embodiment are dialkyl ketals (e.g. dimethyl and diethyl ketal) and alkylene ketals (e.g. ethylene ketal). An interesting class of salts of amides of sulphonic acids which can be used comprise those in which R³ represents a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

According to yet another embodiment of the present process [embodiment (c)], the novel sulphonyl-urea derivatives aforesaid are manufactured by treating an N-substituted oxazolidinone of formula VII with an alkali-metal hydroxide (e.g. sodium hydroxide or potassium hydroxide).

A ring-located keto group which may be present in the reaction product of embodiment (a) or (b) can be subsequently reduced to the hydroxyl group. This can be carried out, for example, by treatment with a complex metal hydride such as sodium borohydride or by catalytic hydrogenation. The *cis* and *trans* isomers which are obtained by the reduction can then, if desired, be separated according to known methods; for example, by crystallization or by chromatography. Further, a hydroxy group present in the reaction product can be oxidised to the keto group in a known manner; for example, by means of chromic acid. Again, any product which carries a ketalised oxo group can be saponified. The saponification can be carried out using acidic agents (for example, mineral acids such as hydrochloric acid), preferably in the presence of an organic solvent such as acetone.

The compounds of formula I hereinbefore form salts with pharmaceutically acceptable

bases, preferred among which are the alkali-metal bases such as sodium hydroxide, potassium hydroxide and the like.

The compounds of formula I hereinbefore can exist in various configurations, (for example, as a racemate or in optically active form) depending upon the stereochemistry of the starting materials of formulae IV or VI. Preferred starting materials of formulae IV and VI are those in which R represents a methyl group. Especially preferred are those which are derived configuratively from DL- or D-camphor or from D-borneol or D-isoborneol.

The bicyclic amines of formula IV can be prepared, for example, by converting the corresponding ketone into the isonitroso ketone (e.g. by treatment with amyl nitrite) and reducing the isonitroso ketone to the amino ketone (e.g. by means of zinc in caustic soda). The amino ketone thus obtained can, if desired, be ketalised or reduced to the amino alcohol. The ketalisation can be carried out, for example, by treatment with the corresponding alcohol in the presence of an anhydrous acid such as paratoluene-sulphonic acid. The reduction of the amino ketone to the amino alcohol can be carried out, for example, using sodium borohydride or by catalytic hydrogenation. The bicyclic isocyanates of formula VI can be obtained from the corresponding amino ketones or ketals by reaction with phosgene.

The N-substituted oxazolidinone starting materials of formula VII hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent No. 55,541/68 (now Serial No. 1155937) and can be prepared according to the process described and claimed therein.

The novel sulphonyl-urea derivatives provided by the invention are distinguished by their blood-sugar depressant activity on oral administration. Thus, they are useful as hypoglycaemic agents or as anti-diabetic agents and can be used as medicaments in the form of pharmaceutical preparations (e.g. tablets, capsules or dragees) which contain them in association with a compatible pharmaceutical carrier. The orally administerable pharmaceutical preparations can contain organic or inorganic carrier materials such as, for example, lactose, starch, talc and magnesium stearate. The pharmaceutical preparations can also contain other active ingredients, including other hypoglycaemic agents.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

13.6 g of 3-endoamino-D-borneol and 19.6 g of tosyl ethyl urethane are ground and mixed together. The mixture is heated with 4 ml of pyridine for 5 hours on a boiling

water-bath with occasional agitation. After cooling, the resulting yellow resin is dissolved at room temperature in 250 ml of 1-*N* sodium hydroxide. The resulting solution is shaken out three times with 50 ml of ether and the aqueous-alkaline phase is acidified with half-concentrated hydrochloric acid; an oil settles out. The mixture is allowed to stand at 0°C for *ca* 1 hour until the mother liquor is only slightly turbid. The supernatant liquid is then decanted off and the solidified residue is washed with *ca* 10 ml of water and recrystallized from alcohol/water to yield 11.5 g of 1-(*paratoluene*-sulphonyl) - 3 - (2 - endo - hydroxy - 3 - endo-*D*-bornyl)-urea of decomposition point 192°—195°C; $[\alpha]_D^{25} = 63.8^\circ$ (in ethanol).

