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(54) **METHOD AND REAGENTS FOR N-ALKYLATING UREIDES**

(75) Inventors: **Daniela Gutman**, Rishon Lezion (IL);
Hershel Herzog, Tarrytown, NY (US)

(73) Assignee: **Taro Pharmaceutical Industries Ltd.**,
 Haifa Bay (IL)

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See application file for complete search history.

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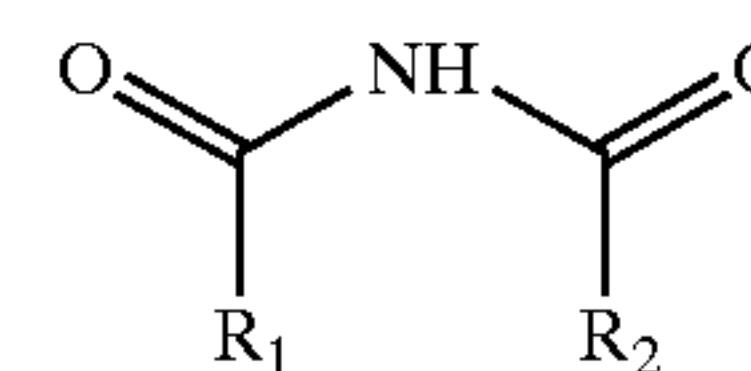
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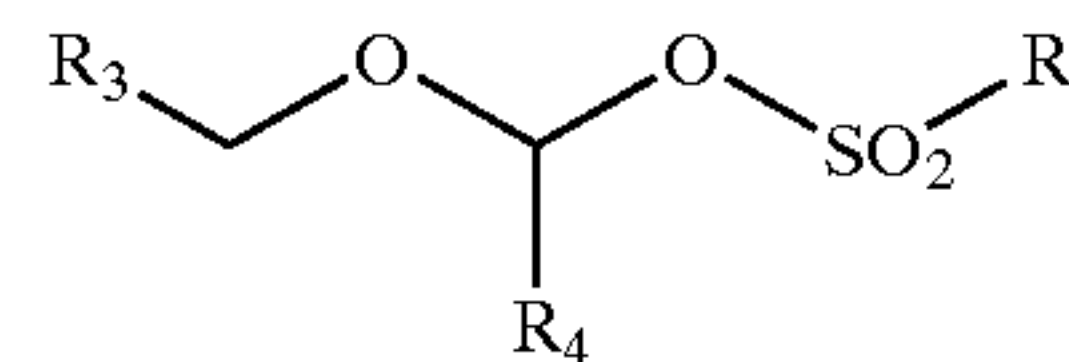
(74) *Attorney, Agent, or Firm*—Darby & Darby

(57) **ABSTRACT**

A method of N-alkoxyalkylating ureides according to the invention comprises reacting a ureide of structure I



with an alkylating agent of structure III



in the presence of a basic catalyst in an aprotic reaction medium. The ureide may be a 5,5-disubstituted barbituric acid, or it may be phenytoin, glutethimide, and ethosuximide. The alkylating agent is an ester of a sulfonic acid. The base may be a hydride or amine. A preferred process comprises N-alkoxyalkylating 5,5-diphenyl-barbituric acid with methoxymethyl methanesulfonate in the presence of di-isopropyl ethyl amine and isolating the resultant N,N'-bismethoxymethyl-5,5-diphenyl-barbituric acid. The invention also contemplates the novel compounds N-methoxymethyl-5,5-diphenylbarbituric acid, N-methoxymethyl ethosuximide, and N-methoxymethyl glutethimide, and a method comprising administering them to a patient.

31 Claims, No Drawings

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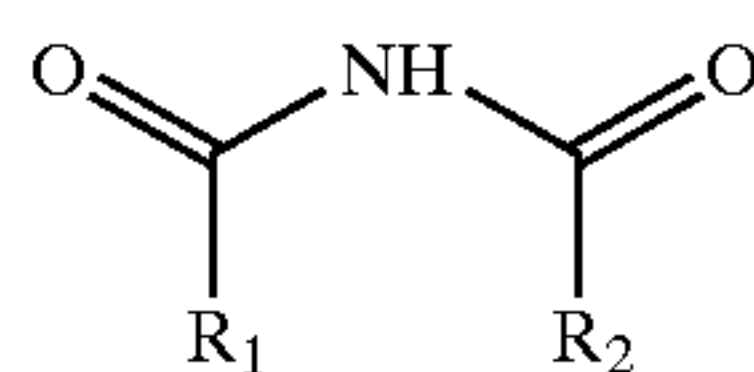
METHOD AND REAGENTS FOR N-ALKYLATING UREIDES

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

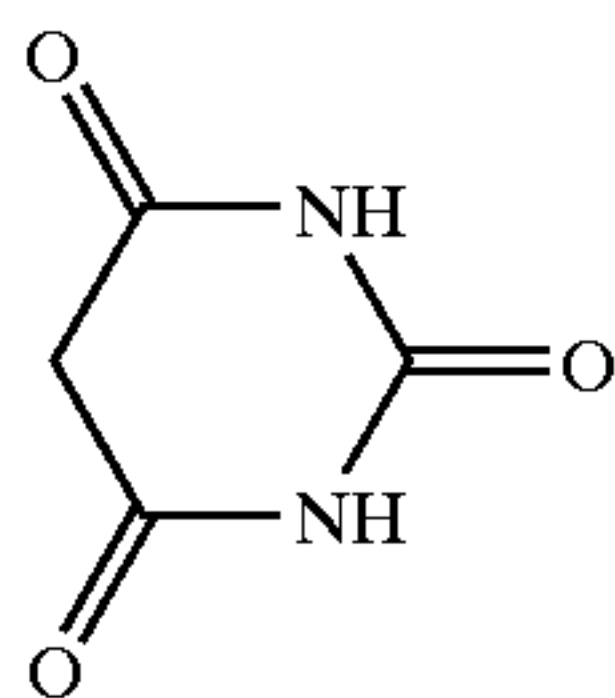
BACKGROUND OF THE INVENTION

The invention relates to a new means for N-alkylating ureides that is higher yielding, more convenient, and safer to use than techniques practiced heretofore. This approach is particularly suited to preparing N-(alkoxyalkylene) ureides, which include anti-convulsant drugs of the N-substituted barbituric acid class.

