# United States Patent [19]

**Rufer et al.**

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[45] **Apr. 15, 1975**


[54] **BLOOD SUGAR LOWERING SULFAMOYL PYRIMIDINES AND ASYMMETRICAL CARBON ATOM**


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**Related U.S. Application Data**

[63] Continuation of Ser. No. 129,948, March 31, 1971, abandoned.

[30] **Foreign Application Priority Data**

Apr. 28, 1970 Germany ..... 2021962

[52] **U.S. Cl.** ..... **260/256.5 R;** 260/556 AR; 424/251

[51] **Int. Cl.** ..... **C07a 51/42**

[58] **Field of Search** ..... 260/256.5 R



[56] **References Cited**

UNITED STATES PATENTS

3,621,026 11/1971 Gutsche et al. ..... 260/256.5 R



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[57] **ABSTRACT**

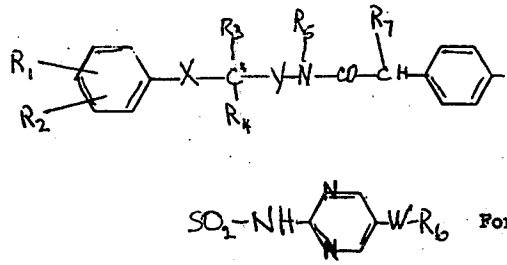
Compounds of the sulfamoyl pyrimidine with asymetric carbon atom are provided for the treatment of Diabetes Mellitus.

Substituted sulfonamides are suitable for the treatment of Diabetes mellitus.

The first clinically tested preparation of this class of substances, N-sulfanilyl-N'-n-butyl urea (Carbutamid), still showed undesirable bacteriostatic side effects. These side effects no longer appear, for example, in N-(4-methylbenzenesulfonyl)-N'-n-butyl urea (Tolbutamid) or in N-[5-(2-methoxyethoxy)-2-pyrimidinyl]-sulfamoyl-benzene (Glymidin). The clinically employed dose of the last-named compounds is of the order of 0.5 – 1 g daily.

The p-substitution of the benzene nucleus in the Glymidin type, in particular the subsitution by aromatic acid amide groups, leads to compounds of considerably increased action, as is evident from Belgian Pat. No. 726,253.

It has now been found that in compounds of the general formula I



Formula I

which have available an asymmetrical C atom C*, the enantiomers exhibit a surprisingly great difference in the blood sugar lowering effect. Thus, one of the enantiomers is generally 30 to 300 times more effective than the other and about twice as effective as the racemate.


**19 Claims, No Drawings**

# BLOOD SUGAR LOWERING SULFAMOYL PYRIMIDINES AND ASYMMETRICAL CARBON ATOM

This is a continuation of application Ser. No. 129,948 filed Mar. 31, 1971, now abandoned.

This invention relates to racemates and optical antipodes of sulfamoyl pyrimidines of the general formula I, above where

C* is an asymmetrical C atom;

X and Y are identical or different and each by itself represents a direct bond or a methylene group;

$R_1$ and $R_2$ Hydrogen or halogen atoms, alkyl groups with 1 – 6 atoms or alkoxy groups with 1 – 4 C atoms;

$R_3$ and $R_4$ are different and represent hydrogen atoms, straightchain or branched alkyl groups, with 1 – 4 C atoms, carboxyl or alkoxycarbonyl groups, with 1 – 4 C atoms;

$R_5$ and $R_7$ are identical or different and represent hydrogen atoms or low alkyl groups with 1 – 4 C atoms;

$R_6$ is a straight-chain or branched alkyl group with 1 – 6 C atoms; and

W is a direct C—C bond or an oxygen or sulfur atom, as well as their salts with physiologically tolerable bases.

Testing for blood sugar reduction was done houron on rabbits fasting for 24 hours, over a time interval of 6 hours. The values shown in the following table under BZ (Blood Sugar) indicate the lowest dose of the particular sulfonamide which lowers the blood sugar as much as 1 mg/kg of 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-5-chloro-2-methoxyanilid, one of the most effective compounds from Belgian Pat. No. 726,253. The dosage gradation is: 30, 3, 1, 0.5, 0.25, 0.1, 0.05 mg/kg).