EXAMPLE 2

1 g of *N*-(*paratoluenesulphonyl*)-carbamoyl) - endo - *D* - bornano[3',2':4,5] - oxazolinidone-(2) [prepared as described in the specification of our copending Application No. 55,541/68 (now Serial No. 1155937)] is suspended in 10 ml of 1-*N* sodium hydroxide solution and heated at reflux for 3 hours. The cooled solution is diluted with 20 ml of water; the oil which has separated is dissolved. The solution is then strongly acidified with 2-*N* hydrochloric acid. The precipitate which forms is removed by filtration, washed with water and recrystallized from alcohol/water to yield 1 - (*paratoluene* - sulphonyl) - 3 - (2 - endo - hydroxy-3-endo-*D*-bornyl)-urea identical with the product obtained in accordance with Example 1.

EXAMPLE 3

26 ml of *paratosyl* isocyanate are added dropwise with stirring to a solution of 20.3 g of 3-endo-amino-*D*-camphor hydrochloride in 150 ml of absolute *N,N*-dimethyl-formamide; the resulting mixture warms to *ca* 40°C. After cooling to 20°C, 28 ml of absolute triethyl amine are added dropwise over a period of 0.5 hour; the mixture once again warms to *ca* 40°. It is cooled and stirred at 20°C for an additional 15 hours. The *N,N*-dimethyl-formamide and the excess of triethyl amine are removed *in vacuo*. The semi-solid residue is treated with 500 ml of 0.5-*N* sodium hydroxide and shaken until dissolved. The resulting solution is shaken out with two 100 ml portions of ether, filtered and acidified with dilute hydrochloric acid. The precipitate which forms is removed by filtration, washed with ice-water, pressed out and recrystallized from methanol/water (*ca* 300 ml of methanol and 50 ml of water. After vacuum drying to a constant weight at 100°C, there are obtained 24.4 g (67% of the theory) of 1 - (*paratoluene* - sulphonyl - 3 - (3 - endo - *D* - camphoryl) - urea of decomposition point 190°C.

EXAMPLE 4

1.06 g of the sodium salt of *paratoluene*-sulphonamide are suspended in 30 ml of absolute *N,N*-dimethyl-formamide and treated at 20°C with 0.97 g of *D*-camphoryl-(3) isocyanate, with stirring until dissolved. The resulting solution is stirred at 20°C for an additional 15 hours, the solvent is evaporated and the oily residue is dissolved in 20 ml of 0.5-*N* sodium hydroxide. The alkaline solution is acidified with dilute hydrochloric acid and the resulting precipitate is isolated, washed with water and recrystallized from methanol/water to yield 1.6 g (88% of the theory) of 1-(*paratoluene*-sulphonyl) - 3 - (3 - endo - *D* - camphoryl) - urea of decomposition point 190°C. The infrared spectrum of this product is identical with that of the product obtained in accordance with Example 3.

EXAMPLE 5

10 g of 1 - (*paratoluene* - sulphonyl) - 3 - (3 - endo - *D* - camphoryl) - urea are dissolved in 120 ml of dilute sodium hydroxide solution (1.4 g of sodium hydroxide in 120 ml of water), treated with 3 g of sodium borohydride (about 71%) and stirred at 20°C for 15 hours. The resulting strongly alkaline solution is carefully acidified with dilute acetic acid. After an initial evolution of hydrogen the desired product precipitates. The product is isolated, washed with ice-water, recrystallized from alcohol/water and dried to constant weight to yield 6.5 g of 1 - (*paratoluene* - sulphonyl) - 3 - (2 - endo - hydroxy - 3 - endo - *D* - bornyl) - urea which can be purified further by recrystallization. After two recrystallizations from acetone/(petroleum ether), there is obtained 1-(*paratoluene* - sulphonyl) - 3 - (2 - endo - hydroxy - 3-endo-*D*-bornyl)-urea of decomposition point 193°C; $[\alpha]_D^{25} = 63.8^\circ$ (in ethanol).