The term ureide is used in e.g. Foye, Principles of Medicinal Chemistry, 3d ed. (1990), pp. 164, 179, which is incorporated herein by reference. Ureides are a class of imides of general structure I:



Examples, include hypnotics, such as acecarbromal, apronalide, bromisolvalum, capuride, carbromal, and ectylurea; and anticonvulsant drugs such as hydantoin, glutarimides, oxazolidinediones, succinimides, and barbiturates such as barbituric acid (structure II).



U.S. Pat. No. 4,628,056 teaches a method of making 1,3 bis(methoxymethyl)-5,5-diphenyl barbituric acid (also called (N,N'-bis(methoxymethyl)-5,5-diphenyl barbituric acid) by dissolving diphenyl barbituric acid in cooled dimethylformamide, adding sodium hydride, then adding chloromethyl methyl ether. Chloromethyl methyl ether has been widely used to alkylate with a methoxymethylene function. However, it is highly toxic and regulated as a carcinogen. It is extremely volatile and flammable under exothermic reaction conditions, and alternatives to its use are strongly desirable.

Almost three decades ago, methoxymethyl methanesulfonate was identified as an agent for alkylating some alcohols and amines in a self-catalyzing reaction. Karger et al., J.A.C.S. 91:5663 (1969). With amines, the reaction was complex and led to salts, dimers, and other side products being formed. This method has not been applied to alkylation of ureides, or imides, for which there are major differences in electron availability at nitrogen.

SUMMARY OF THE INVENTION

The invention method avoids the use of volatile, carcinogenic chloromethyl methyl ether, replacing that reagent with a more reactive, less volatile alternative which may be generated in situ (without risk to the operator).

The invention solves a previously unrecognized problem limiting the applicability of methoxymethanesulfonate alky-

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lation to alcohols and amines. Ureides are much less basic than amines, so a different method for oxyalkylation is required. This invention differs from the method of Karger et al. by using a ureide, a non-aqueous basic catalyst, and an aprotic solvent, modifications which were not previously known or suggested. The inventive method allows use of a variety of sulfonates to prepare a broad variety of oxyalkylated ureides, some not previously known. The simplicity and convenience of the invention provide advantages that were not previously appreciated.

A method of N-alkoxyalkylating ureides according to the invention comprises reacting a ureide of structure I with an alkylating agent of structure III in the presence of a basic catalyst in an aprotic reaction medium. The alkylating agent III may be combined directly with the ureide, or the method may include reacting in situ a mixed anhydride of acetic acid and a sulfonic acid with a dialkoxymethane to provide the alkylating agent III. The method preferably involves isolating the resultant N-alkoxyalkylated ureide.

Preferably, the ureide is a 5,5-disubstituted barbituric acid, phenytoin, glutethimide, or ethosuximide. The alkylating agent may be methoxymethyl methanesulfonate, methoxymethyl benzenesulfonate, or methoxymethyl p-toluenesulfonate. The base may be selected from sodium hydride, triethyl amine, and di-isopropyl ethyl amine.

When the process includes the step of reacting a dialkoxymethane and a mixed acetic sulfonic anhydride to produce the resulting ester of the sulfonic acid, that reaction may be carried out in the same vessel as the following reaction with the ureide (done sequentially).

A preferred process comprises N-alkylating 5,5-diphenylbarbituric acid with a reagent selected from the group consisting of methoxymethyl methanesulfonate, methoxymethyl benzenesulfonate, and methoxymethyl p-toluenesulfonate, in the presence of di-isopropyl ethyl amine and isolating the resultant N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid.

The invention also contemplates the novel compounds N-methoxymethyl-5,5-diphenylbarbituric acid, N-methoxymethyl ethosuximide and N-methoxymethyl glutethimide, methods of making them, and a method comprising administering to a patient an effective amount of a pharmaceutical agent selected from the group consisting of N-methoxymethyl-5,5-diphenylbarbituric acid, N-methoxymethyl ethosuximide and N-methoxymethyl glutethimide.

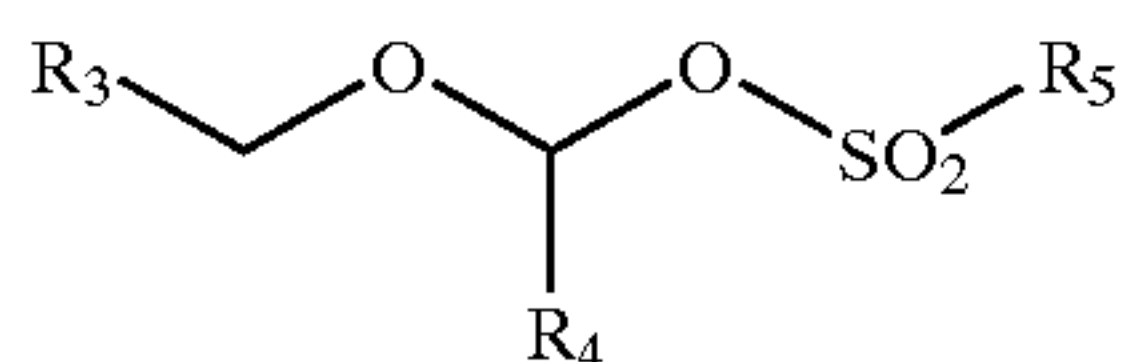
Further objectives and advantages will become apparent from a consideration of the description and examples.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In describing preferred embodiments of the present invention illustrated in the drawings, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected, and it is to be understood that each specific element includes all technical equivalents which operate in a similar manner to accomplish a similar purpose.

