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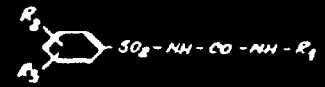
Manufacture of New Sulphonyl-Ureas

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a body corporate recognised under German law, of Frankfurt(M)-Höchst, Germany, 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:—

It is known from literature that certain compounds belonging to the class of aminobenzene sulphonamides are capable of lowering the blood sugar value in test animals, for example, of dogs. Thus, for example, para-aminobenzene-sulphonamido - isopropyl - thiadiazole produces a moderate lowering of the blood sugar value in dogs for 4 to 6 hours (compare: Jean La Barre and Jean Reuse, Arch. Neerland. physiol. *28* [1947] page 475). These compounds, however, have a bacteriostatic action, and have not been proposed as being suitable for the treatment of diabetes mellitus in human beings.

There are also known certain benzene-sulphonyl ureas, such as N-benzenesulphonyl-urea, N-benzenesulphonyl-N'-phenyl-urea, N-benzenesulphonyl - N':N'-diethyl - urea, N-paratoluenesulphonyl - urea and N - paratoluenesulphonyl - N'-phenyl-urea (compare: Chem. Rev., volume 50 pages 28/29). These substances have not yet attained any commercial importance, and have found no application in lowering the blood sugar level in the treatment of diabetes mellitus.

The present invention provides sulphonyl-ureas of the general formula



in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 2 to 8 carbon atoms, and R_3 and R_4 each represent hydrogen or an alkyl or alkoxy group containing at most 6 carbon atoms; and salts of such compounds with bases yielding physiologically tolerable salts with the compounds.

The residue containing R_3 and R_4 may be, for example, a phenyl, methyl-phenyl, more especially para-methyl-phenyl, ethyl-phenyl, propyl-phenyl, butyl-phenyl, pentyl-phenyl or hexyl-phenyl group. The alkyl substituent may be unbranched or branched, and may preferably be bound in the para-position of the phenyl radical or in other positions, more especially in the meta-position. There may also be mentioned disubstituted phenyl radicals, such as dialkyl-, dialkoxy- or alkyl-alkoxyphenyl groups. The substituents may be bound in any desired position to the benzene nucleus.

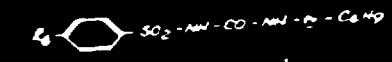
R_1 may be, for example, an ethyl, propyl, allyl, butyl, butenyl, pentyl, hexyl, cyclohexyl or hexahydro-benzyl group. Also in this case, the aliphatic residues may have straight or branched chains.

Among the compounds of the above general formula there may be mentioned more especially those in which R_1 represents an aliphatic or cycloaliphatic radical containing from 3 to 5 carbon atoms; also compounds of the general formula

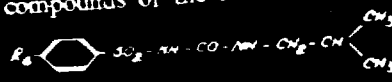


in which R_2 has the meaning given above and R_5 represents an aliphatic or cycloaliphatic hydrocarbon radical containing two to eight, especially three to five, carbon atoms; compounds of the formula

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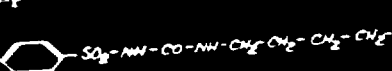
and compounds of the formula



in which R_4 represents an alkyl group containing at most 6 carbon atoms; compounds of the formula



in which R_4 has the meaning given above; and compounds of the formula



in which R_4 has the meaning given above. Especially advantageous is the compound N - 4 - methyl-benzenesulphonyl-N'-*n*-butyl-urea.

The compounds of the above general formula are made by methods in themselves known for making sulphonyl-ureas. As examples the following processes may be mentioned:

A benzenesulphonyl isocyanate, which may be alkylated or alkoxylated, may be reacted with a primary butylamine or another primary alkylamine or an alkenylamine, cycloalkylamine or cycloalkyl-alkylamine containing 2 to 8 carbon atoms. Conversely, the desired sulphonyl-urea can be made by reacting a butyl isocyanate or other appropriate isocyanate with a benzene-sulphonamide, which may be alkylated or alkoxylated, advantageously in the form of a salt thereof. Instead of isocyanates there may be used compounds convertible into isocyanates in the course of the reaction, such as acid azides, for example, valeric acid azide. In another process for making the new compounds there are used, instead of isocyanates, urethanes, and any desired carbamic acid ester, such as methyl, ethyl, propyl, butyl or aryl esters, can be used for this purpose. For example, a benzene sulphonyl-urethane, which may be alkylated or alkoxylated in the benzene nucleus, may be reacted, for example, with butylamine or another primary amine, or, conversely, an alkyl-urethane may be reacted with an appropriate benzene-sulphonamide, advantageously in the form of a salt thereof. Carbamic acid halides can also be used with special advantage. Thus, for example, the new sulphonyl-ureas are formed by reacting a butylcarbamic acid chloride with a benzene sulphonamide, which may be alkylated or alkoxylated, or by reacting a benzene sulphonyl-carbamic acid chloride with a butyl amine or another primary amine. In a further process a benzene sulphonyl-urea, which is unsubstituted in the $-NH_2$ group, is converted into a benzene sulphonyl-alkyl-urea, for example, with butylamine. Alternatively, an alkyl-urea may be reacted with a benzene-sulphonamide. Instead of the alkyl-ureas other derivatives may be used. Furthermore, instead of the alkyl-ureas there may be used the corresponding iso-urea ethers, advantageously in the form of their salts, and they are reacted with benzene sulphonic acid chlorides, and the product so obtained is then converted by acid hydrolysis into the desired sulphonyl-urea.

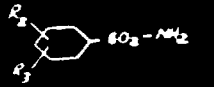
In further processes for making the new compounds the corresponding thiourea is first prepared, and sulphur is eliminated therefrom in a conventional manner; or an N-benzene sulphonyl-N'-alkyl-guanidine is prepared in known manner (for example, by reacting a benzenesulphonyl-cyanamide with a butylamine or with another primary amine), and the resulting guanidine is then hydrolysed. In all cases there may be used, instead of the unsubstituted benzenesulphonyl compound, an alkyl- or alkoxy-benzenesulphonyl compound; and, instead of butylamine, another primary alkylamine, or an alkenylamine, cycloalkylamine or cycloalkyl-alkyl-amine may be used. In these reactions the components must be so chosen that the radical R_1 in the product contains 2 to 8 carbon atoms especially 3 to 5 carbon atoms.

As alkyl residues, of which one or two may be present as substituents in the phenyl radical, and bound, if desired, through an oxygen atom, there are used those containing 1 to 6 carbon atoms. When these residues are of higher molecular weight the activity of the products is generally considerably lower.

The primary amines used as starting materials in the above processes advantageously contain saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals containing 2 to 6 carbon atoms, especially 3 to 5 carbon atoms. However, they may contain radicals of higher molecular weight, but radicals containing more than 8 carbon atoms generally reduce the activity of the products.

The reaction conditions under which the aforesaid processes are carried out may vary within wide limits and are adapted to each particular case. For example, the reactions may be carried out with the use of solvents at room temperature or at a higher temperature. Particularly suitable are the following processes:

(1) The reaction of a compound of the general formula



in which R_2 and R_3 have the meanings given

above, and advantageously in the form of an alkali metal salt, with an isocyanate of the general formula R_1-NCO in which R_1 has the meaning given above, in the presence of a solvent, for example, nitrobenzene or acetone, at the ordinary or a higher temperature.