Table

| Name | BZ (−) form | (+) form | Racemate |
|---|---|---|---|
| 4-[N-(5-isopropoxy-2-pyrmidinyl)-sulfamolyl]-phenylacetic acid-1-phenyl-ethylamide | 0.1 | 30 | 0.25 |
| 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide | 0.1 | 30 | 0.25 |
| 4-[N(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide | 0.1 | 3 | 0.25 |
| 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]1phenylacetic acid-1-phenyl-propylamide | 0.25 | 30 | 0.5 |
| 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide | 0.05 | 3 | 0.1 |

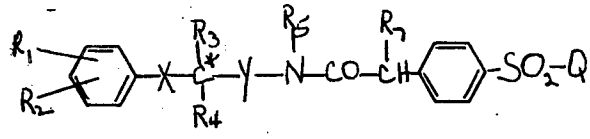
It is surprising that the increase in blood sugar lowering action is brought about by a modification of the molecule in the lengthened side chain of the sulfonized benzene nucleus, that is, a point which does not necessarily have anything to do with the beta-cytotropic action of the sulfonamides, since also compounds which



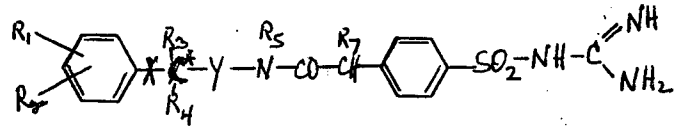
do not have a side chain (e.g., Glymidin) are beta-cytotropically active.

For therapeutical use, the substances according to the invention can be administered by mouth as free sulfonamides, as salts with physiologically acceptable inorganic and/or organic bases, such as hydroxides of sodium, lithium, calcium or ammonium, amines such as methyl glucamine, morpholine, ethanolamine and others, or also in the form of mixtures of the free sulfonamides with a suitable alkali bicarbonate, or respectively carbonate. Especially suitable are bases which in themselves are blood sugar lowering, as for example, butyl biguanide. The confectioning of the substances can be effected without or with the additions, vehicles, taste correctives, etc. common in galenic pharmacy, namely for example in powder form, as tablets, dragees, capsules, pills, or in the form of suspensions or solutions.

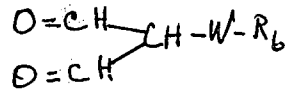
The production of the new compounds of the general formula I is effected by a) reacting a possibly optically active sulfohalide of the general formula



where C*, X, Y, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_7$ have the same meaning as above and Q is a halogen atom, preferably chlorine, with guanidine, and condensing the resulting possibly optically active guanidinesulfonyl compound of the general formula



with a substituted malonedialdehyde of the general formula

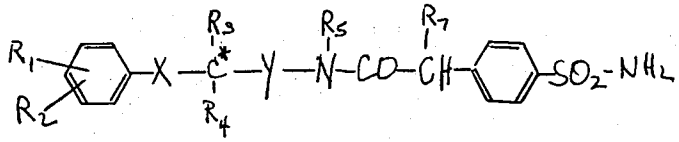


where W and $R_6$ have the same meaning as above, in which the aldehyde groups may also be functionally modified, closing the ring, or

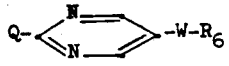
b. reacting the possibly optically active sulfohalide mentioned under a) with a 2-amino-5-W-$R_6$-

pyrimidine, where W and $R_6$ have the same meaning as above, or

c. Reacting a possibly optically active sulfonamide of the general formula

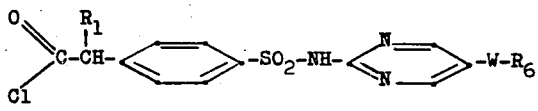


in which C*, X, Y, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_7$ have the same meaning as above, in free form or as alkali salt with a pyrimidine derivative of the general formula

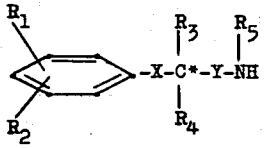


where W and $R_6$ have the same meaning as above and Q is a halogen atom, preferably chlorine, or

d. reacting an acid chloride of the general formula



where W, $R_7$ and $R_6$ have the same meaning as above, with a possibly optically active amine of the general formula

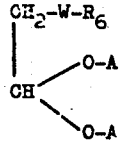


Where C*, X, Y, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ have the same meaning as above, or

e. subjecting a racemate of the general formula I to racemate splitting, and possibly transforming the compounds obtained according to a) to e) with physiologically tolerable inorganic or organic bases into the respective salts.

The racemate splitting according to e) can be effected, for example, by formation of diastereomeric salts with strong, optically active bases.

The substituted malonedialdehyde used for the reaction as per a) can be obtained, for example, in that compounds of the general formula



wherein W and $R_6$ have the above stated meaning, and A indicates a low or medium alkyl radical, are formylated according to Vilsmeier's method. The products thus obtained can be condensed with corresponding guanidine derivatives without isolation.

The following examples illustrate but do not restrict the invention:

## EXAMPLE 1

S-(-)-[N-(5-isopropoxy-2-pyrimidinyl)sulfamoyl]-phenyl-aceticacid-1-phenyl ethylamide.

7.38 g (20 millimole) of 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenyl-acetic acid chloride were suspended in 70 ml of chloroform. At 5° – 10°C 4.88 g (40 millimole) of S(-)-1-phenylethylamine were dropped into 20 ml of chloroform. After boiling for one hour, the product is concentrated and recrystallized out of 20 ml of alcohol with 20 ml of water.