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The reagent class which possesses the desirable N-alkylating properties is characterized as compounds of structure III



where the R groups are preferably as follows:

R₃=H, lower alkyl, phenyl, or substituted phenyl

R₄=H, lower alkyl, phenyl, or substituted phenyl

R₅=lower alkyl, phenyl, or substituted phenyl

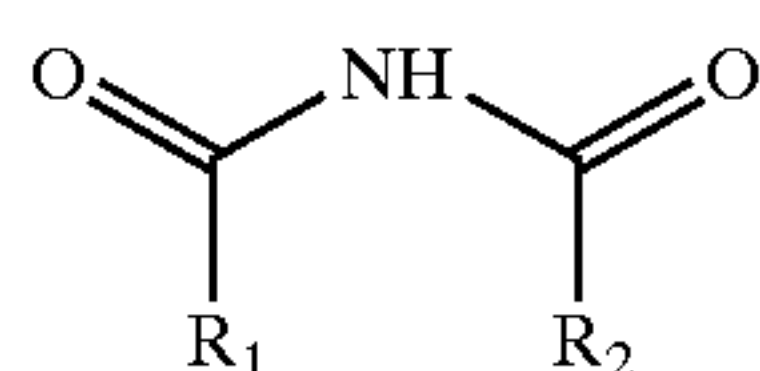
Particular examples of structures belonging to this class are listed in Table 1:

TABLE 1

Compound III	R ₃	R ₄	R ₅
1. methoxymethyl methanesulfonate	H	H	CH ₃
2. ethoxymethyl methanesulfonate	CH ₃	H	CH ₃
3. benzyloxymethyl methanesulfonate	phenyl	H	CH ₃
4. methoxymethyl ethanesulfonate	H	H	C ₂ H ₅
5. methoxymethyl benzenesulfonate	H	H	phenyl
6. methoxymethyl p-toluenesulfonate	H	H	tolyl
7. methoxybenzylidene methanesulfonate	H	phenyl	CH ₃
8. methoxyethylidene methanesulfonate	H	CH ₃	CH ₃

A particularly preferred reagent is methoxymethyl methanesulfonate.

The ureides which have been shown to be alkylated belong to the family of compounds having structure I:



which may be linear (with R₁ and R₂ being alkyl, aryl, or arylalkyl), or cyclic (R₁ and R₂ bonded to form a ring). Tables 2 and 3 (taken from Foye et al., Principles of Medicinal Chemistry, 3rd Edition (Lea and Febiger 1990), pp.164 and 179) depict ureide drugs.

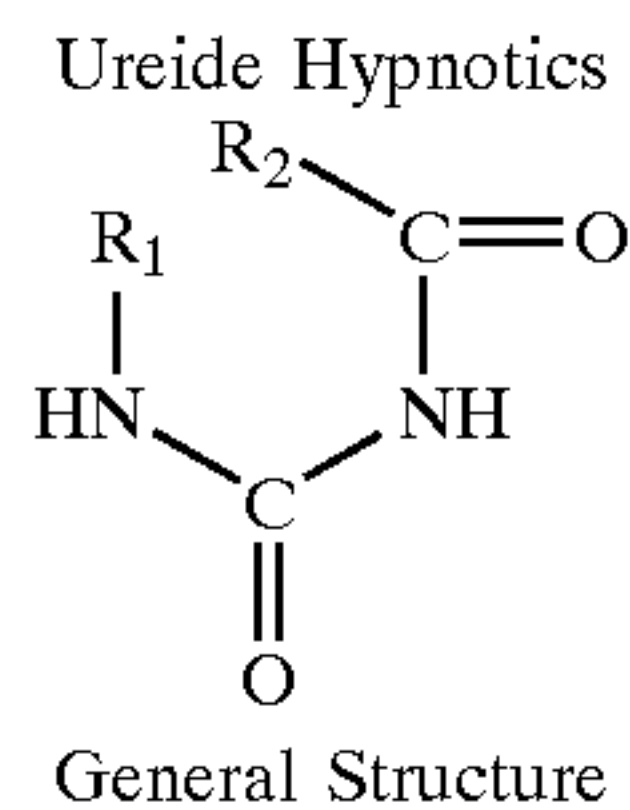
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TABLE 2

Structure of Anticonvulsant Drugs Containing the Ureide Structure

Class of Compounds	Structure
Barbiturates	
Hydantoias	
Glutarimides	
Oxazolidipediopes	
Succinimides	