(2) The reaction of a benzene sulphonyl-carbamic acid ester of the general formula



in which R_2 and R_3 have the meaning given above, and R_4 represents any desired, preferably lower, hydrocarbon residue, with an equivalent quantity of an amine of the formula R_1-NH_2. In this case it is advantageous to conduct the reaction at a temperature within the range of 100°C to 140°C.

To obtain the products in as pure a state as possible, it is advantageous to separate the product thoroughly from the benzene sulphonamide used as starting material or formed in the course of the reaction. Advantageously, this is carried out taking up the product in dilute ammonia (1 part by volume of ammonia to 20—30 parts by volume of water), since the sulphonamides are generally sparingly soluble in this medium at room temperature.

Many of the starting materials suitable for use in the present process have been described in literature. There may be mentioned, for example, benzene-sulphonamide, 4-methyl-benzene-sulphonamide, 4-ethyl-benzene-sulphonamide, 4 - *n* - propyl-benzene-sulphonamide, 4-isopropyl-benzene-sulphonamide, 4-*n* - butyl-benzene-sulphonamide, 4 - isobutyl-benzene - sulphonamide, 4-methoxy-benzene-sulphonamide and 4 - ethoxy - benzene-sulphonamide. Examples of suitable corresponding isocyanates and carbamic acid esters are: benzene - sulphonyl isocyanate 4 - methyl - benzenesulphonyl isocyanate, 4 - ethoxy - benzenesulphonyl isocyanate, 4 - methyl - benzenesulphonyl ethyl carbamate and 4 - ethoxy - benzenesulphonyl-methyl carbamate. Instead of compounds substituted in the 4-position of the benzene nucleus, there may be used the corresponding compounds substituted in the 2-position or more especially in the 5-position.

Further suitable starting materials are the correspondingly substituted benzenesulphonyl-urethanes containing in the urethane component an alkyl radical having up to 6 carbon atoms, for example, a methyl, ethyl, propyl or butyl group, and more especially a methyl group, or an aryl radical; correspondingly substituted benzenesulphonyl-ureas; and correspondingly substituted benzene sulphonic acid halides.

There may also be used as starting materials, for example, dimethyl benzene-sulphonyl compounds in the form of the chlorides, amides, isocyanates, carbamic acid halides, carbamic acid esters or ureas, or the corresponding dimethoxy-benzenesulphonyl compounds or methoxy-methyl-benzene-sulphonyl derivatives. Instead of the methyl group, an ethyl, propyl, butyl or an alkyl group containing up to 6 carbon atoms may be present.

For the reaction with the compounds mentioned above there may be used the following primary amines; as alkylamines there may be mentioned, for example, ethylamine, *n*-propyl-amine, isopropylamine, *n*-butylamine isobutyl-amine, secondary butylamine, tertiary butyl-amine pentylamine-(1), pentylamine-(2), pentylamine-(3), 3-methylbutylamine-(1), 2-methyl-butylamine-(1), 2:2-dimethyl-propyl-amine-(1), 3-methyl-butylamine-(2), hexyl-amines such as hexylamine-(1) and 2-methyl-pentylamine-(1), heptylamines such as heptyl-amine-(1) and heptylamine-(4), and octyl-amines such as octylamine-(1).

There may be mentioned as examples of alkenylamines, allylamine and crotylamine; as cycloalkylamines, cyclohexylamine and cyclopentylamine; and as cycloalkyl-alkyl-amines, cyclohexyl-methylamine and cyclo-ethylamine.

Instead of using the aforesaid amines, the corresponding isocyanates, urethanes, carbamic acid halides, ureas or isourea ethers (obtainable from the aforesaid amines) may be reacted with suitably substituted benzene sulphonamides or halides.

When the synthesis of the desired sulphonyl-urea starts from a corresponding thio-urea, for example, from N-4-methyl- or N-4 - methoxy - benzenesulphonyl - N' - alkyl-, alkenyl-, -cycloalkyl- or -cycloalkylalkyl-thio-ureas, the hydrocarbon radicals of which contain 2 to 8 carbon atoms, the sulphur may be eliminated with a heavy metal oxide or a salt thereof, for example, an oxide or salt of lead, copper or silver, in an aqueous or alcoholic solution.

Alternatively, the desired sulphonyl-urea can be prepared by hydrolysing an appropriately constituted guanidine with an alkaline solution.

The products of the invention have been extensively tested; all those specifically mentioned in the present specification have given satisfactory results in experiments on animals and/or clinical tests on human beings demonstrating that the products produce a substantial and useful lowering of the blood sugar level and are well tolerated.

The products may be used as such or in the form of their salts, or in the presence of substances that cause salt formation. For salt formation there are used bases which yield physiologically tolerated salts with the compounds, for example, ammonia, an alkaline substance such as an alkali metal or alkaline earth metal hydroxide, an alkali metal carbonate or bicarbonate, or a suitable organic base. The compounds can be made up, inter

alia, into preparation suitable for oral administration and lowering the blood sugar in the treatment of diabetes mellitus.

As is well known and practised in the art such preparations may comprise tablets, pills, capsules, cachets, mixtures, solutions or powders. The compounds are preferably made up in admixture or conjunction with an adjuvant facilitating the administration of the compound, for example, in admixture with a pharmaceutical organic or inorganic carrier material suitable for oral arministration.

The pharmaceutical preparations can be made up enveloping a suitable dosage quantity, for example, 0.5 grams, of the sulphonyl urea compound; and it is to be understood that the present invention includes such preparations which comprise a sulphonyl-urea compound or salt thereof in accordance with the invention in admixture or conjunction with a pharmaceutically suitable carrier.

In animal tests the action on the blood sugar level has been demonstrated, for example, on mice, rats, guinea pigs, rabbits, cats and dogs. When, for instance, a compound of the invention (as specified in Table 1 below) is administered to normally fed rabbits in a single average dose of 400 mg/kg in, for example, a solution rendered alkaline with bicarbonate, or in the form of an alkali metal salt, a lowering of the blood sugar level sets in rapidly and reaches a maximum (about 30 to 40 per cent of the initial value) in the course of about 3 to 4 hours.

The blood sugar level can be measured by hourly analyses by the method of Hagedorn-Jensen. The lowering of the blood sugar is determined by comparison with the blood-sugar level of control animals fed in the same way but not so treated.

