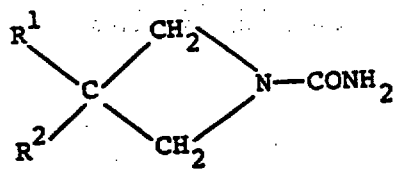
Description

The present invention relates to novel N-formyl and N-hydroxymethyl-3-phenoxy-1-azetidinecarboxamides which exhibit anticonvulsant activity in animals and are effective in treatment of epilepsy in humans.

N-Loweralkyl-3-phenoxy-1-azetidinecarboxamides are disclosed in US—A—4226861 as having anticonvulsant activity and useful in the treatment of epilepsy.

Unsubstituted-3-phenoxy-1-azetidinecarboxamides are the subject of copending European Patent Application No. 83304348.2, Publication No. EP—A—0102194, of the same date as this application and claiming priority from U.S. Serial No. 409,476, filed August 19, 1982, which compounds have longer lasting anticonvulsant effect and anti-epilepsy utility, with the absence of muscle relaxant side effects, at effective anticonvulsant doses.

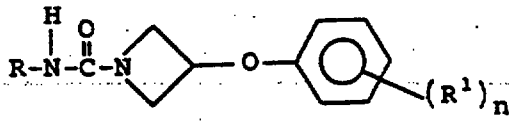
GB—A—872447 discloses anticonvulsive carbamylazetidines of the formula



where R^1 represents hydrogen, (C_1—C_8) alkyl, cycloalkyl, phenyl or phenylalkyl and R^2 represents (C_1—C_8) alkyl, cycloalkyl, phenyl or phenylalkyl.

Certain of the compounds of the present invention were discovered as metabolites in the blood-stream of animals treated with the above-mentioned N-lower alkyl compounds of US—A—4226861 and have greater longevity in the blood-stream and greater persistence in their anticonvulsant effect.

According to a first aspect of the invention, there are provided compounds of the formula:



wherein

R represents formyl or hydroxymethyl;

R^1 represents hydrogen, fluoro, (C_1—C_8) alkyl, (C_1—C_8) alkoxy, trifluoromethyl, acetyl, N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different.

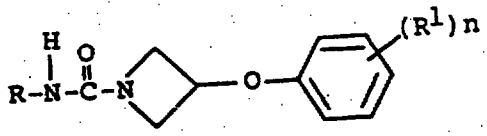
In the further definition of symbols in Formula I and where they appear elsewhere throughout this specification and in the claims the terms have the following significance.

The term "(C_1—C_8) alkyl" includes straight and branched chain hydrocarbon radicals of up to eight carbon atoms inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary-butyl, amyl, isoamyl, hexyl, heptyl and octyl.

The term "(C_1—C_8) alkoxy" has the formula O—(C_1—C_8) alkyl.

The compounds of Formula I are useful because of their pharmacological action on the central nervous system.

According to a second aspect of the present invention, there are provided N-formyl and N-hydroxymethyl-3-phenoxy-1-azetidinecarboxamides of the formula:



Formula 1

wherein

R represents formyl or hydroxymethyl,

R^1 represents hydrogen, fluoro, (C_1—C_8) alkyl, (C_1—C_8) alkoxy, trifluoromethyl, acetyl, N-formylcarboxamido or N-hydroxymethylcarboxamido; and

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different

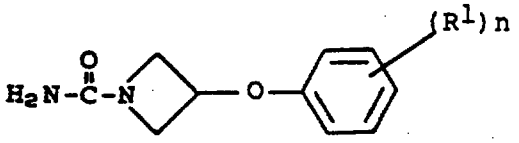
for use in medicine, particularly for use in the treatment or prophylaxis of disorders of the central nervous system such as epilepsy.

According to a third aspect of the present invention, there is provided a pharmaceutical composition comprising

a) an effective amount of a compound as defined above in accordance with the first aspect of the invention and

b) a pharmaceutically acceptable carrier therefor.

According to a fourth aspect of the present invention, there is provided a process for the preparation of a compound in accordance with the first aspect of the invention, which process comprises reacting a compound of the formula



wherein R^1 and n is as defined in relation to the first aspect, in which however the carboxamido group of R_1 is unsubstituted with formaldehyde, formic acid or a salt thereof, methyl orthoformate, ethyl orthoformate or acetic-formic anhydride.