TABLE 3

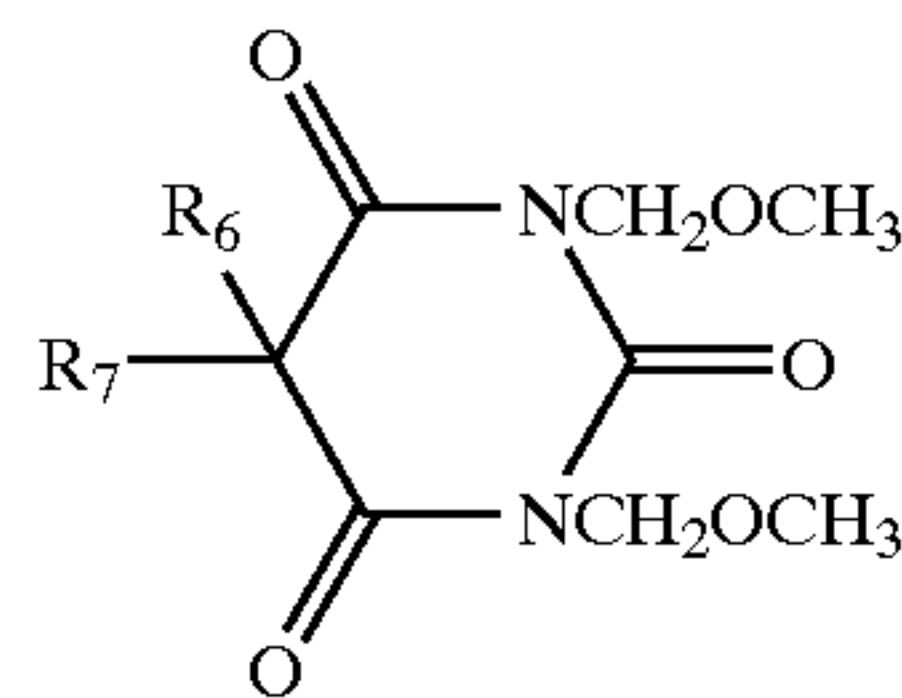


Generic Name	Chemical Name	R ₁	R ₂
55 Acecarbromal	(1-acetyl)-2-(2-bromo-2-ethylbutyryl)urea	CH ₃ CO	(C ₂ H ₅) ₂ C— Br
60 Aprohalide	(2-isopropyl-4-pentencyl)urea	H	(CH ₃) ₂ CH—CH— CH ₂ =CH—CH ₂
65 Bromisovalum	(2-bromo-3-methylbutyryl)urea	H	(CH ₃) ₂ CH—CH— Br

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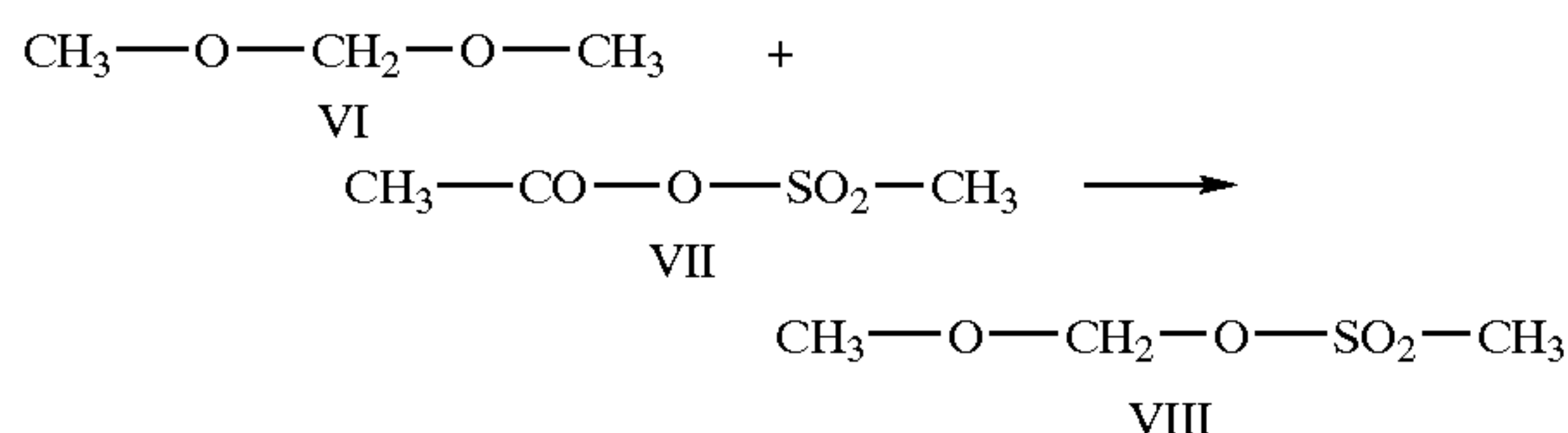
other advantages of the inventive method including the facts that it is much safer, more convenient, and economical, and allows for ready synthesis of new compounds.

A preferred embodiment of the inventive alkylation process (which employs the preferred substrate and preferred reagent illustrated above) affords the N,N' disubstituted barbituric acid depicted as structure V where the R groups are phenyl.



N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid

The alkylation preferably takes place in a solvent which is usually a dipolar aprotic solvent like an N,N'-dialkylamide. However, other types of aprotic solvents may also be employed, so long as they are compatible with the base. This alkylating technique is particularly novel and convenient in that the active alkylating species may also be generated in situ by employing precursor substances without isolation of the sulfonate reagent itself. Thus, dimethoxymethane (structure VI) may be reacted with the mixed anhydride of acetic and methanesulfonic acids (structure VII) and the resulting in situ generated sulfonate ester, methoxymethyl methanesulfonate (structure VIII, which is structure III where R₃=H, R₄=H, and R₅=CH₃) may be applied without isolation or purification to the N-alkylation of the barbituric acid.