Yield 5.3 g = 56 percent of the theory of melting point 148°C, $[\alpha]_D^{20} = 29°$ ($c$=1, chloroform).

## EXAMPLE 2

R(+)-4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 with R(+)-1-phenylethylamine.

Yield: 57 percent of the theory.

Melting point: 148°C. $[\alpha]_D^{20} = +30°$ ($c = 1$, chloroform).

## EXAMPLE 3

4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was procured analogously to example 1 with 1-phenylethylamine.

Yield: 64 percent of the theory. Melting point: 172°–174°C. (from methylglycol-water). The sodium salt of this compound was obtained in ethanol with an equivalent quantity of sodium alcoholate. Melting point: 285°C.

## EXAMPLE 4

S(-)-4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

The compound was produced analogously to example 1 with S-(-)-1-phenyl-propylamine. Recrystallization from ethanol, then from a mixture of methylglycol and water 3:1.

Yield: 27 percent of the theory. Melting point: 177°C. $[\alpha]_D^{20} = -37°$ ($c = 1$, chloroform).

## EXAMPLE 5

R(+)-4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

The compound was produced analogously to example 1 with R-(+)-1 -phenyl-propylamine. Recrystallization from ethanol.

Yield: 53 percent. Melting point: 178°C. /alpha/$_D^{20}$ = +38° ($c = 1$, chloroform).

## EXAMPLE 6

4[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

The compound was produced analogously to example 1 with 1-phenyl-propylamine.

Yield: 57 percent of the theory. Melting point: 173°–175°C.

## EXAMPLE 7

S-(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and S-(-)-1-phenylethylamine.

Yield: 72 percent of the theory. Melting point: 148°C.

[alpha]$_D^{20}$ = −29° (c = 1, chloroform). The sodium salt of this compound was obtained in ethanol with an equivalent quantity of sodium alcoholate. Melting point 274°C.

[alpha]$_D^{20}$ = −29° (c = 2.6, water).

## EXAMPLE 8

R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and R-(+)-1-phenylethylamine.

Yield: 78 percent of the theory. Melting point: 150°C.

[alpha]$_D^{20}$ = +29° (c = 1, chloroform). Sodium salt: Melting point: 273°C. [alpha]$_D^{20}$ = +29° (c = 2, water).

## EXAMPLE 9

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenylethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-phenyl-ethylamine.

Yield: 81 percent of the theory. Melting point: 114°–116°C.

The sodium salt was obtained with an equivalent quantity of sodium alcoholate in ethanol. Melting point: 254°C.

## EXAMPLE 10

S-(−)-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

3.70 g (10 millimole) of 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenyl-acetic acid chloride were suspended in 35 ml of chloroform. At 0°–5°C a solution of 3.03 g (30 millimole) triethylamine and 1.6 g (11.8 millimole) S-(−)-1-phenyl-propylamine in 15 ml chloroform was added drop by drop. After boiling for one hour, the product was concentrated and recrystallized twice out of ethanol.

Yield: 0.47 g = 10 percent of the theory. Melting point: 195°C.

[alpha]$_D^{20}$ = −35° (c = 1, chloroform).

## EXAMPLE 11

R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and R-(+)-1-phenyl-propylamine and recrystallized twice out of ethanol.

Yield: 51 percent of the theory. Melting point: 198°C.

[alpha]$_D^{20}$ = +35° (c = 1, chloroform).

## EXAMPLE 12

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide

The compound was produced analogously to example 1 from 4 -[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-phenyl-propylamine.

Yield: 58 percent of the theory. Melting point: 168°–170°C.

## EXAMPLE 13

S-(−)-4-[N-(5-ethyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamine

The compound was produced analogously to example 1 with 4-[N-(5-ethyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and recrystallized twice out of ethanol.

Yield: 64 percent of the theory. Melting point: 169°C.

[alpha]$_D^{20}$ = −33° (c = 1, chloroform).

## EXAMPLE 14

4-[N-(5-ethyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-ethyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-phenylethylamine.

Yield: 47 percent of the theory. Melting point: 122°–124°C.

## EXAMPLE 15

S-(−)-4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 with 4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride. Recrystallization out of ethanol.

Yield: 90 percent of the theory. Melting point: 174°C.

[alpha]$_D^{20}$ = −33° (c = 1, chloroform).

## EXAMPLE 16

4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-phenylethylamine.

Yield: 90 percent of the theory. Melting point: 175°–177°C.

## EXAMPLE 17

4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-butylamid

The compound was produced analogously to example 1 with 1-phenylbutylamine and recrystallized out of ethanol.

Yield: 72 percent of the theory. Melting point: 182°–183°C.