The activity of some of the products of the inventions is shown in the following Table:

TABLE I

SUBSTANCE (in the form of sodium salt)	maximum lowering of blood sugar in the rabbit; dose: 400 mg/kg per os
N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea	45%
N-(4-*n*-propyl-benzenesulphonyl)-N'-*n*-butyl-urea	30%
N-(4-methoxy-benzenesulphonyl)-N'-isobutyl-urea	30%
N-(3-methyl-benzenesulphonyl)-N'-*n*-butyl-urea	40%
N-benzenesulphonyl-N'-isobutyl-urea	40%
N-(4-methyl-benzenesulphonyl)-N'-tertiary-butyl-urea	30%
N-(4-ethyl-benzenesulphonyl)-N'-cyclohexyl-urea	30%
N-(4-methyl-benzenesulphonyl)-N'-*n*-propyl urea	35%
N-(4-methyl-benzenesulphonyl)-N'-hexyl-urea	33%
N-(4-methyl-benzenesulphonyl)-N'-allyl-urea	45%
N-(3:4-dimethoxy-benzenesulphonyl)-N'-hexyl-urea	50%
N-(2:4-dimethylbenzenesulphonyl)N'-cyclohexyl-urea	30%

The testing of the compounds on dogs has the advantage that the resorption conditions in the alimentary canal are similar to those of human beings, and that the blood sugar level exhibits smaller individual variations than in rabbits. In the canine tests the administration of small doses even of the free sulphonyl-ureas yields readily reproducible values. When the compound to be tested is administered to a dog, prior to feeding it, in a single dose of 100 mg/kg, and the blood sugar level is determined at certain intervals, the reductions in the blood sugar level shown in the following Table are observed:

TABLE II

Substance	Lowering of blood sugar level of the dog	
	%	after.....Hours
N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea	45	1
	40	24
	22	48
	0	72—96
N-(4-methyl-benzenesulphonyl)-N'-isobutyl-urea	47	1
	47	24
	20	48
	10	72
	0	96
N-benzenesulphonyl-N'-*n*-butyl-urea	25	1
	25	24
	16	48
	0	72
N-(4-ethyl-benzenesulphonyl)-N'-*n*-butyl-urea	25	1
	30	2
	33	3
	27	24
	0	48
N-(4-methoxy-benzenesulphonyl)-N'-*n*-butyl-urea	35	2
	30	24
	0	48
N-(3-methyl-benzenesulphonyl)N'-isobutyl-urea	48	3
	30	6
	14	24
	0	48
N-(4-methyl-benzenesulphonyl)-N'-cyclohexyl-urea	39	1
	43	24
	10	48
	0	72
N-(4-methyl-benzenesulphonyl)-N'-allyl-urea	32	1
	34	2
	34	24
	35	48
	20	72
	0	96
N-(4-methyl-benzenesulphonyl-N'-cyclopentyl-urea	40	1
	40	24
	25	48
	0	72
N-(4-methyl-benzenesulphonyl)-N'-hexyl-urea	30	1
	35	6
	16	24
	10	72
	0	96

The above values were determined by comparison with the blood sugar levels measured on similarly fed, but untreated control animals. It has also been found that even a single dose, for example, of N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea of 5 mg/kg produced a decrease of 30% in the blood sugar level for 48 hours.

Clinical tests performed on a large number of patients have fully established the efficacy of N-(4-methyl-benzenesulphonyl)-N'-(*n*-butyl)-urea and N-(4-methyl-benzenesulphonyl)-N'-isobutyl-urea, in lowering the blood sugar level. For example, the first named compound lowers the blood sugar level of healthy human beings by an average of 20—40 mg/per cent. In the case of certain diabetics a lowering, for example, of about 300 mg/per cent to the normal value of about 120 mg/per cent has been observed. A number of the products of the invention have been tested as anti-diametics in light and severe cases of diabetes mellitus. In many cases an impressive improvement in the metabolism was observed, more especially in sthenic adipose patients of advanced age. High glycosuriae and hyperglycaemiae have been normalised to a far-reaching extent, and the patients were freed from troublesome polydypsia and polyuria. In some cases the products develop their action on the very first day, and in general between the 2nd and 5th day. The reduced glycosuria is invariably accompanied by a distinct lowering of the blood sugar level. The renal threshold for glucose is not raised. During the administration of the compounds the usual diabetes diet must be strictly observed. Observations so far made show that the compounds are effective in most, but not in all forms of diabetes mellitus. In a few cases (which are thought to be mainly young diabetics whose pancreas produces no insulin) the compounds are not effective.

With some patients successfully treated for a prolonged period with some of the compounds of the invention the metabolism remains compensated for some time after the compounds have ceased to be administered and can be reestablished, if necessary, by renewed administration. So far no insulin-resistance has been observed. The patients can be changed over to insulin treatment at any stage after treatment with the compounds of the invention. The blood count, function of the liver and the urine of the patients treated were carefully checked and displayed no pathological changes. The patients can also be treated with a combination of the products of the invention and insulin, whereby a saving in insulin and an improvement of the metabolism are achieved. In these cases the patients must be treated under particularly strict supervision, because the combined effects involve an increased risk of insulin shock.

The disposition for hypoglycemic shock with the compounds of the invention that have been clinically tested, especially N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl urea, is considerably lower than with insulin treatment.

The compounds of the invention may be administered in accordance with the following guiding principles, in which N-(4-methyl-benzenesulphonyl)-N'-(*n*-butyl) urea is used as an example.

To produce rapidly a sufficiently low blood sugar level, 2—3 grams of this compound are administered on the first day with careful checks of the metabolism. On the second day the dose is reduced to 1.5—2 grams, and on the following days 1 to 1.5 gram each are administered. In some cases the dose can be further reduced or entirely dispensed with, while keeping constant check on the sugar in the blood and in the urine. Owing to the protracted action of the compound the daily dose can be administered all at once. Higher doses do not as a rule produce an increased action.

The compounds of the invention are usually extremely well tolerated. Their acute toxicity (tested on mice or rats), as can be seen from the following Table, is between 1 and several gram/kg at an LD_{50}, for oral administration:

TABLE III

	Ld_{50}, in gram/kg of body weight, administered orally to mice
N-(3-methyl-benzenesulphonyl)-N'-isobutyl-urea	4.5 grams
N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea	2.5 „ (rats: 4 gr)
N-(4-methyl-benzenesulphonyl)-N'-isobutyl-urea	4 grams
N-(4-methyl-benzenesulphonyl)-N-tertiary-butyl-urea	6 grams
N-(4-methyl-benzenesulphonyl)-N'-propyl-urea	5 grams
N-(4-methyl-benzenesulphonyl)-N'-hexyl-urea	5 grams
N-(4-methyl-benzenesulphonyl)-N'-cyclohexyl-urea	5.5 grams
N-(4-*n*-propyl-benzenesulphonyl)-N'-*n*-butyl-urea	4.5 grams
N-(4-isopropyl-benzenesulphonyl)-N'-*n*-butyl-urea	4 grams

Tests conducted with N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea, marked with the radioactive sulphur isotope S ^{35}, have shown that the blood very rapidly absorbs the compounds from the alimentary canal. Their discharge into the urine also occurs relatively rapidly and almost quantitatively. No detectable amounts accumulate in particular organs, and the good tolerance of the compounds can be attributed to this fact. Thorough pharmacological investigations, more especially with respect to muscle and liver glycogen, have shown that the lowering of the blood sugar by the compounds of the invention is not the sympton of a toxic action. Moreover, the tolerance in the endurance test, as has been demonstrated on animals by administering over a period of several months a daily dose of 100 mg/kg of N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea, is very high.

Extensive clinical tests performed on numerous patients have demonstrated the good tolerance of the compounds N-(4-methyl-benzene sulphonyl)-N'-*n*-butyl urea and of N-(4-methyl-benzenesulphonyl)-N'-isobutyl-urea.

As compared with compounds of similar constitution of the sulphanilyl series the compounds of the present invention possess the advantage that they have no bacteriostatic action, and do not produce the secondary effects of sulphonamides on the blood (Heinz bodies) or on the thyroid gland, nor the digestive disturbances caused by action on the bacterial flora of the alimentary tract.