The following examples are intended to illustrate various embodiments of the invention without limiting its scope.

EXAMPLE 1

N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid

A. Using a Hindered Tertiary Amine Catalyst

Dimethoxymethane (10.85 g) was added at 0° C. to 19.7 g of acetylmethanesulfonate. The reaction was stirred at 25° C. for 2 hours. The resultant solution was then added gradually over 45 minutes to a mixture of 10 g of 5,5-diphenylbarbituric acid and 13.85 g of N,N-diisopropyl ethyl amine in 60 ml of dry dimethylformamide. The resultant reaction mixture was stirred for about 15 minutes and then diluted with 180 ml of 2 N HCl, followed by 300 ml of ethyl acetate. The phases were separated and the ethyl acetate phase was washed first with 150 ml of saturated aqueous sodium chloride and then with 150 ml of 2N aqueous NaOH. The organic (ethyl acetate) phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness to give 12.2 g of N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid. Crystallization from 48 ml of toluene afforded 10.5 g of pure product (79.6% yield).

B. Using Triethylamine as Catalyst

By the procedure of example A, using 10.84 g, of triethylamine (in place of 13.85 g of diisopropylethylamine), there

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resulted 10.62 g of crude alkylated product. Crystallization from 40 ml of toluene afforded 7.6 g (58.5%) of N,N'-bismethoxymethyl 5,5-diphenylbarbituric acid.

C. Using Sodium Hydride as Catalyst

By the procedure of example A, using 3.57 g of sodium hydride (60% dispersion in mineral oil) in place of the amine catalyst, there resulted after crystallization from toluene 5.0 g (38%) of N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid.

V D. Using Acetylbenzenesulfonate in place of acetylmethanesulfonate

By the procedure of example A, using 28.55 g of acetylbenzenesulfonate in place of acetylmethanesulfonate (19.7 g), the pure alkylated product resulted in 75.5% yield.

Completion of the reaction may be checked using conventional methods such as by TLC on silica (mobile phase chloroform methanol 98:2). The reaction mixture is diluted with 360 ml of water and extracted with 480 ml of ethyl acetate. The organic layer is separated and washed twice with 150 ml of water. The solvent is removed by distillation under reduced pressure in order to obtain crude product. The crude product may be purified by crystallization from 4 parts of toluene. The mixture is heated to reflux to dissolve and cooled to room temperature. According to HPLC the product of the inventive method has 98–100% purity, and yields of about 60–80% may be expected.

EXAMPLE 2

N,N'-Bisethoxymethyl-5,5-diphenylbarbituric acid

By the procedure of Example 1A, using diethoxymethane (15.42 g) in place of dimethoxymethane (10.85 g), there is obtained a 68% yield of pure N,N'-bismethoxymethyl-5,5-diphenylbarbituric acid.

EXAMPLE 3

3-Methoxymethylphenytoin

By the procedure of 1A, using phenytoin (18 g) in place of 5,5-diphenylbarbituric acid (10 g), there is obtained a 70% yield of 3-methoxymethylphenytoin.

EXAMPLE 4

N-Methoxymethylglutethimide

By the procedure of 1A, using glutethimide (15.5 g) in place of 5,5-diphenylbarbituric acid (10 g) there is obtained a 65% yield of N-methoxymethylglutethimide.

EXAMPLE 5

N-Methoxymethylethosuximide

By the procedure of 1A, using ethosuximide (10 g) in place of 5,5-diphenylbarbituric acid (10 g), there is obtained a 60% yield of N-methoxymethylethosuximide.

EXAMPLE 6

N-Methoxymethyl-5,5-diphenylbarbituric acid

The monosubstituted methoxymethyl derivative is obtained by optimizing the procedure of Example 1A to favor monosubstitution, using an excess of NaH and one equivalent of alkylating agent per equivalent of ureide. The monosubstituted product is separated and characterized.

The compounds of examples 2–6 have advantageous pharmaceutical properties over a sustained period of time.

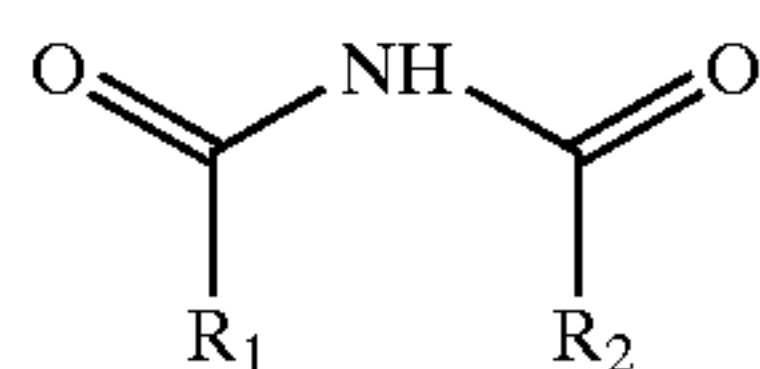
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They may be used to treat mammals including humans for convulsions, seizures, muscle stiffness, nervous strain or anxiety, by administering an effective amount of the compound in a pharmaceutically acceptable carrier to the patient.