## EXAMPLE 18

4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-2-methylpropylamide

The compound was produced analogously to example 1 from 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-phenyl-2-methyl-propylamine and recrystallized from ethanol.

Yield: 58 percent of the theory. Melting point: 191°–193°C.

## EXAMPLE 19

4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenyl-2-butylamide

The compound was produced analogously to example 1 with 2-phenyl-2-butylamine.

Yield: 48 percent of the theory. Melting point: 197°–199°C.

## EXAMPLE 20

4[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-chloro-2-methoxy-phenyl)-ethylamide

The compound was produced analogously to example 1 with 1-(5-chloro-2-methoxy-phenyl)-ethylamine.

Yield: 50 percent of the theory. Melting point: 122°C (from ethanol).

1-(chloro-2-methoxy-phenyl)-ethylamine was obtained as follows:

52.5 of 5-chlor-2-methoxy-acetophenone and 90 g of ammonium formate were stirred at 160°C, water being distilled off. Then the product was boiled with 230 ml of concentrated hydrochloric acid, washed with benzene, the aqueous phase was rendered alkaline, the distillate extracted with ether, and the extract distilled.

Yield: 57 percent of the theory of boiling point 143°C at 18 mm Hg.

## Example 21

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-chloro-2-methoxy-phenyl)-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-(5-chloro-2-methoxy-phenyl)-ethylamine.

Yield: 70 percent of the theory. Melting point: 122°C (from ethanol-water).

## EXAMPLE 22

4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide.

The compound was produced analogously to example 1 with 1-(5-fluoro-2-methoxy-phenyl)-ethylamine

Yield: 44 percent of the theory. Melting point: 118°C.

1-(5-fluoro-2-methoxy-phenyl)-ethylamine was obtained analogously to 1-(5-chloro-2-methoxy-phenyl)-ethylamine (see example 20) from 5-fluoro-2-methoxy-acetophenone.

Yield: 48 percent. Boiling point: 111°C at 13 mm Hg.

## EXAMPLE 23

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(l-(5-fluoro-2-methoxy-phenyl)-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-(5-fluoro-2-methoxy-phenyl)-ethylamine.

Yield: 66 percent. Melting point: 134°C.

## EXAMPLE 24

4-[N-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(2,5-dimethoxy-phenyl)-ethylamide

The compound was produced analogously to example 1 with 1-(2,5-dimethoxy-phenyl)-ethylamine.

Yield: 90 percent, Melting point: 176°C. 1-(2,5-dimethoxy-phenyl)-ethylamine was obtained analogously to 1-(5-chloro-2-methoxy-phenyl)-ethylamine (see example 20) from 2,5-dimethoxy-acetophenone.

Yield: 27 percent of boiling point 150°C at 13 mm Hg.

## EXAMPLE 25

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(2,5-dimethoxy-phenyl)-ethylamide

The compound was obtained analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-2(2,5-dimethoxy-phenyl)-ethylamine.

Yield: 84 percent. Melting point: 192°C.

## EXAMPLE 26

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(4-n-propyl-phenyl)-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-(4-n-propyl-phenyl)-ethylamine.

Yield: 55 percent. Melting point: 120°C.

## EXAMPLE 27

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(2-ethoxy-5-methyl-phenyl)-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-(2-ethoxy-5-methyl-phenyl)-ethylamine.

Yield: 45 percent. Melting point: 165°C.

The 1-(2-ethoxy-5-methyl-phenyl)-ethylamine was produced as follows:

17.8 g (0.1 mole) of 2-ethoxy-5-methyl-acetophenone were heated with 22.5 g (0.5 mole) of formamide for 6 hours at 180°–200°C. After cooling, the product was diluted with water and extracted three times with 100 ml of ether each time. The organic residue from the ether solution (15.2 g) was heated with 30 g NaOH in 300 ml of water for 3 hours with reflux. After cooling, the separated oil was extracted with 3 × 150 ml of ether, and the organic phase was washed and dried over $K_2CO_3$. After removal of the ether, the remaining oil was distilled under high vacuum.

Yield: 10 g (55.8 percent). Boiling point: 99°–102°C at 0.01 mm Hg. Melting point of the picrate: 211°C (ethanol)

## EXAMPLE 28

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-chloro-2-methyl-phenyl)-ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-(5-chloro-2-methyl-phenyl)-ethylamine.

Yield: 60 percent. Melting point: 166°C.

The 1-(5-chloro-2-methyl-phenyl)-ethylamine was produced as follows:

To a solution of 0.5 mole methyl magnesium iodide in 300 ml absolute ether there was added drop by drop while stirring a solution of 38 g of 5-chloro-2-methylbenzonitrile (0.25 mole) in 150 ml absolute ether. Then the solution was boiled for about 8 hours with reflux. After cooling, 10 g of lithium alanate were added in portions and the mixture boiled for 3 hours with reflux.