French specification No. 993465 describes *inter alia* a process for the manufacture of compounds of the general formula,

$$R—SO_2—NH—CX—NH—R^1$$

in which R represents an organic residue, for example, a benzene residue, X represents oxygen or sulphur and R^1 represents an organic residue, for example, a methyl, ethyl or hexyl group. It contains, however, no specific example of a compound in which R is a benzene residue, R^1 is an aliphatic or cyclo-aliphatic residue containing from 2 to 8 carbon atoms, and X is oxygen, nor does it disclose or suggest that the compounds are useful for lowering the blood sugar level. In fact, none of the compounds specifically exemplified in that specification is useful as an anti-diabetic for oral administration.

Specification No. 34857/45, as open to public inspection under Section 91(4) of the Patents and Designs Acts, 1907—46, describes a process for the manufacture of substituted sulphonyl-ureas of the general formula

$$R_1—SO_2—\underset{\displaystyle R_2}{\underset{|}{N}}—CO—NH—R_3,$$

in which R_1 represents an aromatic or araliphatic residue, R_2 represents hydrogen or an organic residue and R_3 represents an organic residue, which comprises reacting an aromatic or araliphatic N-sulphonyl-urea, for example, benzenesulphonyl-urea or para-toluenesulphonyl-urea, with an amine or salt thereof, especially a primary amine; the specification mentions *inter alia* aliphatic amines as the amine component but it contains no specific disclosure of the preparation of any of the sulphonyl-urea compounds of the present invention and, moreover, there is no disclosure or suggestion therein that any of the substituted sulphonyl-ureas are useful for lowering the blood sugar level. Furthermore, none of the compounds specifically exemplified in Specification No. 34857/45 is useful as an anti-diabetic for oral administration.

The following Examples illustrate the invention:

EXAMPLE 1.

N-4-methyl-benzenesulphonyl-N'-*n*-butyl-urea

50 grams of *n*-butyl isocyanate are stirred at room temperature into a suspension of 96 grams of sodium 4-methyl-benzene-sulphonamide in 120 cc of dry nitrobenzene, and the whole is then heated for 7 hours at 100°C. After being cooled, the reaction mixture, which is a thick magma, is diluted with methylene chloride or ethyl acetate, and the sodium salt of the sulphonyl-urea formed is separated by centrifuging. The centrifuged crystalline residue freed from organic solvents is dissolved in 500—600 cc of water heated at 50 C, and decolorised with animal charcoal. The precipitate obtained by acidification with dilute hydrochloric acid is dissolved in an equivalent quantity of dilute ammonia solution (about 1:20), again treated with animal charcoal and reprecipitated with dilute hydrochloric acid. In this manner N-4-methyl-benzenesulphonyl-N'-*n*-butyl-urea is obtained in analytically pure form in a yield of 70 to 80 per cent of theory. It melts at 125—127°C (with decomposition).

By reacting another 4-alkylbenzene-sulphonamide or an alkali metal salt thereof, for example, the sodium salts of 4-ethyl-, 4-*n*-propyl, 4-isopropyl- or 4-*n*-butyl-benzenesulphonamide, or a 4-alkoxy-benzene-sulphonamide such as 4-ethoxy-benzene-sulphonamide, with *n*-butyl isocyanate there are obtained in the same manner the analogues of N-4-methyl-benzenesulphonyl-N'-*n*-butyl-urea. The yields and properties of these compounds are similar.

By reacting 2-methyl-benzene-sulphonamide in similar manner with *n*-butyl isocyanate, N-2-methyl-benzenesulphonyl-N'-*n*-butyl-urea is obtained melting at 160—161° C. Instead of 2-methyl-benzene-sulphonamide there may be used other benzene-sulphonamides substituted by lower alkyl or alkoxy groups.

100 grams of N-4-methyl-benzenesulphonyl-N'-*n*-butyl-urea are dissolved with

slight heating in 370 cc of a 1 N.-solution of sodium hydroxide, and the clear colourless solution (pH = 8.5—9.5) is evaporated at 50—60°C under reduced pressure. The residue, which at first is only partially solid, crystallises completely after being allowed to stand for some time. It is triturated with acetone, filtered off with suction, washed with acetone, and dried at 100°C. Yield: 90—100 grams of the sodium salt of N-4-methyl-benzenesulphonyl - N¹-*n*-butyl-urea (83—92 per cent of theory). It melts at 130—133°C. On cooling the salt of N-4-methyl-benzenesulphonyl-N¹-*n*-butyl-urea crystallises out as the tetrahydrate. It melts at 41—43°C.

EXAMPLE 2.

N-benzenesulphonyl-N¹-*n*-butyl-urea

63 grams of benzene-sulphonamide, 120 grams of finely ground potassium carbonate and 600 cc of dry acetone are stirred for 1 hour at 56°C. While refluxing and stirring the mixture, 40 grams of *n*-butyl isocyanate are then slowly added dropwise. The mixture is heated for 6 hours at 50—55°C, the acetone is completely evaporated, the residue is dissolved in water, and the solution is treated with animal charcoal and acidified with dilute hydrochloric acid. The sulphonyl-urea, which even at this stage is in a state of high purity, is dissolved in an equivalent quantity of dilute ammonia solution (about 1:20), again treated with animal charcoal, and precipitated with dilute hydrochloric acid. In this manner N-benzenesulphonyl-N¹-*n*-butyl-urea is obtained in analytically pure state and in a yield of 70 to 80% of theory. It melts at 129—131°C.

In analogous manner N-benzenesulphonyl-N¹-isobutyl-urea melting at 132—133°C, is obtained from benzene-sulphonamide and isobutyl isocyanate.

EXAMPLE 3.

N¹-4-methyl-benzenesulphonyl-N¹-*n*-butyl-urea

60 grams of 4-methyl-benzenesulphonyl-isocyanate are dissolved in 30 cc of absolute anhydrous dioxane, and 22 grams of *n*-butyl-amine dissolved in 30 cc of dioxane are slowly added dropwise, while stirring, at room temperature. When the addition is complete the mixture is stirred for 1 hour at 80°C, a part of the dioxane is evaporated, and the sulphonyl-urea is precipitated by adding water. By dissolving the product in dilute ammonia solution, treating the solution with animal charcoal and precipitation with dilute hydrochloric acid, there is obtained a good yield of N - 4 - methyl - benzenesulphonyl - N¹ - *n*-butyl-urea melting at 125—127°C.

EXAMPLE 4.

N-4-methyl-benzenesulphonyl-N¹-*n*-butyl-urea

97 grams of N-4-methyl-benzenesulphonyl-carbamic acid ethyl ester melting at 84—85°C (prepared by reacting 4 - methyl-benzene-sulphonamide with chloroformic acid ethyl ester in the presence of potassium carbonate) are dissolved in 130 cc of glycol monomethyl ether, 29 grams of *n*-butylamine are added to the solution, and the reaction mixture is refluxed for 20 hours. The residue, obtained after distilling off the glycol monomethyl ether, is caused to crystallise by trituration with water, filtered off with suction, dissolved in dilute ammonia solution (1:20), and the solution is decolorised with animal charcoal, and the sulphonyl-urea is precipitated by acidifying the solution with dilute hydrochloric acid. By recrystallisation from ethanol of 50% strength a good yield of N-4-methyl-benzenesulphonyl - N¹-*n*-butyl-urea is obtained in analytically pure form. It melts at 125—127°C.