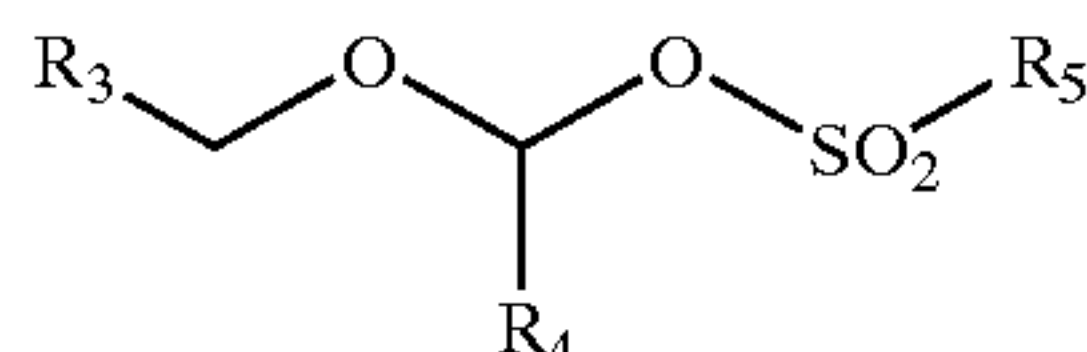
The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A method of N-alkylating ureides comprising reacting a ureide of formula I

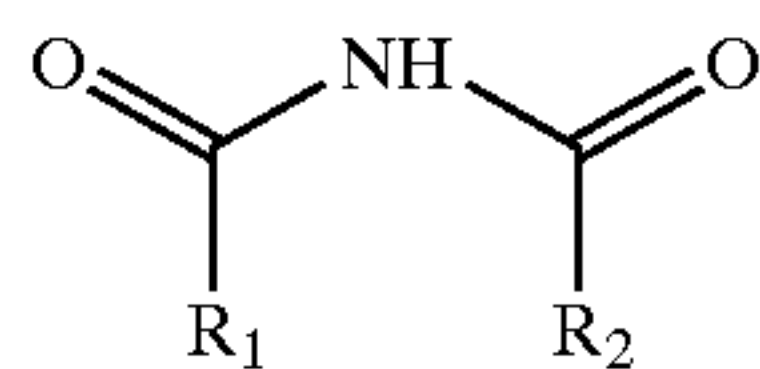


with an ester of a sulfonic acid of formula III

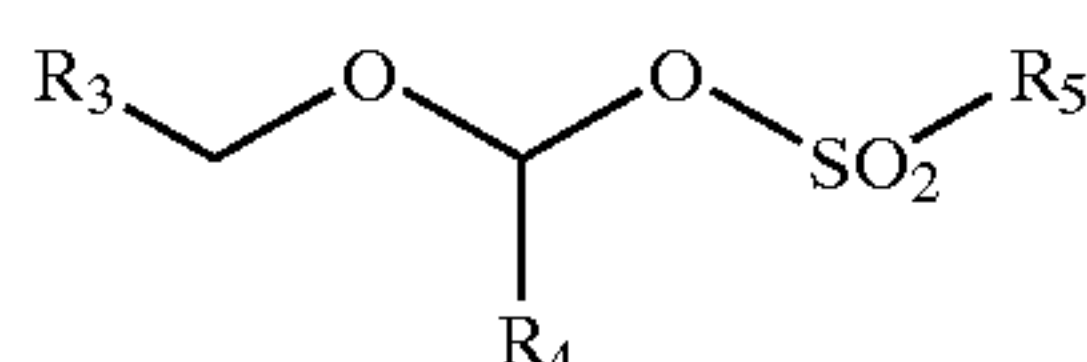


in the presence of a base in an aprotic reaction medium, to provide a corresponding alkylated ureide, wherein R_1 and R_2 are each either non-cyclic alkyl, aryl, arylalkyl, or R_1 and R_2 together form a cyclic group having a total of at least 5 atoms each of which is selected from the group consisting of carbon, nitrogen and oxygen, and wherein $\text{R}_3=\text{H}$, lower alkyl, phenyl, or alkyl substituted phenyl, $\text{R}_4=\text{H}$, lower alkyl, phenyl, or alkyl substituted phenyl, and $\text{R}_5=\text{lower alkyl, phenyl, or alkyl substituted phenyl}$.

2. A process of N-alkylation of a ureide comprising: reacting a ureide of formula I



with an ester of a sulfonic acid of Formula III



in the presence of a base and an aprotic solvent, wherein one of R_1 and R_2 is NH_2 , NHCOCH_3 , or non-cyclic alkyl, aryl, arylalkyl, or haloalkyl, and the other of R_1 and R_2 is non-cyclic alkyl, aryl, arylalkyl, or haloalkyl, or wherein R_1 and R_2 together form a cyclic group selected from the group consisting of $\text{NHCOC}(\text{R}_6)(\text{R}_7)$, $\text{NHC}(\text{R}_6)(\text{R}_7)$, $\text{CH}_2\text{CH}_2\text{C}(\text{R}_6)(\text{R}_7)$, $\text{OC}(\text{R}_6)(\text{R}_7)$ and $\text{CH}_2\text{C}(\text{R}_6)(\text{R}_7)$, wherein R_6 and R_7 , are each either noncyclic alkyl, aryl or arylalkyl, and wherein $\text{R}_3=\text{H}$,

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lower alkyl, phenyl, or alkyl substituted phenyl, $\text{R}_4=\text{H}$, lower alkyl, phenyl, or alkyl substituted phenyl, and $\text{R}_5=\text{lower alkyl, phenyl, or alkyl substituted phenyl}$, to provide a resultant N-alkoxyalkylated ureide.

3. A process according to claim 2, wherein the ureide is a 5,5-disubstituted barbituric acid.

4. A process according to claim 2, wherein the ureide is 5,5-diphenyl barbituric acid, the ester of a sulfonic acid is selected from the group consisting of methoxymethyl methanesulfonate, methoxymethyl ethanesulfonate, methoxymethyl benzenesulfonate, and methoxymethyl p-toluenesulfonate, the base is di-isopropyl ethyl amine, and the resultant ureide is N,N'-bismethoxymethyl-5,5-diphenyl barbituric acid.