EXAMPLE 6

1 g of a mixture of 3-endo-tosylureido-(*D*-borneol-isoborneol) isomers (according to specific rotation, 58% *cis* and 42% *trans*) is dissolved in 10 ml of absolute acetone and treated dropwise with stirring at room temperature with an amount of chromic acid standard solution (26.7 g of chromium trioxide dissolved in 23 ml of concentrated sulphuric acid and sufficient water to make 100 ml of solution) sufficient to colour the supernatant solution orange-brown. The resulting mixture is diluted with 80 ml of water to dissolve the green chromium salts present. The crystalline oxidation product is removed by filtration, washed well with water and recrystallized from methanol/water to yield 0.83 g (83% of the theory) of 1-(*paratoluene*-sulphonyl) - 3 - (3 - endo - *D* - camphoryl) - urea. The infrared spectrum of the product

is identical with that of the product obtained in accordance with Example 3.

EXAMPLE 7

A) The preparation of the starting material:

15 g of isonitroso-*D,L*-camphor are dissolved in 120 ml of sodium hydroxide solution (15 g of sodium hydroxide). The solution is charged with 18 g of zinc dust. The resulting oily 3-endo-amino-*D,L*-camphor is dissolved in ether, and the ethereal solution is dried with potassium carbonate, then treated with a saturated ethereal solution of hydrogen chloride up to a strongly acidic reaction. The resulting precipitate is separated and washed with divided portions of ether to yield 13.5 g of 3-endo-amino-*D,L*-camphor hydrochloride of decomposition point 227°C.

B) The process:

13.5 g of 3-endo-amino-*D,L*-camphor hydrochloride are reacted with 15 ml of *para*-tosyl isocyanate according to the procedure of Example 3 to yield 15.3 g of 1-(*para*-toluene-sulphonyl)-3-(3-endo-*D,L*-camphoryl)-urea of decomposition point 164°C.

By reduction of 1-(*para*-toluene-sulphonyl)-3-(3-endo-*D,L*-camphoryl)-urea in a manner analogous to that described in Example 5 there is obtained 1-(*para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-*D,L*-bornyl)urea of decomposition point 189°C [after recrystallization from acetone/(petroleum ether)].

EXAMPLE 8

A) The preparation of the starting material:

In a manner analogous to that described in J. Org. Chem., 1963, 28, 304, from *L*-camphor there is obtained 3-isonitroso-*L*-camphor. This is converted in accordance with the procedure of Example 7A into 3-endo-amino-*L*-camphor, which is obtained as an ethereal solution of the crude product. This ethereal solution is reacted with a methanolic solution of *D*-camphor-10-sulphonic acid. The salt which precipitates, 3-endo-amino-*L*-camphor *D*-camphor-10-sulphonate, has a decomposition point of 199°C; $[\alpha]_D^{20} = 14.8^\circ$ (in methanol, $c=6$).

B) The process:

15 g of 3-endo-amino-*L*-camphor *D*-camphor-10-sulphonate are reacted with 15 ml of *para*-tosyl isocyanate in a manner analogous to that described in Example 3 to yield 10.4 g of 1-(*para*-toluene-sulphonyl)-3-(3-endo-*L*-camphoryl)-urea of decomposition point 190°C; $[\alpha]_D^{20} = 17.5^\circ$ (in chloroform, $c=3$).

By reduction of 1-(*para*-toluene sulphonyl)-3-(3-endo-*L*-camphoryl)-

urea in a manner analogous to that described in Example 5 there is obtained 1-(*para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-*L*-bornyl)-urea of decomposition point 193°C; $[\alpha]_D^{20} = -62.5^\circ$ (in ethanol, $c=4$).