EXAMPLE 5.

N-4-ethyl-benzenesulphonyl-N¹-*n*-butyl-urea

56 grams of 4-ethyl-benzene-sulphonamide (melting at 110°C) are suspended in 100 cc of acetone and dissolved by the addition of 200 cc of an aqueous solution of 12 grams of sodium hydroxide. While stirring and cooling the mixture to about 10°C, 33 grams of *n*-butyl isocyanate are added dropwise and, when the addition is completed, the mixture is stirred for a further hour. The whole is diluted with water, a small amount of undissolved matter is filtered off with suction, the clear filtrate is filtered with suction through a layer of carbon and slowly acidified, while being stirred, with 2N-hydrochloric acid to a pH value of 3. At first the precipitate is obtained in a semi-solid form, but it soon becomes crystalline. It is filtered off with suction, the crude product is thoroughly washed with water, taken up in dilute ammonia solution (1.25), the solution is treated with animal charcoal and acidified with 2N-hydrochloric acid, while being stirred. The precipitated pure white sulphonyl-urea is filtered off with suction, washed with water and recrystallised from ethanol of 70% strength. A good yield of N-4-ethyl-benzenesulphonyl - N¹-*n*-butyl-urea melting at 100—102°C is obtained.

In analogous manner there is obtained by reacting 4-ethyl-benzene-sulphonamide (melting at 110°C) in the form of its sodium salt with isobutyl isocyanate, N-4-ethyl-benzenesulphonyl-N¹-isobutyl-urea melting at 144—146°C.

EXAMPLE 6.

N-4-*n*-propyl-benzenesulphonyl - N¹-*n*-butyl-urea

By reacting 4-*n*-propyl-benzene-sulphonamide (melting at 108—110°C) in the form of its sodium salt with *n*-butyl isocyanate in acetone of 30% strength in the manner described in Example 5, a good yield of N-4-*n*-propyl-benzenesulphonyl - N¹-*n*-butyl - urea melting at 104—105°C is obtained.

In analogous manner there is obtained from

the sodium salt of 4-isopropyl - benzene-sulphonamide and *n*-butyl isocyanate, N-4-isopropyl-benzenesulphonyl - N^1-*n*-butyl - urea melting at 135—137°C.

EXAMPLE 7.

N-4-methoxy-benzenesulphonyl - N^1-*n*-butyl-urea.

72 grams of 4-methoxy-benzene-sulphonamide, 120 grams of finely ground potassium carbonate and 800 cc of acetone are stirred for 1 hour at 50 to 60°C. 40 grams of *n*-butyl-isocyanate are then slowly added dropwise, while refluxing and stirring, the reaction mixture is heated for a further six hours at 50—55°C, and the acetone is completely evaporated. The residue is dissolved in water, treated with animal charcoal and acidified with dilute hydrochloric acid. The sulphonyl-urea that precipitates is at first semi-solid, but after being allowed to stand for several hours at 0°C it becomes crystalline. It is filtered off with suction, re-precipitated from dilute ammonia solution and finally re-crystallised from ethanol of 30% strength. Yield: 70 to 75% of theory. It melts at 118—119°C.

EXAMPLE 8.

N-4-methyl-benzenesulphonyl-N^1-isobutyl-urea

62.0 grams of N - 4-methyl - benzene-sulphonyl-carbamic acid ethyl ester are reacted as described in Example 4 with 20.5 grams of isobutylamine in glycol monomethyl ether as solvent. The resulting reaction mixture is worked up as described in Example 4. A good yield of N-4-methyl-benzenesulphonyl-N^1-isobutyl-urea, melting at 169—170°C, is obtained.

To prepare the sodium salt of N-4-methyl-benzenesulphonyl-N^1-isobutyl-urea, 30 grams of this compound are shaken with 160 cc of an aqueous solution of 4 grams of sodium hydroxide for several minutes, the solution is filtered and evaporated under reduced pressure. A good yield of a crystalline magma of the sodium salt of N-4-methyl-benzene-sulphonyl-N^1-isobutyl-urea is obtained which is filtered off with suction and washed on the filter with acetone. The dried compound melts at 199—200° C.

The potassium salt of N-4-methyl-benzene-sulphonyl - N^1-isobutyl - urea, prepared in analogous manner, melts at 200—201°C. Solutions of the two salts in water are not coloured by phenol-phthalein.

The ammonium salt of N-4 - methyl-benzene-sulphonyl-N^1-isobutyl-urea crystallises from a solution of the compound in an excess of a concentrated ammonia solution after standing for some time.

EXAMPLE 9.

N-4-methyl-benzenesulphonyl-N^1-secondary-butyl-urea

A solution of 55 grams of N-4-methyl-benzene-sulphonyl-carbamic acid methyl ester, 115 grams of glycol monomethyl ether and 20 grams of secondary-butylamine is refluxed at the boil for 4½ hours. The whole is then evaporated *in vacuo*, water is added to the residue, while still warm, and it is then dissolved by adding a concentrated aqueous solution of ammonia. The solution is clarified with carbon and, while being stirred, is mixed with hydrochloric acid until the reaction is acid to Congo. A crystalline precipitation of N-4-methyl-benzenesulphonyl - N^1-secondary-butyl-urea is obtained. The substance is purified by being dissolved in ammonia solution (1:20) and reprecipitated with dilute hydrochloric acid. Yield: 48 grams. After being recrystallised from aqueous ethanol, the compound melts at 128—130°C.

EXAMPLE 10.

N-4-methoxy-benzenesulphonyl - N^1-isobutyl-urea.

38 grams of 4-methoxy-benzene-sulphonamide, 60 grams of finely ground potassium carbonate and 400 cc of acetone are stirred for 1 hour at 50—55°C. 22 grams of isobutyl isocyanate are then slowly added dropwise, while stirring under reflux. The mixture is heated for 4 hours at 50°C, the acetone is completely evaporated, the residue is dissolved in water, treated with animal charcoal and acidified with 2N-hydrochloric acid. The precipitated sulphonyl-urea is taken up in dilute ammonia solution (1:25), treated with animal charcoal and reprecipitated with dilute hydrochloric acid. Recrystallisation from 400 cc of 50% ethanol gives a yield of 50 grams (87% of theory) of N-4-methoxy-benzene-sulphonyl-N^1-isobutyl-urea. It melts at 141—142°C.

EXAMPLE 11.

N-3-methylbenzenesulphonyl-N^1-isobutyl-urea

85.5 grams of 3-methyl-benzene-sulphonamide are suspended in 167 cc of acetone, and 333 cc of an aqueous solution of 20 grams of sodium hydroxide are added. 50 grams of isobutyl isocyanate are slowly added dropwise at 10°C, and crystallisation of the sodium salt of toluenesulphonamide being immaterial. The whole is stirred for 1—2 hours, filtered through animal charcoal, and the filtrate is acidified while being stirred, with dilute hydrochloric acid. A good yield of crystalline N-3-methyl - benzenesulphonyl - N^1-isobutyl-urea is obtained. For purification it is dissolved in 1 litre of dilute ammonia solution (1:20) and reprecipitated with hydrochloric acid. The resulting product is recrystallised from isopropanol and melts at 105—106°C.