Preferred compounds of the first aspect of the invention are those in which n is 1 or 2, especially 1. R^1 may represent 2-, 3- or 4-trifluoromethyl especially 3-trifluoromethyl. R^1 may also represent 4-alkoxy, especially 4-methoxy, or dialkoxy, especially dimethoxy, such as 3,5-dialkoxy. Compounds in which R^1 represents 3-fluoro or acetyl, especially 4-acetyl, are also preferred, as are compounds in which R^1 represents 2-, 3- or 4- (N-formylcarboxamide) or 2-, 3- or 4- (N-hydroxymethylcarboxamide). Further preferred compounds are those in which R^1 represents methyl such as 4-methyl and other 4-alkyl substituents.

Preferred features of the second, third and fourth aspects of the invention are as for preferred features of the first aspect *mutatis mutandis*.

The procedure for establishing anticonvulsant activity of the compounds of this invention and comparison with prior art compounds is based on evaluation techniques using Metrazole as convulsant published by Swinyard, E. A. in EPILEPSIA *10*: 107—19 (1969) and in J. PHARMAC. EXPTL. THERAP. *106*: 319—30 (1952) as described in greater detail hereinbelow.

A reaction sequence for the preparation of compounds of Formula I is shown in Chart I. A preparation of certain of the compounds of Formula III is also disclosed in US—A—4379151 filed on April 5th 1983 and a preparation of the compounds of Formula II is also disclosed in the previously mentioned copending European Application. Compounds of Formula IV wherein R^2 is α-methylbenzyl or diphenylmethyl can be prepared by reacting compounds of Formula V and VI at temperatures up to about 80—100°C. for periods of 2 to 5 hours in dimethylformamide. Compounds of Formula III can be prepared by hydrogenolysis of compounds of Formula IV, usually in the presence of a lower-alkanol solvent, ethanol being preferred. The rate of hydrogenolysis is dependent somewhat on time and temperature, a higher temperature generally decreasing the time required for complete hydrogenolysis. Typical times vary from about 3 hr to about 24 hr at temperatures of 50—90°C.