EXAMPLE 9

1 g of 39-endo-amino-*D*-isoborneol, 1.3 g of tosyl ethyl urethane and 12 drops of absolute pyridine are heated on a boiling water-bath with occasional agitation for 7 hours. The resulting mixture is dissolved in 30 ml of 0.5-N sodium hydroxide. The solution obtained is extracted with two 20 ml portions of ether and the aqueous phase is acidified with half-concentrated hydrochloric acid. The product which separates out is taken up in ether and the ethereal solution is evaporated. The residue is recrystallized from acetone/(petroleum ether) to yield 0.75 g of 1-(*para*-toluene-sulphonyl)-3-(2-exo-hydroxy-3-endo-*D*-bornyl)-urea of melting point 158°C; $[\alpha]_D^{20} = 34.4^\circ$ ($c=3$ in methanol).

EXAMPLE 10

A) The preparation of the starting material:

Sodium *tert*butylate prepared from 24 g of 50% sodium hydride and 150 ml of *tert*-butanol is introduced at -10°C into a solution of 17.5 g of *D,L*-norcamphor and 32.5 g of amyl nitrite in 150 ml of benzene and 50 ml of absolute ether; the temperature of the reaction mixture is not allowed to rise above about -8°C . The mixture is thereafter stirred at -10°C for 1 hour and allowed to stand overnight at -5°C . The mixture is then added to 500 ml of ice-water, and the aqueous phase is washed with two 300 ml portions of ether and acidified with cold dilute hydrochloric acid. The oily 3-isonitroso-*D,L*-norcamphor is extracted with ether, and the ether solution is dried over sodium sulphate and evaporated.

A solution of 27.5 g of the foregoing 3-isonitroso-*D,L*-norcamphor in 100 ml of absolute ether is added dropwise to a suspension of 15 g of lithium aluminium hydride in 400 ml of ether. The resulting mixture is allowed to boil for 4 hours and then is decomposed by the addition of water. The resulting solution is mixed with dilute potassium hydroxide solution. The ether phase is decanted off and the desired product is precipitated with ethereal hydrochloric acid. The precipitate is filtered off and recrystallized from alcohol/acetone to yield 3-endo-amino-*D,L*-norborneol hydrochloride of melting point 255°-260°C (with decomposition).

B) The process:

3-Endo-amino-*D,L*-norborneol is reacted with *para*-tosyl ether urethane in a

manner analogous to that described in Example 1 to yield 1-(*paratoluene-sulphonyl*)-3-(2-endo-hydroxy-3-endo-*D,L*-norbornyl)-urea of melting point 196°—198°C (from acetone).

EXAMPLE 11

A) The preparation of the starting material:

5.05 g of 3-isonitroso-*D,L*-norcamphor (prepared as described in the first paragraph of Example 10A) are dissolved in a solution of 10 g of sodium hydroxide in 60 ml of water. 15 g of zinc dust are then added over a 15-minute period. 0.25 hour thereafter, 150 ml of ether are added and the mixture is stirred for 10 minutes. The ethereal solution is decanted and the desired product is precipitated with ethereal hydrochloric acid. The precipitate is recrystallized from alcohol/acetone and alcohol/ether to yield 3-endo-amino-*D,L*-norcamphor hydrochloride of melting point 171°—174°C.

B) The process:

A solution of 1.4 g of *paratosyl* isocyanate in 3 ml of *N,N*-dimethyl-formamide is added to a solution of 1.1 g of 3-endo-amino-*D,L*-norcamphor hydrochloride in 5 ml of *N,N*-dimethyl-formamide. The resulting solution is allowed to stand at 20°C for 3 hours, then is cooled with ice and added to 20 ml of 1-*N* sodium hydroxide solution. The mixture is extracted with ether. The aqueous phase is acidified with dilute acetic acid and there crystallizes 1-(*paratoluene-sulphonyl*)-3-(3-endo-*D,L*-norcamphor)-urea of melting point 202°C (from ethanol/water).