From 3-methyl-benzene-sulphonamide and *n*-butyl isocyanate there is obtained in similar manner N-3-methyl-benzenesulphonyl - N^1-*n*-butyl-urea melting at 108—109°C.

EXAMPLE 12.

N-4-methyl-benzenesulphonyl-N'-tertiary-butyl-urea

65.7 grams of 4-methyl-benzenesulphonyl-isocyanate are dissolved in 500 cc of benzene. While stirring continuously, 24.3 grams of tertiary butylamine are slowly added dropwise. The temperature rises to about 40° C. The solution is then refluxed at the boil for 1 hour and subsequently evaporated. The residue is treated with dilute ammonia solution (1:20), whereby dissolution is almost complete. The solution is filtered, if desired, with the addition of animal charcoal, and slow acidification with dilute hydrochloric acid produces a good yield of crystalline N-4-methyl-benzenesulphonyl - N'-tertiary butyl-urea. After being filtered off with suction, washed with water and dried, it melts at 166—167° C. After recrystallisation from methanol the product melts at 167—168° C.

EXAMPLE 13.

N-4-methyl-benzenesulphonyl - N'-isobutyl-urea

5 grams of N-4-methyl-benzenesulphonyl-carbamic acid chloride (prepared by passing dry hydrogen chloride into 4-methyl-benzene-sulphonyl isocyanate; and melting at 95—96° C with decomposition) are added, while cooling, to an excess of isobutylamine. The reaction product is diluted with water, a small amount of flocculent matter is filtered off, and glacial acetic acid is added to the filtrate to give an acid reaction. A very good yield of crystalline N-4-methyl-benzenesulphonyl-N'-isobutyl-urea, melting at 169—170° C, is obtained.

EXAMPLE 14.

N-4-methyl-benzenesulphonyl-N'-cyclo-hexyl-urea

33 grams of cyclohexylamine and 81 grams of N-4-methyl - benzene-sulphonyl - ethyl-urethane, melting at 84—85° C (prepared by reacting 4-methyl-benzenesulphonamide with chloroformic acid ethyl ester in the presence of potassium carbonate) are heated in 150 cc of methyl-glycol for 18 hours at 110° C. The warm reaction mixture is stirred into a solution of sodium carbonate and then cooled. The undissolved matter is filtered off with suction, and the cold mother liquor is cautiously acidified. The resulting precipitate is dissolved in dilute ammonia solution, filtered and reprecipitated with acetic acid. A good yield of N - 4-methylbenzenesulphonyl-N'-cyclohexyl-urea is obtained. It is filtered off with suction, thoroughly washed with water, dissolved in hot ethanol, and precipitated by adding water. It melts at 170° C.

EXAMPLE 15.

N-4-methyl-benzenesulphonyl-N'-cyclo-hexyl-urea

17.1 grams of para-toluenesulphonamide and 30 grams of finely ground potassium carbonate are suspended in 250 cc of dry acetone, and the whole is thoroughly stirred for 1 hour under reflux. 12.5 grams of cyclohexyl isocyanate are slowly stirred dropwise into the reaction mixture. After refluxing for 6 hours, the acetone is distilled off, and the residue is dissolved in water. The undissolved matter is filtered off with suction, and the filtrate is cautiously acidified with hydrochloric acid. The N-4-methyl-benzenesulphonyl-N'-cyclohexyl-urea so obtained, very pure and in good yield, is further purified as described in Example 14 by reprecipitation from dilute ammonia solution and then recrystallised from a mixture of ethanol and water. It melts at 170° C.

EXAMPLE 16.

N-4-ethyl-benzenesulphonyl-N'-cyclohexyl-urea

40 grams of 4-ethyl-benzenesulphonamide (m.p. 110° C) are suspended in 150 cc of acetone and dissolved with 105 cc of a 2N-solution of sodium hydroxide. While stirring, 32 grams of cyclohexyl isocyanate are added dropwise in the course of 30 minutes at about 10° C, and, when the addition is complete, the mixture is stirred for 2½ hours. The reaction mixture is diluted with 2 litres of water and acidified with 2N-hydrochloric acid. The precipitate so obtained is filtered off with suction and extracted twice with 2½ litres of dilute ammonia solution (1:75) on each occasion. The ammoniacal extracts are combined, filtered and acidified with 2N-hydrochloric acid. The precipitated crude sulphonyl-urea is further purified by being taken up in 3 litres of dilute ammonia solution (1:75), a small amount of undissolved matter is filtered off, the filtrate is treated with animal charcoal, again filtered and acidified with 2N-hydrochloric acid. The resulting white crystallisate is recrystallised from 800 cc of ethanol of 50 per cent strength and a good yield of N-4-ethyl-benzenesulphonyl-N'-cyclohexyl-urea is obtained. It melts at 159—160.5° C.

EXAMPLE 17

N-4-methyl-benzenesulphonyl-N'-allyl-urea

28.7 grams of N-4-methyl-benzenesulphonyl-carbamic acid methyl ester (prepared by reacting 4-methyl-benzene-sulphonamide with chloroformic acid methyl ester in the presence of potassium carbonate) and 7.8 grams of allylamine are refluxed for 4½ hours in 55 grams of glycol monomethyl ether. The reaction mixture is evaporated under reduced pressure, and the warm residue is mixed with water and dissolved by adding ammonia solution. The pale coloured solution is decolorised with animal charcoal, filtered and acidified, while being stirred well, with dilute hydrochloric acid until the reaction is acid to Congo. A good yield of crystalline N-4-methylbenzenesulphonyl-N'-allyl-urea is obtained which is purified by dissolving it in dilute ammonia solution (1:20) and pre-

cipitating it with dilute hydrochloric acid. After recrystallisation from dilute ethanol the product melts at 141—143°C.

In an analogous manner there is obtained from N-4-methyl-benzenesulphonyl-carbamic acid methyl ester and *n*-propylamine by boiling in glycol monomethyl ether as solvent, N-4-methylbenzenesulphonyl-N'-*n*-propyl-urea melting at 151—152°C.

In analogous manner there is obtained with the use of isopropylamine, N-4-methyl-benzenesulphonyl-N'-isopropyl-urea melting at 141—143°C.

EXAMPLE 18.

N-4-methyl-benzenesulphonyl-N'-allyl-urea

65.7 grams of 4-methyl-benzenesulphonyl isocyanate are dissolved in 500 cc of benzene. While stirring, 20.9 grams of allylamine are slowly added dropwise at room temperature. The temperature rises slightly, and a good yield of N-4-methyl-benzenesulphonyl-N'-allyl-urea is obtained. It is filtered off with suction and recrystallised from dilute ethanol. It melts at 141—143°C.

EXAMPLE 19.