5. A process according to claim 2, wherein the ureide is selected from the group consisting of 5,5-diphenyl barbituric acid, phenytoin, glutethimide, ethosuximide, 5-phenyl-5-ethylbarbituric acid, and 5,5-diethylbarbituric acid.

6. A process according to claim 2, wherein the ureide is selected from the group consisting of acecarbromal, apronalide, bromisolvalum, capuride, carbromal, ectylurea, hydantoin, glutarimides, oxazolidinediones, succinimides, and barbiturates.

7. A process according to claim 2, wherein the ester of a sulfonic acid is methoxymethyl methanesulfonate.

8. A process according to claim 2, wherein the ester of a sulfonic acid is selected from the group consisting of ethoxymethyl methanesulfonate, benzyloxymethyl methanesulfonate, methoxymethyl ethanesulfonate, methoxymethyl benzenesulfonate, methoxymethyl p-toluenesulfonate, methoxylbenzylidene methanesulfonate, and methoxyethylidene methanesulfonate.

9. A process according to claim 2, wherein the base is non-aqueous with a strength between sodium hydride and a tertiary amine.

10. A process according to claim 2, wherein the base is a tertiary amine.

11. A process according to claim 2, wherein the base is selected from the group consisting of sodium hydride, potassium hydride, lithium hydride, triethyl amine tri-n-propylamine, and di-isopropyl ethyl amine.

12. A process according to claim 2, wherein the ester of a sulfonic acid is produced in situ and is combined directly with the ureide without isolating the ester of a sulfonic acid.

13. A process according to claim 2, further comprising reacting a mixed anhydride of acetic acid and a sulfonic acid with a dialkoxymethane to provide the ester of the sulfonic acid in situ and combined with the ureide without isolating the ester of the sulfonic acid.

14. A process according to claim 2, wherein the ureide is 5,5-disubstituted barbituric acid, which is converted to its di-anion salt with a strong base, and one equivalent of the ester of a sulfonic acid is added, to provide the corresponding mono-alkylated barbituric acid.

15. A process according to claim 2, wherein the aprotic reaction medium is a dipolar solvent.

16. A process according to claim 2, wherein the dipolar solvent is selected from the group consisting of dimethyl formamide, dimethyl sulfoxide, dimethylacetamide, sulfolane, and N-methylpyrrolidone.

17. A process according to claim 3, wherein the [the] ureide is 5,5-diphenyl barbituric acid, the ester of a sulfonic acid is selected from the group consisting of methoxymethyl methanesulfonate, ethoxymethyl methanesulfonate, benzyloxymethyl methanesulfonate, methoxymethyl ethanesulfonate, methoxymethyl benzenesulfonate, methoxymethyl p-toluenesulfonate, methoxylbenzylidene

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methanesulfonate, *and* methoxyethylidene methanesulfonate, the base is a non-aqueous base selected from a hydride or an amine, and the process further comprises isolating the resultant alkoxyalkylated 5,5-diphenylbarbituric acid.

18. A process according to claim 17, wherein the ureide is alkoxyalkylated to an N-mono-alkoxyalkylated 5,5-diphenyl barbituric acid.

19. A process according to claim 18, wherein the ester is a methoxymethyl ester, the base is very strong and is present in excess, and the isolated compound is N-methoxymethyl-5,5-diphenylbarbituric acid.

20. An alkoxyalkylated ureide compound selected from the group consisting of N-methoxymethyl ethosuximide[,] *and* N-methoxymethyl glutethimide[, *and* N-methoxymethyl-5,5-diphenylbarbituric acid].

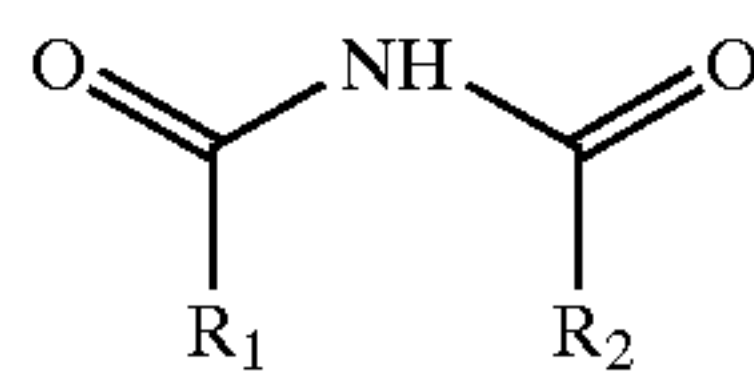
21. A compound according to claim 20, wherein the compound is N-methoxymethyl ethosuximide.