EXAMPLE 12

3.5 g of *N*-(*paratoluenesulphonyl*-carbamoyl)-endo-*D,L*-norbornano[3',2':4,5]-oxazolidinone-(2) [prepared as described in the specification of our copending Application No. 55,541/68 (now Serial No. 1155937)] in 70 ml of 1-*N* sodium hydroxide solution are heated on a water-bath for 3 hours. Upon cooling, the solution is acidified with dilute acetic acid and the resulting precipitate is crystallized from ethyl acetate to yield 1-(*paratoluene-sulphonyl*)-3-(2-endo-hydroxy-3-endo-*D,L*-norbornyl)-urea identical with that obtained as described in Example 10B.

Oxidation of 1-(*paratoluene-sulphonyl*)-3-(2-endo-hydroxy-3-endo-*D,L*-norbornyl)-urea with chromic acid in a manner analogous to that described in Example 6 yield 1-(*paratoluene-sulphonyl*)-3-(3-endo-*D,L*-norcamphoryl)-urea identical with that obtained as described in Example 11B.

EXAMPLE 13

20.3 g of 3-endo-amino-*D*-camphor hydro-

chloride are dissolved in 150 ml of *N,N*-dimethyl-formamide and treated with 26 ml of 4-chloro-benzenesulphonyl isocyanate; the temperature rises to 42°C as the reaction proceeds. The mixture is then allowed to cool to 20°C and 28 ml of triethyl amine are added dropwise thereto with stirring; the temperature again rises to 40°C. The mixture is cooled and stirred at room temperature for 15 hours. The solvent is then removed by evaporation *in vacuo* and the residue is dissolved in 0.5-*N* sodium hydroxide. The resulting solution is shaken out twice with ether and acidified with hydrochloric acid. The crystals which form are removed by filtration, washed with water and dried *in vacuo* at 50°C to yield 1-(4-chloro-benzenesulphonyl)-3-(3-endo-*D*-camphoryl)-urea of melting point 187°—189°C (from acetonitrile); $[\alpha]_D^{25} = -29.4^\circ$ ($c=3$ in chloroform).

EXAMPLE 14

45 g of the sodium salt of 4-methylthio-benzenesulphonamide in 200 ml of *N,N*-dimethyl-formamide are stirred at -10°C with 39.2 g of carbonyl-diimidazole and 49.7 g of 3-endo-amino-*D*-camphor hydrochloride. After complete reaction, the solvent is removed by distillation *in vacuo* and the residue is dissolved in 1-*N* sodium hydroxide. The resulting solution is extracted with ether and made congo-acid with hydrochloric acid to yield 1-(4-methylthio-benzenesulphonyl)-3-(3-endo-*D*-camphoryl)-urea which, after recrystallization from butyl acetate, has a melting point of 183°—185°C; $[\alpha]_D^{25} = -42.6^\circ$ ($c=3$ in chloroform).

EXAMPLE 15

A solution of 8 g of *D*-camphoryl-(3)-isocyanate in 80 ml of absolute benzene is mixed with 7.5 g of 1-sulphamyl-piperidine and 6 ml of triethyl-amine and the mixture is heated at reflux temperature for 3 hours, then allowed to stand at 20°C for a period of 20 hours. The benzene is subsequently removed by evaporation and the residue is dissolved in 150 ml of 0.5-*N* sodium hydroxide solution. The alkaline solution is extracted with ether and then acidified with hydrochloric acid to a strong acid reaction. The precipitate which forms is recrystallized from ethanol/water to yield 7 g of 1-(piperidino-sulphonyl)-3-(3-endo-*D*-camphoryl)-urea of decomposition point 190°C; $[\alpha]_D^{19} = -5.2^\circ$ (in chloroform, $c=1.5$).