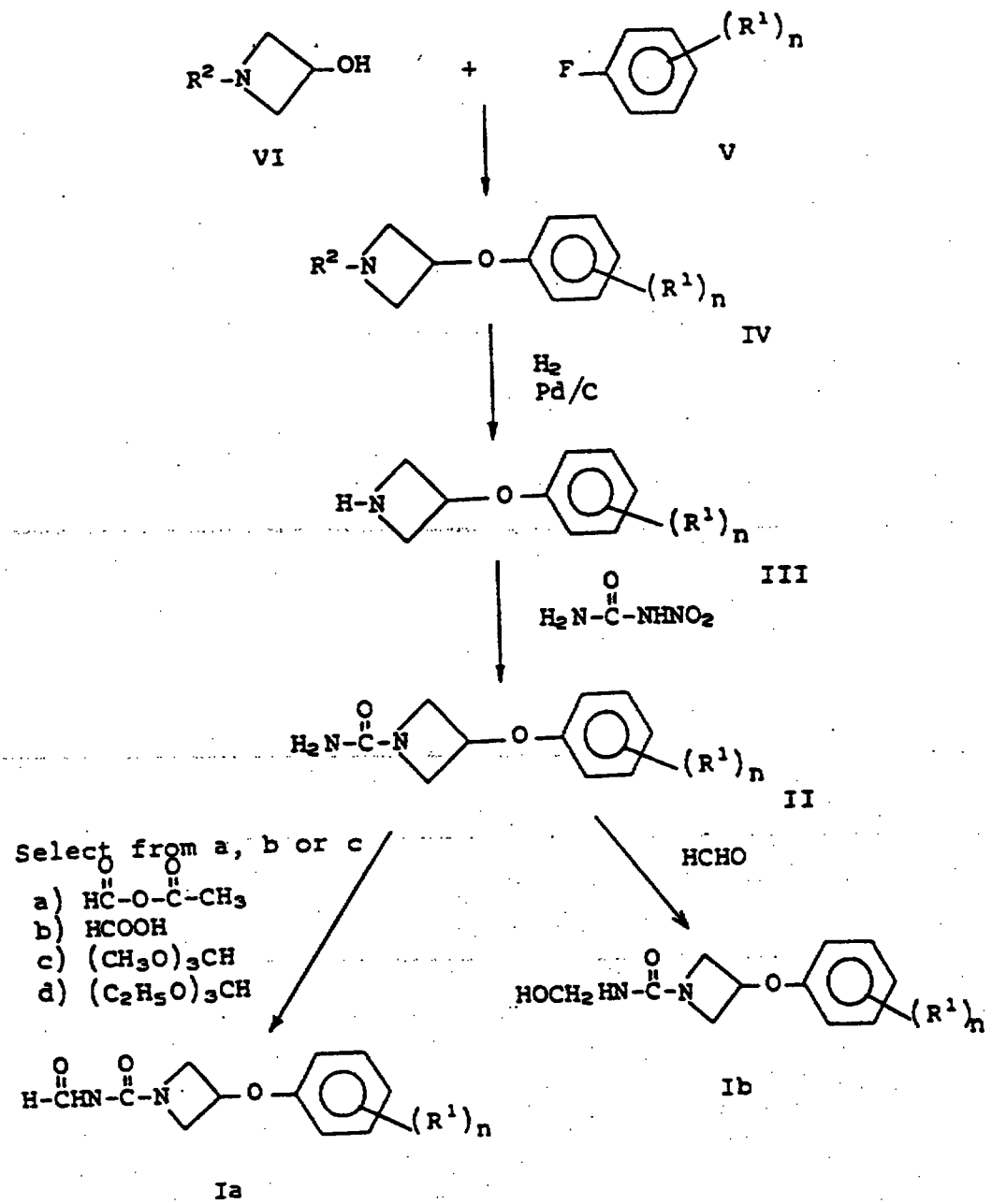
Compounds of Formula II can be prepared by reacting compounds of Formula III with nitrourea in solution, conveniently for example in a mixture of ethanol and methylene chloride or acetone at room temperature usually until analysis indicates substantial reaction has occurred and isolating by evaporation of reaction solvent, partitioning with water and an organic solvent for the compound, separating and evaporating the organic solvent layer and recrystallizing.

Compounds of Formula I wherein R is formyl can be prepared by reacting compounds of Formula II with formic acid such as the free acid or its salts, acetic-formic anhydride or methyl and ethyl orthoformate, preferably acetic-formic anhydride. Conveniently, a solvent such as methylene chloride is employed in the reaction mixture. When acetic-formic anhydride is the source of formic acid, temperatures of 10 to 60°C. for the reaction are appropriate, preferably 20—30°C. and the product may be isolated by evaporating, partitioning the residue in a solvent such as methylene chloride and water, separating, drying and evaporating, partitioning the residue in a solvent such as methylene chloride and water, separating, drying and evaporating the solvent layer to dryness, triturating the residue with ether, filtering and drying as in Example 1.

Compounds of Formula I wherein R is hydroxymethyl can be prepared by reacting compounds of Formula II with warm formaldehyde solution, preferably at about 60—70°C. The product is extracted with a solvent such as ether and worked up for purification as in Example 4.

Preparations 1—18 illustrate the preparation of compounds of Formula III and their precursors and Preparations 19—21 illustrate the preparation of compounds of Formula II. The examples illustrate the conversion of 3-phenoxy-1-azetidinecarboxamides to their N-formyl and N-hydroxymethyl derivatives (Formula I). It will be apparent to those skilled in the art that modifications may be practised within the frame of the aspects claimed and the examples to illustrate the claimed subject matter.