After cooling, the excess lithium alanate as well as Grignard's reagent were decomposed by careful addition of about 250 ml of 2*n* NaOH. After extracting with ether, the combined ether phases were washed and concentrated under vacuum.

Yield: 36.6 g (86 percent). For purification the product was distilled under vacuum. Boiling point: 90°C at 1 mm Hg. Melting point of the picrate: 233°C (ethanol).

## EXAMPLE 29

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-N-methyl-1-phenyl ethylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and N-methyl-1-phenylethylamine.

Yield: 40 percent of the theory. Melting point: 169°–171°C.

## EXAMPLE 30

S-(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide

To 3167 g (10 millimole) of 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride in 35 ml of chloroform there was added a mixture of 1.86 g (11 millimole) of S-(−)-1-(5-fluoro-2-methoxy)-phenyl-ethylamine and 1.11 g (11 millimole) of triethylamine in 20 ml of chloroform at 0° – 5°C. drop by drop. After another 2½ hours of agitation at 20°C, the product was heated to boiling for 1 hour, the solvent evaporated, and the residue suspended in 75 ml of water. After acidification with hydrochloric acid, the product was suction-filtered and recrystallized twice out of ethanol.

Yield: 3.2 g = 64 percent of the theory. Melting point 156°C, $[\alpha]_D^{20} = -24°$ ($c$ = 1, chloroform).

The splitting of the racemic 1-(5-fluoro-2-methoxy-phenyl) ethylamine can be effected as follows:

141 g (0.834 mole) of the racemic amine in 200 ml of methanol were added to a boiling solution of 126 g (0.84 mole) of L-(+)-tartaric acid in 1800 ml of methanol. After standing over night at 20°C, the salt was suction filtered; the working up of the mother liquor M is described below. The salt (189 g = 0.59 mole) was recrystallized five times from a minimum of hot methanol, 29 g = 0.11 mole being obtained. This was dissolved in 150 ml of water, the base being liberated with concentrated sodium hydroxide solution, ether extracted, and distilled. The obtained free, dextrorotating base (14 g = 0.083 mole, $[\alpha]_D^{20} = +29°$) was added to a suspension of 1.75 g (0.010 mole) of $Ni(SCN)_2$ in 200 ml of toluene, the mixture being heated for 5 minutes to 85°C and left at 20° for 16 hours. After cooling to 0°C, the complex was filtered out, the filtrate concentrated and the residue distilled. 8.5 g = 0.05 mole of R-(+)-1-(5-fluoro-2-methoxy-phenyl)-ethylamine of boiling point 113°–114°C at 13 mm Hg was obtained. The rotation of the base without solvent was $[\alpha]_D^{20} = +36°$. The above-mentioned mother liquor M was concentrated to 1 liter, filtered, the filtrate was concentrated to dryness, and from the salt the base was liberated as usual, distilled with steam, extracted with benzene, the extract concentrated and the residue distilled; one obtained 34 g = 0.2 mole of free, levorotating base. The latter was added in 50 ml of methanol to a boiling solution of 27 g (0.18 mole) D-(−)-tartaric acid in 400 ml of methanol. After standing over night, the salt was suction-filtered. The salt (43 g = 0.135 mole) was recrystallized once out of a minimum of hot methanol; one obtained 32 g = 0.1 mole. The levorotating base liberated therefrom as usual (14 g = 0.083 mole, $[\alpha]_D^{20} = -25°$) was further purified with 1.75 g (0.010 mole) $Ni(SCN)_2$ in 60 ml of toluene and 10 ml of tertiary butylbenzene as described above. 7.7 g = 0.046 mole of S-(−)-1-(5-fluo-2-methoxy-phenyl)-ethylamine of boiling point 112°–114° C at 13 mm Hg were obtained. The rotation of the base without solvent was $[\alpha]_D^{20} = -36°$.

## EXAMPLE 31

R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenlacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide

The compound was produced analogously to example 30 with R-(+)-1-(5-fluoro-2-methoxy-phenyl)-ethylamine and 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride. Yield 68 percent of the theory. Melting point 157°C. $[\alpha]_D^{20} = +24°$ ($c$—1, chloroform).

## EXAMPLE 32

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-methoxycarbonyl-benzylamide

The compound was produced analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 2-phenyl-glycine-methyl ester.

Yield: 65 percent. Melting point 124°C.

## EXAMPLE 33

S-(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenylethylamide

33 g (0.1 mole) of S-(−)-4-chlorosulfonyl-phenylacetic acid-1-phenylethylamide were charged in a solution of 15.0 g 2-amino-5-isobutylpyrimidine in 80 ml pyridine and the mixture was heated for 2 hours at 50°C. Then 350 ml of water was added and the precipitated product was recrystallized from ethanol.