22. A compound according to claim 20, wherein the compound is N-methoxymethyl glutethimide.

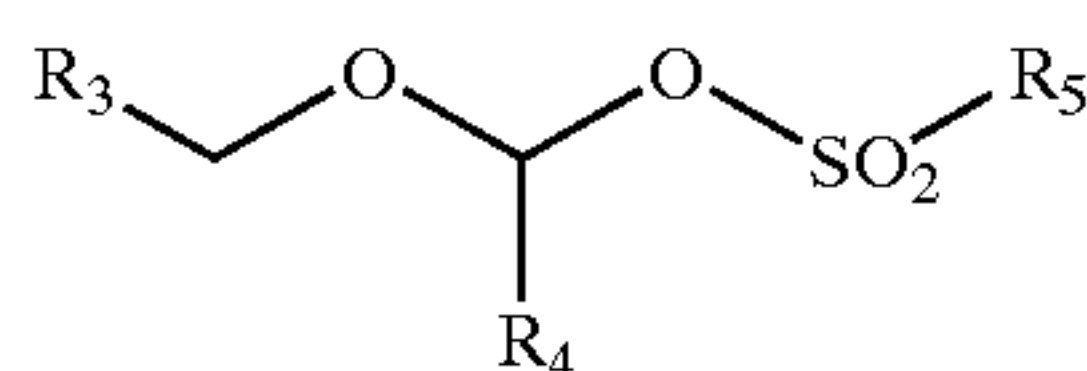
[23. A compound according to claim 20, wherein the compound is N-methoxymethyl-5,5-diphenylbarbituric acid.]

24. A method of treating a mammal for a condition selected from the group consisting of convulsions, seizures, muscle stiffness, or anxiety comprising administering to a patient in need of such treatment an effective amount of a pharmaceutical agent comprising a compound according to claim 20.

25. A method of N-alkylating ureides comprising reacting a ureide of formula I



with an ester of a sulfonic acid of formula III



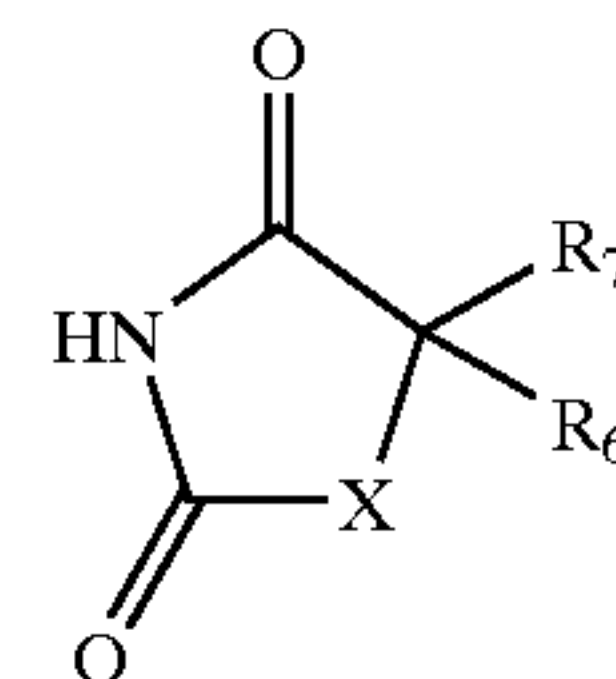
in the presence of a base in an aprotic reaction medium, to provide a corresponding alkylated ureide, wherein R₁ and R₂ together form a cyclic group having a total of at least 5 atoms each of which is selected from the group consisting of

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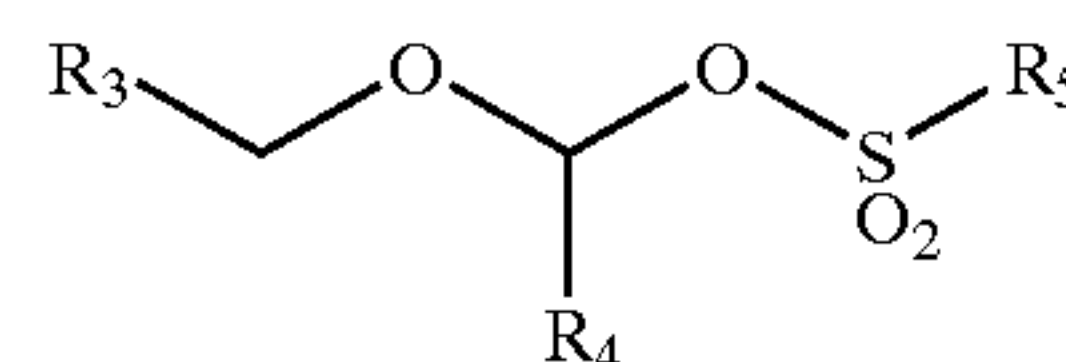
carbon nitrogen and oxygen, and wherein R₃=H, lower alkyl, phenyl, or alkyl substituted phenyl, R₄=H, lower alkyl, phenyl, or alkyl substituted phenyl, and R₅=lower alkyl, phenyl, or alkyl substituted phenyl.

26. A process for N-alkoxyalkylation of a ureide comprising:

reacting a ureide of formula IV



with an ester of a sulfonic acid of Formula III



in the presence of a base and an aprotic solvent, wherein X is O, NH, CH₂, CH₂—CH₂ or C(O)NH, and wherein R₆ and R₇ are each either noncyclic alkyl, aryl or arylalkyl, and wherein R₃=H, lower alkyl, phenyl, or alkyl substituted phenyl, R₄=H, lower alkyl, phenyl or alkyl substituted phenyl, and R₅=lower [alkyl] alkyl, phenyl, or alkyl substituted phenyl, to provide a resultant N-alkoxyalkylated ureide.

27. Isolated N-methoxymethyl-5,5-diphenylbarbituric acid.

28. A method of treating a mammal in need of treatment for a condition selected from the group consisting of convulsions, seizures, muscle stiffness, and anxiety, comprising administering to the mammal an effective amount of a pharmaceutical agent comprising N-methoxymethyl-5,5-diphenylbarbituric acid.

29. The method of claim 28, wherein the condition is convulsions.

30. The method of claim 28, wherein the condition is seizures.

31. The method of claim 28, wherein the condition is muscle stiffness.

32. The method of claim 28, wherein the condition is anxiety.

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