CHART I



Preparation 1

3-(3-Chorophenoxy)-1-(α-methylbenzyl)azetidine Oxalate

1-(α-Methylbenzyl)-3-hydroxyazetidine maleate (393 g., 1.3 moles) was partitioned in dilute potassium hydroxidebenzene. The separated dried benzene solution was concentrated, the residual oil dissolved in 250 ml. of dimethylformamide and added dropwise to a stirred suspension of 53 g. (1.1 moles) of 50% sodium hydride in 750 ml. of dimethylformamide at 90°C. The mixture was heated at 90°C for 1 hr. and 130.5 g. (1 mole) of 3-chlorofluorobenzene added dropwise at 90°C. The mixture was refluxed for 3 hrs., cooled and partitioned between isopropyl ether and dilute sodium hydroxide. The isopropyl ether solution was dried, concentrated, and the residue added to 1200 ml. of isopropyl alcohol containing 90 g. (1 mole) of oxalic acid. The oxalate salt was recrystallised from ethanol. Yield 263 g. (69%); m.p. 141—144°C.

Analysis: Calculated for $C_{19}H_{20}ClNO_5$: C, 60.40; H, 5.34; N, 3.71
Found: C, 60.19; H, 5.55; N, 3.60

(13)

Preparation 2

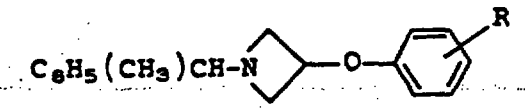
1-(α-Methylbenzyl)-3-(4-trifluoromethylphenoxy)azetidine

The maleate salt of 1-(α-methylbenzyl)-3-hydroxyazetidine (78.6 g., 0.20 mole) was partitioned between benzene and dilute sodium hydroxide, the benzene layer dried, filtered, and concentrated at reduced pressure. The residue was dissolved in 100 ml. of dry dimethylformamide and added at a rapid dropwise rate, to a stirring suspension of 10.1 g. (0.22 mole) of sodium hydride (50% in mineral oil) in 150 ml. of dry dimethylformamide at 90°C. The solution was heated at 90°C. for one hour and then treated dropwise with 32.0 g. (0.20 mole) of 4-trifluoromethylfluorobenzene. The solution was refluxed for three hours. The cooled solution was partitioned between water and isopropyl ether, and the ether layer extracted with dilute hydrochloric acid. The aqueous acid layer was made basic with concentrated sodium hydroxide and ice, and extracted with isopropyl ether. The ether layer was concentrated and the residue distilled at 150—160°C./0.2 mm. to give 25.6 g. of product.

Analysis: Calculated for $C_{18}H_{18}F_3NO$: C, 67.28; H, 5.65; N, 4.36
Found: C, 67.27; H, 5.84; N, 4.34

Preparations 3 to 7 were prepared according to the procedures set forth in detail in Preparations 1 and 2 by reacting 1-(α-methylbenzyl)-3-azetidinol with the appropriately substituted fluorobenzene. The physical constants are shown in Table I.

TABLE I



Preparation	R	M.p. (b.p.) °C.	Salt
3	2—$CONH_2$	148—52	—
4	4—CN	65—8	—
5	3—CF_3	150—3	$(COOH)_2$
6	2—CF_3	162—3	$(COOH)_2$
7	3—CN	[1](185—90)	—

[1]At 0.2 mm.

The analytical data of Preparations 3 to 7 are shown in Table II.

TABLE II

Preparation	Empirical Formula	Analytical Data on Preparations 3 to 7 Calculated C	H	N	Found C	H	N
3	$C_{18}H_{20}N_2O_2$	72.95	6.80	9.45	72.56	6.78	9.32
4	$C_{18}H_{18}N_2O$	77.67	6.52	10.06	77.61	6.53	10.01
5	$C_{20}H_{20}F_3NO_5$	58.39	4.90	3.41	57.99	4.97	3.39
6	$C_{20}H_{20}F_3NO_5$	58.39	4.90	3.41	58.15	4.89	3.37
7	$C_{18}H_{18}N_2O$	77.67	6.52	10.06	77.32	6.54	9.87

Preparation 8

3-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzamide Oxalate

3-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzonitrile (50.0 g., 0.18 mole) in 500 ml of t-butyl alcohol was treated with 50.0 g. of finely ground potassium hydroxide. The mixture was stirred at reflux for 30 min. Ice

and water were added to the reaction mixture and the organic layer was separated and dried over sodium sulphate. The dried filtered solution was concentrated at reduced pressure. The residue was dissolved in methanol and treated with an equivalent of oxalic acid, and the oxalate salt was recrystallized from ethanol to give 11.4 g. (16%) of product, (m.p. 145°C.).