Yield: 30 g = 66 percent of the theory. Melting point: 148°C $[\alpha]_D^{20} = 29°$ ($c$=1, chloroform).

S-(−)-4-chlorosulfonylphenylacetic acid-1-phenylethylamide was obtained as follows: 57 g (0.2 mole) of S-(−)-4-nitrophenylacetic acic-1-phenylethylamide (produced from 4-nitrophenylacetic acid chloride with S-(−)-1-phenylethylamine in pyridine, melting point 145°C, $[\alpha]_D^{20} = -86°$ ($c$—1, in methanol) were hydrated in 500 ml of dioxane at 70°–80°C and 50 atm excess pressure in the presence of Raney nickel. After removal of the catalyst by suction, the solvent was distilled off under vacuum and the residue recrystallized from benzene-petroleum ether.

Yield: 45 g = 88 percent of the theory. Melting point: 142°C, $[\alpha]_D^{20} = -65°$ (
=1, in methanol).

25 g of this S-(−)-4-amino-phenyl-acetic acid-1-phenylethylamide were dissolved in 150 ml of glacial acetic acid plus 25 ml of concentrated hydrochloric acid and admixed with S.5 g of sodium nitrite while cooling to 0° – 5°C. Then the diazonium salt solution was dropped at room temperature into a mixture consisting of 100 ml of an approximately 11 percent sulfur dioxide solution in glacial acetic acid, 6 g of copper(II) chloride in 10 ml of water, and 100 ml of benzene. After that, agitation was continued for 5 hours at 30°C, the mixture poured on ice, and the precipitated sulfochloride suctioned off, washed with iced water, and dissolved in chloroform was drawn off under vacuum. The crude sulfochloride was coupled with bases without further purification.

EXAMPLE 34

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

34 g of 4-aminosulfonyl-phenylacetic acid-1-phenylethylamide sodium salt and 17.5 g of 2-chloro-5-isobutylpyrimidine were dissolved in 320 ml of dimethyl formamide and stirred for 3½ hours at 150°C. The dimethyl formamide was distilled off and the remaining oil residue was stirred into 500 ml of water. The precipitate was suctioned off and recrystallized out of ethanol.

Yield: 13 percent of the theory. Melting point: 113°–115°C.

The starting product, 4-aminosulfonyl-phenylacetic acid-1-phenyl-ethylamide sodium salt, was produced by known methods by dropping the 4-chlorosulfonyl-phenylacetic acid1-phenylethyl chloride into excess ammonium hydroxide, distilling the excess ammonium hydroxide, drying the amide, and reacting with sodium ethylate. Melting point 300°C (with decomposition).

EXAMPLE 35

4-[N-(5-isopropylthio-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenylethylamide.

15 g (44.5 millimole) of 4-chlorosulfonyl-phenylacetic acid-1-phenylethylamide in 70 ml of acetone were added drop by drop at 0°–5°C to a mixture of 11.2 g of guanidine nitrate and 37 g of sodium hydroxide in 40 ml of acetone-water 1:1. After 2 hours, the crude 4-guanidino-sulfonyl-phenylacetic acid-1-phenyl-ethyl amide was precipitated with 40 ml of water, suctioned off and dried (7 g).

Besides, 4 g of phosgene were passed into a solution of 2.8 g of dimethyl formamide in 12 ml of toluene (temperature 0°C). 3.7 g of isopropyl mercaptoacetaldehyde diethylacetal were added in drops at 5°C, the mixture was stirred for 2 hours at 65°C, the toluene drawn off under vacuum, and the residue neutralized in 4 ml of methanol with a methanolic sodium methylate solution. The reaction product thus obtained was added to a solution of 0.9 g sodium in 21 ml methanol, the solution admixed with the 7 g of sulfaguanidine (see above) and the mixture heated for 12 hours with reflux. After neutralization with hydrochloric acid (pH 6) the product was suctioned off the common salt, the filtrate evaporated under vacuum, and the residue taken up in water. After acidification with hydrochloric acid one obtains the desired product, which was once more dissolved in sodium hydroxide solution and precipitated with hydrochloric acid.

Yield: 3.2 g = 15 percent of the theory. Melting point 125°–129°C.

Isopropyl mercapto-acetaldehyde-diethyl acetal was obtained as follows: 48 g (250 millimole) of acetylmercapto-acetaldehyde-diethyl acetal were added to a solution of 12.5 g sodium in 175 ml ethanol, the mixture was heated for 15 minutes with reflux and at the boiling heat mixed with 64.6 g of isopropyl bromide without further testing. After another hour of heating with reflux, the product was concentrated under vacuum, added with 300 ml of iced water, and extracted with ether-benzene 1:1. The organic phases were concentrated and the residue was distilled.

Yield: 42 g = 88 percent of the theory. Melting point 90°–92°C at 13 mm Hg.