EXAMPLE 16

4.8 g of 50% sodium hydride are suspended in 100 ml of *N,N*-dimethyl-formamide and reacted with stirring, with 38.6 g of 4-[2-(2-methoxy-5-chloro-benzamido)-ethyl]-benzenesulphonamide. After stirring at room temperature for 1 hour, the resulting solution is cooled to -10°C and

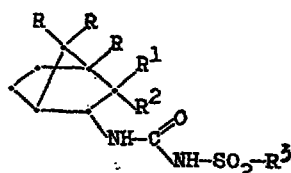
mixed portionwise with 20.3 g of carbonyl-diimidazole. The mixture is stirred at -10°C for a period of 3 hours, then 20.3 g of 3-endo-amino-D-camphor hydrochloride are added. The temperature of the mixture is allowed to rise slowly to room temperature, then the mixture is stirred overnight. The solvent is subsequently removed by distillation *in vacuo* at 65°C and the residue is dissolved in 2,000 ml of 0.1-N sodium hydroxide solution. The resulting solution is extracted with 500 ml of ether and the aqueous-alkaline solution is acidified with 3-N hydrochloric acid to a congo-acid reaction. The separated oil is extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried over sodium sulphate, filtered and dried *in vacuo*. The residue is crystallized from butyl acetate to yield 34 g of 1-[4-[2-(2-methoxy-5-chloro-benzamido)-ethyl]-benzene-sulphonyl]-3-(3-endo-D-camphoryl)-urea.

The following Example illustrates pharmaceutical preparations containing the novel derivatives provided by the invention:

Tablets each containing 50 mg of 1-(*para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-D-bornyl)-urea, 90 mg of microcrystalline cellulose, 9.9 mg of corn starch and 0.1 mg of magnesium stearate and each having a total weight of 150 mg are prepared utilising conventional procedures.

WHAT WE CLAIM IS:—

1) A compound of the general formula



wherein R stands for a hydrogen atom or a methyl group, R¹ stands for a hydrogen atom and R² stands for a hydroxyl group or R¹ and R² together stand for an oxo or ketalised oxo group and R³ stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benz-amidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom, and salts thereof with pharmaceutically acceptable bases.

2) A compound as formulated in claim 1, wherein R³ stands for a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

3) A compound as formulated in claim 1 or as set forth in claim 2, wherein R stands for a methyl group.

4) A compound as set forth in claim 3, wherein R¹ stands for a hydrogen atom and R² stands for a hydroxy group.

5) A compound as set forth in claim 3, wherein R¹ and R² together stand for an oxo group.

6) 1-(*Para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-D,L-bornyl)-urea.

7) 1-(*Para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-L-bornyl)-urea.

8) 1-(*Para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-D-bornyl)-urea.

9) 1-(*Para*-toluene-sulphonyl)-3-(3-endo-D,L-camphoryl)-urea.

10) 1-(*Para*-toluene-sulphonyl)-3-(3-endo-L-camphoryl)-urea.

11) 1-(*Para*-toluene-sulphonyl)-3-(3-endo-D-camphoryl)-urea.

12) 1-(4-Chloro-benzenesulphonyl)-3-(3-endo-D-camphoryl)-urea.

13) 1-(4-Methylthio-benzenesulphonyl)-3-(3-endo-D-camphoryl)-urea.

14) 1-(*Para*-toluene-sulphonyl)-3-(2-exo-hydroxy-3-endo-D-bornyl)-urea.

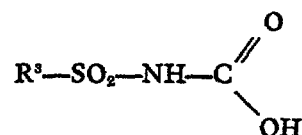
15) 1-(*Para*-toluene-sulphonyl)-3-(3-endo-D,L-norcamphoryl)-urea.

16) 1-(*Para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-D,L-norbornyl)-urea.

17) 1-(Piperidino-sulphonyl)-3-(3-endo-D-camphoryl)-urea.

18) 1-[4-(2-Methoxy-5-chloro-benzamido)-ethyl]-benzenesulphonyl-3-(3-endo-D-camphoryl)-urea.