N-4-methyl-benzenesulphonyl-N'-isoamyl-urea

51 grams of 4-methyl-benzene-sulphonamide, 90 grams of finely ground potassium carbonate and 560 cc of acetone are stirred for 1 hour at 50—60°C. While refluxing and stirring, 37 grams of isoamyl isocyanate are then slowly added dropwise, the reaction mixture is then heated for 6 hours at 50—55°C, and the acetone is completely evaporated. The residue is dissolved in water, and the solution is treated with animal charcoal and acidified with dilute hydrochloric acid. The precipitated N-4-methyl-benzenesulphonyl-N'-isoamyl-urea is filtered off with suction, reprecipitated from dilute ammonia solution and from dilute hydrochloric acid as described in Example 17, and recrystallised from 1.2 litres of ethanol of 50 per cent strength.

Yield: 60 grams (70% of theory). It melts at 142—144°C. N-4-methyl-benzenesulphonyl-N'-*n*-amyl-urea prepared in analogous manner melts at 103—105°C.

EXAMPLE 20.

N-4-methyl-benzenesulphonyl-N'-cyclopentyl-urea

49.3 grams (0.25 mol) of 4-methyl-benzenesulphonyl-isocyanate are dissolved in 250 cc of absolute benzene, and 21.3 grams (0.25 mol) of cyclopentylamine are slowly added dropwise, while stirring, at 20°C. The mixture is stirred until the smell of isocyanate has disappeared, cooled, and the N-4-methyl-benzenesulphonyl-N'-cyclopentyl urea, which has precipitated in a good yield, is filtered off with suction. To purify it, it is dissolved in dilute ammonia, the solution is clarified with animal charcoal, and the compound is reprecipitated with dilute acid. After recrystallisation from acetonitrile the compound melts at 169—170°C.

EXAMPLE 21.

N-4-methyl-benzenesulphonyl-N'-heptyl-(4)-urea

By the procedure described in Example 20, there is obtained from 39.5 grams (0.2 mol) of 4-methyl-benzenesulphonyl-isocyanate and 23 grams (0.2 mol) of 4-heptylamine a good yield of N-4-methyl-benzenesulphonyl-N'-heptyl-(4)-urea melting at 147—149°C (after recrystallisation from acetonitrile).

EXAMPLE 22.

N-4-methyl-benzenesulphonyl-N'-cyclohexylmethyl-urea

49.3 grams of 4-methyl-benzenesulphonyl isocyanate are slowly added dropwise, while cooling and stirring vigorously, to a solution of 28.3 grams (0.25 mol) of cyclohexylmethylamine in 200 cc of absolute benzene, and the mixture is then refluxed for 1 hour, cooled, diluted with ether, and the precipitate is filtered off with suction. A good yield of N-4-methyl-benzenesulphonyl-N'-cyclohexylmethyl-urea is obtained. It is dissolved in dilute ammonia solution. The solution is clarified with charcoal and acidified with dilute hydrochloric acid, while stirring vigorously. The precipitate is filtered off with suction, thoroughly washed with water, and recrystallised from acetonitrile. It melts at 178—179°C.

EXAMPLE 23.

N-4-methyl-benzenesulphonyl-N-*n*-hexyl-urea

40 grams of 4-methyl-benzenesulphonyl isocyanate are dissolved in 150 cc of absolute benzene. While stirring continuously, 21 grams of 1-amino-*n*-hexane are slowly added dropwise, the temperature rising to about 55°C. The solution is then heated for 3 hours at 60—70°C and evaporated under reduced pressure. The residue is treated with dilute ammonia solution (1:10), and undissolved matter is filtered off, the filtrate is filtered with suction through a layer of charcoal, and acidified with 2N-hydrochloric acid. The precipitate is dissolved in dilute ammonia solution (1:25), filtered, again treated with charcoal and slowly acidified with 2N-hydrochloric acid. A good yield of crystalline N-4-methyl-benzenesulphonyl-N'-*n*-hexyl-urea is obtained which, after recrystallisation from methanol of 50 per cent strength, melts at 120—122°C.

EXAMPLE 24.

N-(2:4-dimethyl-benzenesulphonyl)-N'-cyclohexyl-urea

29.5 grams of 2:4-dimethyl-benzene-sulphonamide are suspended in 60 cc of acetone, and a solution of 7 grams of sodium hydroxide in 120 cc of water is added to the suspension. At about 15°C, 21.6 grams of cyclohexyl isocyanate are added dropwise, while stirring, to the solution of the sodium salt of 2:4-

dimethyl-benzenesulphonamide, any temporary precipitation being disregarded. A small amount of precipitate is filtered off, and the filtrate is clarified with animal charcoal and acidified with dilute hydrochloric acid while stirring. A crystalline precipitate is obtained which is filtered off with suction, taken up in 600 cc of dilute ammonia solution (1 part by volume of concentrated ammonia to 20 parts by volume of water), and the undissolved matter is filtered off. Acidification of the filtrate with dilute hydrochloric acid produces a good yield of N-(2:4-dimethyl-benzenesulphonyl)-N'-cyclohexyl-urea which is filtered off with suction and recrystallised from ethanol. The product melts at 183—185°C.

EXAMPLE 25.

N-(3:4-dimethoxy-benzenesulphonyl)-N'-isobutyl-urea

27 grams of 3:4-dimethoxy-benzene-sulphonamide are suspended in 41 cc of acetone, and dissolved with 82 cc of a solution of 5 grams of sodium hydroxide. 12.4 grams of isobutyl isocyanate are slowly added dropwise at about 15°C, the reaction mixture is stirred for ½ hour, a small amount of precipitate is filtered off, and the solution is slowly acidified with dilute hydrochloric acid, while stirring. A precipitate is obtained which is purified by dissolution in dilute ammonia solution, and acidification with hydrochloric acid as described in Example 24. A god yield of N-(3:4-dimethoxy-benzenesulphonyl) - N' - isobutyl-urea is obtained; after recrystallisation from ethanol it melts at 196°C.

By reacting 3:4-dimethoxy-benzenesulphonamide with *n*-hexyl isocyanate in an analogous manner N-(3:4-dimethoxybenzene-sulphonyl)-N'-*n*-hexyl-urea melting at 176—177°C is obtained.

EXAMPLE 26.

N-(meta-methoxy-benzenesulphonyl)-N'-*n*-hexyl-urea

14 grams of meta-methoxy-benzene-sulphonamide are suspended in 25 cc of acetone and covered with 50 cc of a solution of 3 grams of sodium hydroxide. 9.5 grams of *n*-hexyl isocyanate are then slowly added dropwise, while stirring, at 10°C. The reaction mixture is stirred for one hour. After filtration, the N-(meta-methoxy-benzene-sulphonyl)-N'-*n*-hexyl-urea is precipitated with dilute hydrochloric acid. The urea, obtained in a good yield, is purified by dissolving it in ether, filtering the solution with carbon, and causing it to crystallise by evaporating the ether. The crystallisate is taken up in dilute ammonia solution (1:20), filtered and precipitated with glacial acetic acid. After recrystallisation from isopropanol, the urea melts at 111—112°C. Yield: 8 grams.

EXAMPLE 27.

N-(3-methoxy-benzenesulphonyl)-N'-cyclohexyl-urea

11 grams of meta-methoxy-benzene-sulphonamide are suspended in 25 cc of acetone and covered with 45 cc of a solution of 2.3 grams of sodium hydroxide, whereby dissolution is produced. 7.3 grams of cyclohexyl isocyanate are then slowly added dropwise at 10°C. To obtain a quantitative reaction, the mixture is stirred for 1 hour. The whole is filtered, and the filtrate is acidified with dilute hydrochloric acid. The precipitated N-(3-methoxy-benzenesulphonyl) - N' - cyclohexyl-urea is filtered off with suction, dried and dissolved in diisopropyl ether. It melts at 140—142°C.