EXAMPLE 36

R-(+)-4-[N-(5-ethyl-2-pyrimidinyl) sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was produced analogously to example 10 from 5.35 g (15 millimole) of 4-[N-(5-ethyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride, 1.8 g (18 millimole) of triethylamine and 2.18 g (18 millimole) of R-(+)-10 -phenylethylamine, digested in aqueous hydrochloric acid, dissolved in pyridine, and precipitated with water and subsequently recrystallized twice out of isopropanol-water.

Yield: 3 g = 39 percent of the theory. Melting point: 167°C.

$[\alpha]_D^{20} = +35°$ ($c$ = 1, chloroform).

EXAMPLE 37

R-(+)-4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenylethylamide

The compound was produced analogously to example 10 from 5.5 g (15 millimole) of 4-[N-(5-ethoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride, 1.8 g (18 millimole) of triethylamine and 2.18 g (18 millimole) of R-(+)-1-phenylethylamine and recrystallized from ethanol. Yield: 5.5 g = 83 percent of the theory. Melting point: 173°C, $[\alpha]_D^{20} = +32°$ ($c$ = 1, chloroform).

EXAMPLE 38

S-(−)-4-[N-(5-ethylmercapto-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-ethylamide

The compound was obtained analogously to example 33 from S-(−)-4-chlorosulfonyl-phenylacetic acid-1-phenylethylamide and 5-ethyl mercapto-2-amino-pyrimidine.

Yield: 20 percent of the theory. Melting point: 149°C.

$[\alpha]_D^{20} = -44°$ ($c$ = 1, chloroform).

5-ethylmercapto-2-amino-pyrimidine was produced as follows: To 38.4 g of ethylmercapto-acetaldehyde-diethylacetal, produced analogously to the isopropyl mercapto compound in example 35 with ethylbromide,

Yield: 88 percent of the theory, boiling point at 13 mm Hg (84°–86°C), there were added 42 g of $PCL_5$ at 30°–35°C and then 45 ml of dimethylformamide at 15°–20°C. The mixture was heated for 90 minutes at 65°C, admixed with 50 ml of methanol at 20°–30°C, brought to pH 8 with sodium ethylate solution (21g Na in 200 ml ethanol), and the solution added drop by drop to a mixture consisting of 40 g guanidine nitrate in 60 ml methanol and 7.6 g sodium in 80 ml methanol, at 30°–35°C. Within 2 hours the solvent was distilled off, the residue dissolved in 350 ml water, extracted with chloroform, and the concentrated extract recrystallized twice out of 100 ml $CCl_4$.

Yield: 7.9 g = 25 percent of the theory. Melting point: 116°C.

EXAMPLE 39

R-(+)-4-[N-(5-ethylmercapto-2-pyrimidinyl)-sulfamoyl]-phenyl-acetic acid-1-phenylethylamide

The compound was obtained analogously to example 33 from R-(+)-chlorosulfonyl-phenylacetic acid-1-phenylethylamide (preparation analogously to the levorotating compound in example 33) and 5-ethylmercapto-2-amino-pyrimidine.

Yield: 20 percent of the theory. Melting point: 149°C.

[alpha]$_D^{20}$= +46° ($c$ = 1, chloroform).

EXAMPLE 40

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-carboxy-benzylamide

The compound was obtained by saponification of the methyl ester (example 32) with 2n aqueous potash lye for 2 hours at 30°C and subsequent acidification.

Yield: 81 percent of the theory. Melting point: 192°C.

EXAMPLE 41

4-[N-(5-isobutyl-2-pyrimidinyl-sulfamoyl]-phenylacetic acid-1-methyl-2-phenylethylamide

The compound was obtained analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 1-methyl-2-phenylethylamine

Yield: 50 percent of the theory. Melting point: 146°C.

EXAMPLE 42

4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenylpropylamide

The compound was obtained analogously to example 1 from 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid chloride and 2-phenyl-propylamine.

Yield: 94 percent of the theory. Melting point: 212°C.

EXAMPLE 43

R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenylpropylamide

The production was effected analogously to example 42 by means of R-(+)-2-phenylpropylamine.

EXAMPLE 44

S-(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenylpropylamide

The production was effected analogously to example 42 by means of S-(−)-2-phenylpropylamine.

EXAMPLE 45

(+)-2-((4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenyl))-propionic acid-1-R-phenylethylamide

The compound was obtained analogously to example 1 from 2-((4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenyl))-propionic acid chloride and R-(+)-1-phenylethylamine.

Yield: 50 percent of the theory. Melting point: 100°C.

[alpha]$_D^{20}$= +15° ($c$ = 1, chloroform).

The acid chloride was prepared as follows:

27.0 g of 2-penylpropionic acid chloride were charged drop by drop in 80 ml of dimethylamine solution (40 percent aqueous) while stirring at +10° to +15°C.