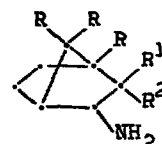
19) A process for the manufacture of the derivatives claimed in claim 1, which process comprises either (a) reacting a reactive derivative of a sulphonylcarbamic acid of the general formula



or a sulphonylisocyanate of the general formula



with a bicyclic amine of the general formula



or (b) reacting a salt of the amide of a sulphonic acid of the general formula

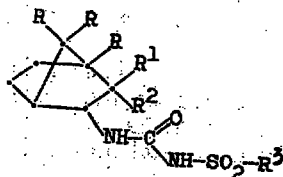
mixed portionwise with 20.3 g. of carbonyl-diimidazole. The mixture is stirred at -10°C for a period of 3 hours, then 20.3 g of 3-endo-amino-*D*-camphor hydrochloride are added. The temperature of the mixture is allowed to rise slowly to room temperature, then the mixture is stirred overnight. The solvent is subsequently removed by distillation *in vacuo* at 65°C and the residue is dissolved in 2,000 ml of 0.1-N sodium hydroxide solution. The resulting solution is extracted with 500 ml of ether and the aqueous-alkaline solution is acidified with 3-N hydrochloric acid to a congo-acid reaction. The separated oil is extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried over sodium sulphate, filtered and dried *in vacuo*. The residue is crystallized from butyl acetate to yield 34 g of 1-[4-[2-(2-methoxy-5-chloro-benzamido)-ethyl]-benzene-sulphonyl]-3-(3-endo-*D*-camphoryl)-urea.

The following Example illustrates pharmaceutical preparations containing the novel derivatives provided by the invention:

Tablets each containing 50 mg of 1-(*para*-toluene-sulphonyl)-3-(2-endo-hydroxy-3-endo-*D*-bornyl)-urea, 90 mg of microcrystalline cellulose, 9.9 mg of corn starch and 0.1 mg of magnesium stearate and each having a total weight of 150 mg are prepared utilising conventional procedures.

WHAT WE CLAIM IS:—

1) A compound of the general formula



wherein R stands for a hydrogen atom or a methyl group, R^1 stands for a hydrogen atom and R^2 stands for a hydroxyl group or R^1 and R^2 together stand for an oxo or ketalised oxo-group and R^3 stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benz-amidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom, and salts thereof with pharmaceutically acceptable bases.

2) A compound as formulated in claim 1, wherein R^3 stands for a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

3) A compound as formulated in claim 1 or as set forth in claim 2, wherein R stands for a methyl group.

4) A compound as set forth in claim 3, wherein R^1 stands for a hydrogen atom and R^2 stands for a hydroxy group.

5) A compound as set forth in claim 3, wherein R^1 and R^2 together stand for an oxo group.

6) 1-(*Paratoluene*-sulphonyl)-3-(2-endo-hydroxy-3-endo-*D,L*-bornyl)-urea.

7) 1-(*Paratoluene*-sulphonyl)-3-(2-endo-hydroxy-3-endo-*L*-bornyl)-urea.

8) 1-(*Paratoluene*-sulphonyl)-3-(2-endo-hydroxy-3-endo-*D*-bornyl)-urea.

9) 1-(*Paratoluene*-sulphonyl)-3-(3-endo-*D,L*-camphoryl)-urea.

10) 1-(*Paratoluene*-sulphonyl)-3-(3-endo-*L*-camphoryl)-urea.

11) 1-(*Paratoluene*-sulphonyl)-3-(3-endo-*D*-camphoryl)-urea.

12) 1-(4-Chloro-benzenesulphonyl)-3-(3-endo-*D*-camphoryl)-urea.

13) 1-(4-Methylthio-benzenesulphonyl)-3-(3-endo-*D*-camphoryl)-urea.

14) 1-(*Paratoluene*-sulphonyl)-3-(2-exo-hydroxy-3-endo-*D*-bornyl)-urea.

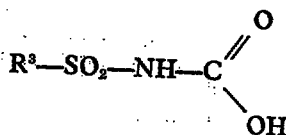
15) 1-(*Paratoluene*-sulphonyl)-3-(3-endo-*D,L*-norcamphoryl)-urea.