EXAMPLE 28

(I) 50 kg of N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea, 2.95 kg of wheat or maize starch, 0.75 kg of talcum and 0.3 kg of magnesium stearate were well mixed and kneaded for a short while (about 15 minutes) in a Werner-Pfleiderer type kneader with 1 kg of wheat or maize starch as a starch paste which has been prepared by heating with 6 litres of distilled water on a water bath. The moist mass was passed through a sieve having meshes of 2 mm in diameter, then collected on 20 drying plates, and dried for 12 hours at 40°C in a circulating air drying chamber. The dry mass was again passed through a sieve having meshes of 1.2 mm in diameter.

(II) 10 kg of wheat or maize starch were moistened with distilled water and kneaded in a Werner-Pfleiderer type kneader. The moist starch was passed through a sieve having meshes 0.75 mm in diameter, collected in not too thick a layer on aluminium plates, and dried for 12 hours at 40°C in an air-circulating drying chamber.

(III) Granulate (I) and granulate (II) were mixed with one another in a ratio of 50 parts by weight (I) to 10 parts by weight of (II).

(IV) The uniform mixture (III) was tabletted on a rotating press.

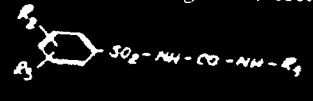
COMPOSITION OF ONE TABLET:

Dosage per tablet: 0.5 gram of N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea
Final weight per table: 0.650 gram
Diameter per tablet: 13 mm
Column Height of 10 tablets: 45 mm
Depth of curvature of seal: 0.3 mm

Instead of N-(4-methyl-benzenesulphonyl)-N'-*n*-butyl-urea there may be used in the above preparation N-(4-methyl-benzenesulphonyl) - N' - isobutyl - urea, N-(4-methyl-benzenesulphonyl)-N'-cyclohexyl-urea, N-(4-methoxy - benzenesulphonyl)-N'-*n*-butyl-urea, N - (4-ethyl-benzenesulphonyl)-N'-butyl-urea, N - (3-methyl-benzenesulphonyl)-N'-isobutyl-urea, N-(4-methyl-benzenesulphonyl)-N'-allyl-urea or N-(3:4-dimethoxy-benzenesulphonyl)-N'-*n*-hexyl-urea.

WHAT WE CLAIM IS:

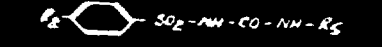
1. Compounds of the general formula



in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 3 to 8 carbon atoms, and R_2 and R_3 each represents hydrogen or an alkyl or alkoxy group containing at most 6 carbon atoms.

2. Compounds of the general formula given in Claim 1, wherein R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 3 to 5 carbon atoms.

3. Compounds of the general formula



in which R_4 represents hydrogen or an alkyl or alkoxy group containing at most 6 carbon atoms, and R_5 represents an aliphatic or cycloaliphatic hydrocarbon radical containing two to eight, especially three to five, carbon atoms.

4. Compounds of the formula



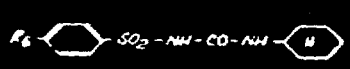
in which R_6 represents an alkyl group containing at most 6 carbon atoms.

5. Compounds of the formula



in which R_6 represents an alkyl group containing at most 6 carbon atoms.

6. Compounds of the formula



in which R_6 represents an alkyl group, containing at most 6 carbon atoms.

7. Compounds of the formula



in which R_6 represents an alkyl group containing at most 6 carbon atoms.

8. N - 4 - Methyl - benzenesulphonyl - N'-*n*-butyl-urea.

9. N - Benzenesulphonyl - N' - *n* - butyl-urea.

10. N - 4 - Ethyl - benzenesulphonyl - N'-*n*-butyl-urea.

11. N - 4 - *n* - propyl - benzenesulphonyl-N'-*n*-butyl-urea.

12. N - 4 - Methoxy - benzenesulphonyl-N'-*n*-butyl-urea.

13. N - 4 - Methyl - benzenesulphonyl-N'-isobutyl-urea.

14. N - 4 - Methyl - benzenesulphonyl-N'-secondary-butyl-urea.

15. N - 4 - Methoxy - benzenesulphonyl-N'-isobutyl-urea.

16. N - 3 - Methyl - benzenesulphonyl-N'-isobutyl-urea.

17. N - 4 - Methyl-benzenesulphonyl - N'-tertiary-butyl-urea.

18. N - 4 - Methyl - benzenesulphonyl-N'-cyclohexyl-urea.

19. N - 4 - Ethyl - benzenesulphonyl - N'-cyclohexyl-urea.

20. N - 4 - Methyl - benzenesulphonyl-N'-allyl-urea.

21. N - 4 - Methyl - benzenesulphonyl-N'-isoamyl-urea.

22. N - 4 - Methyl - benzenesulphonyl-N'-*n*-amyl-urea.

23. N - 4 - Methyl - benzenesulphonyl-N'-cyclopentyl-urea.

24. N - 4 - Methyl - benzenesulphonyl-N'-heptyl-(4)-urea.

25. N - 4 - Methyl - benzenesulphonyl-N'-cyclohexylmethyl-urea.

26. N - 4 - Methyl - benzenesulphonyl-N'-*n*-hexyl-urea.

27. N - (2:4-Dimethyl-benzenesulphonyl)-N'-cyclohexyl-urea.

28. N - (3:4-Dimethoxy-benzensulphonyl)-N'-isobutyl-urea.

29. N - (3 - Methoxy - benzenesulphonyl)-N'-*n*-hexyl-urea.

30. N - (3 - Methoxy - benzenesulphonyl)-N'-cyclohexyl-urea.

31. Salts of any one of the compounds claimed in any one of claims 1—30 with bases yielding physiologically tolerable salts with such compound.

32. A process for the manufacture of a compound claimed in any one of claims 1—30 conducted substantially as hereinbefore described.

33. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

34. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 2 to 30 in admixture or conjunction with a pharmaceutically suitable carrier.

35. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt of a compound as claimed in claim 1 with a base yielding a physiologically tolerable salt with such compound, in admixture or conjunction with a pharmaceutically suitable carrier.

36. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt of a compound as claimed in any one of claims 2 to 30 with a base yielding a physiologically toerable salt with such com-

pound, in admixture or conjunction with a pharmaceutically suitable carrier.

37. A preparation as claimed in any one of claims 33 to 36, which contains a dosage quantity of 0.5 grams of the sulphonyl-urea compound or salt thereof.

38. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, substantially as described in Example 28 herein.

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ERRATA

SPECIFICATION NO. 808,071

Page 3, line 87, *for* "cyclo" *read* "cyclohexyl-".

Page 4, line 1, *for* "preparation" *read* "preparations".

Page 4, line 12, *for* "arninistration" *read* "administration".

Page 8, line 106, *for* "1.25" *read* "1:25".

Page 10, line 55, *for* "methylbenzenesulphonyl" *read* "methyl-benzenesulphonyl".

Page 12, line 32, *for* "500" *read* "5001".

THE PATENT OFFICE,
2nd July, 1959

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