Stirring was continued for 1 hour at +15°C, then leaving stand over night. The solution was shaken out with chloroform and the organic phase concentrated. The 29.0 g of 2-phenylpropionic acid dimethylamide thus obtained were dissolved in 150 ml of perchloroethylene, and 75 ml of chlorosulfonic acid were added drop by drop at 55°C while stirring. Agitation was continued for 45 minutes at 60°–65°C, the product being slowly placed on ice, while much heat tone occurred. The iced water was diluted with 200 ml of chloroform and thoroughly stirred. The organic phase was concentrated.

Yield: 38 g.

21.1 g of 2-amino-5-isopropoxy-pyrimidine (138 millimole) were dissolved in 80 ml of pyridine, and while stirring 38.0 g (138 millimole) of the sulfochloride were added. Agitation was continued for 2 hours at 60°–65°C, the solution was charged in 400 ml of iced water and acidified with hydrochloric acid. After suction-filtering and repeated rewashing with water the crude product was saponified. The crude acid amide was heated for 8 hours with reflux in 60 ml of 10 percent sodium hydroxide solution. After treatment of the alkaline solution with carbon, the product was acidified with 20 percent hydrochloric acid while stirring and cooling, and sanctioned off. The product was prepurified by reprecipitation with dilute ammonia and dilute hydrochloric acid and treatment with carbon. The dried crude product was recrystallized from 150 ml of ethanol-water 9:1.

Yield: 14.3 g. Melting point: 161°–163°C.

From this the acid chloride was obtained with thionyl chloride in the usual manner.

EXAMPLE 46

(−)-2-(4-[N-(5-isopropoxy-2-pyrimidinyl)-sultamoyl]-phenyl)-propionic acid-1-s-phenylethylamide

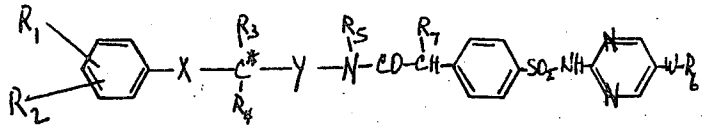
The compound was obtained analogously to example 45 by means of S-(−)-1-phenylethylamine.

Yield: 71 percent of the theory. Melting point: 99°C.

[alpha]$_D^{20}$= −15° ($c$ = 1, chloroform)

We claim:

1. Racemates and optical antipodes of sulfamoyl pyrimidines of the general formula



wherein

C* is an asymmetric C atom,

X and Y are identical or different and each by itself represents a direct bond or a methylene group except that X and Y cannot both be a direct bond,

$R_1$ and $R_2$ hydrogen or halogen atoms, alkyl groups with 1 – 6 C atoms or alkoxy groups with 1 – 4 C atoms,

$R_3$ and $R_4$ are different and represent hydrogen atoms, straight-chain or branched alkyl (with 1–4 C atoms), carboxyl or alkoxy carbonyl groups (with 1–4 C atoms)

$R_5$ and $R_7$ are identical or different and represent hydrogen atoms or low alkyl groups with 1–4 C atoms,

$R_6$ a straight-chain or branched alkyl group with 1–6 C atoms, and

W a direct C—C bond or an oxygen or sulfur atom, as well as their salts with physiologically tolerable bases.

**2.** A compound as set forth in claim **1**, which is S(−)-4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide.

**3.** A compound as set forth in claim **1**, which is R(+)-4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic-1-phenyl-propylamide.

**4.** A compound as set forth in claim **1**, which is 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide.

**5.** A compound as set forth in claim **1**, which is S(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide.

**6.** A compound as set forth in claim **1**, which is R(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide.

**7.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-propylamide.

**8.** A compound as set forth in claim **1**, which is 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-butylamide.

**9.** A compound as set forth in claim **1**, which is 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-phenyl-2-methyl-propylamide.

**10.** A compound as set forth in claim **1**, which is 4-[N-(5-isopropoxy-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenyl-2-butylamide.

**11.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide.

**12.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluoro-2-methoxy-phenyl)-ethylamide.

**13.** A compound as set forth in claim **1**, which is R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-(5-fluor-2-methoxy-phenyl)-ethylamide.

**14.** A compound as set forth in claim **1**, which is 4-[N-(5(-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-methoxy-carbonyl-benzylamide.

**15.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-carboxy-benzylamide.

**16.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-1-methyl-2-phenyl-ethylamide.

**17.** A compound as set forth in claim **1**, which is 4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-phenylpropylamide.

**18.** A compound as set forth in claim **1**, which is R-(+)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenlacetic acid-2-phenylpropylamide.

**19.** A compound as set forth in claim **1**, which is S-(−)-4-[N-(5-isobutyl-2-pyrimidinyl)-sulfamoyl]-phenylacetic acid-2-phenylpropylamide.

* * * * *