16) 1-(*Paratoluene*-sulphonyl)-3-(2-endo-hydroxy-3-endo-*D,L*-norbornyl)-urea.

17) 1-(Piperidino-sulphonyl)-3-(3-endo-*D*-camphoryl)-urea.

18) 1-[4-[2-(2-Methoxy-5-chloro-benzamido)-ethyl]-benzenesulphonyl]-3-(3-endo-*D*-camphoryl)-urea.

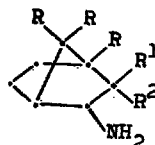
19) A process for the manufacture of the derivatives claimed in claim 1, which process comprises either (a) reacting a reactive derivative of a sulphonylcarbamic acid of the general formula



or a sulphonylisocyanate of the general formula



with a bicyclic amine of the general formula

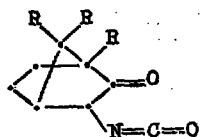


or (b) reacting a salt of the amide of a sulphonic acid of the general formula

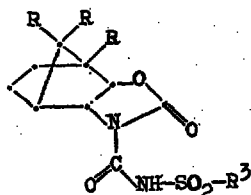




with a bicyclic isocyanate of the general formula



- 5 or a ketal thereof or (c) treating an N-substituted oxazolidinone of the general formula



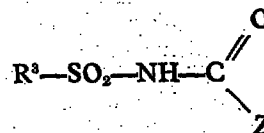
- 10 with an alkali-metal hydroxide and, if desired, reducing the ring-located keto group if present in the reaction product of embodiment (a) or (b) and separating the isomers obtained thereby or, if desired, oxidising any product which carries a hydroxy group or if desired, saponifying any product which carries a ketalised oxo group and, also if desired, converting any product into a salt with a pharmaceutically acceptable base; in the foregoing formulae R, R¹, R² and R³ have the significance given in claim 1.

- 20 20) A process as set forth in claim 19, wherein either a reactive derivative of a sulphonylcarbamic acid of the formula first written in that claim or a sulphonylisocyanate of the formula second written in that claim is reacted with a bicyclic amine of the formula third written in that claim or a salt of the amide of a sulphonic acid of the formula fourth written in that claim is reacted with a bicyclic isocyanate of the formula fifth written in that claim or a ketal thereof.

- 30 21. A process as set forth in claim 20, wherein R³ in said reactive derivative, sul-

phonylisocyanate or salt stands for a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group. 35

- 22) A process as set forth in any one of claims 19 to 21 inclusive, wherein said reactive derivative is a compound of the general formula 40



wherein R³ has the significance given in claim 19 or in claim 21 and Z stands for a lower-alkoxy, aryloxy, lower-alkylthio, arylthio, imidazolyl-(1) or 3,5-di(lower alkyl)-pyrazolyl-(1) group. 45

- 23) A process as set forth in claim 22 insofar as said reactive derivative is an imidazolidine, wherein same is reacted with the bicyclic amine of the formula third written in claim 18 without isolating said imidazolidine from the medium in which it is prepared. 50

- 24) A process as set forth in any one of claims 19 to 23 inclusive, wherein said bicyclic amine is 3-endo-amino-D,L-camphor, 3-endo-amino-D-camphor, 3-endo-amino-D-borneol or 3-endo-amino-D-isoborneol. 55

- 25) A process as set forth in claim 19, wherein said alkali-metal hydroxide is sodium hydroxide or potassium hydroxide. 60

- 26) A process for the manufacture of the derivatives claimed in claim 1 substantially as described with reference to Examples 1 to 16. 65

- 27) Derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 19 to 26 inclusive.

- 28) A pharmaceutical preparation comprising a derivative as set forth in claim 1 in association with a compatible pharmaceutical carrier. 70

W. D. WHITAKER
Patent Agent

for F. Hoffmann-la Roche & Co.,
Aktiengesellschaft.