Analysis: Calculated for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25
Found: C, 62.17; H, 5.80; N, 7.20

Preparation 9

4-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzamide

To 45.0 g. (0.16 mole) of 4-[1-(α-methylbenzyl)-3-azetidinyloxy]benzonitrile in 500 ml of t-butyl alcohol was added 45.0 g. of finely ground potassium hydroxide. The mixture was stirred and refluxed for 30 minutes. Ice and water were added and a thick white solid separated. The solid was recrystallized from toluene to give 30.0 g. (63%) of product melting at 174—178°C.

Analysis: Calculated for $C_{18}H_{20}N_2O_2$: C, 72.05; H, 6.80; N, 9.45
Found: C, 73.06; H, 6.79; N, 9.44

Preparation 10

1-Diphenylmethyl-3-phenoxyazetidine.

To a stirred suspension of 8.6 g. (0.22 mole) of sodium amide in 100 ml. of dry toluene was added 18.2 g. (0.2 mole) of phenol in 50 ml. of dry toluene. After stirring for 2 hrs. at 60°C. the pot temperature was raised to 80°C. and a solution of 1-diphenylmethyl-3-methylsulphonyloxyazetidine (63.4 g., 0.2 mole) in 200 ml. of dry toluene was added dropwise. After an additional 2 hrs. at 80°C. the cooled mixture was treated with water, the toluene layer was extracted with dilute sodium hydroxide solution, dried and concentrated at reduced pressure. The residue was crystallized twice from a water-isopropanol mixture. The free base melted at 83—85°C.

Analysis: Calculated for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44
Found: C, 83.69; H, 6.81; N, 4.41

Preparation 11

3-(Phenoxy)acetidine Methanesulphonate.

A 200 ml. solution of 7.8 g (0.025 mole) of 1-diphenylmethyl-3-phenoxyazetidine in ethanol was treated with 20% Pd $(OH)_2$ on carbon and hydrogenated for 23 hrs. at about 45 psi and 80°C. The mixture was filtered and the filtrate concentrated. The residue was diluted to 30 ml. with ethanol and 2.5 g. of methanesulphonic acid added. The isolated methanesulphonate salt was recrystallized from ethanol. The salt weighed 2.3 g. (37.5%) and melted at 128—130°C.

Analysis: Calculated for $C_{10}H_{15}NO_4S$: C, 48.97; H, 6.16; N, 5.71
Found: C, 48.40; H, 6.19; N, 5.63

The compound was also prepared by hydrogenolysis of 1-(α-methylbenzyl)-3-(3-chlorophenoxy)azetidine in isopropyl alcohol using the same type catalyst and conditions.

Preparation 12

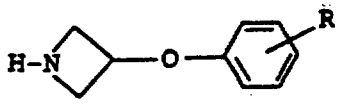
3-[4-(Trifluoromethyl)phenoxy]azetidine Oxalate.

To 24.0 g. (0.075 mole) of 3-[4-(trifluoromethyl)phenoxy]-1-(α-methylbenzyl)azetidine in 150 ml. of ethanol was added 0.5 g. of 20% Pd $(OH)_2$ on carbon, and the mixture was hydrogenated for five hours at 80°C. and 45 psi. The mixture was cooled, filtered, and the filtrate concentrated at reduced pressure. The residue was dissolved in ethanol and treated with oxalic acid, and the oxalate salt was recrystallized three times in ethanol. The yield was 3.0 g. (13%) and the salt melted at 176—178°C.

Analysis: Calculated for $C_{12}H_{12}F_3NO_3$: C, 46.91; H, 3.94; N, 4.56
Found: C, 47.07; H, 3.96; N, 4.59

The compounds in Preparations 13 to 17 are prepared according to the procedure set forth in detail in Preparations 11 and 12 by hydrogenolysis of the α-methylbenzyl radical attached to the azetidine nitrogen. The physical constants are shown in Table 1.

TABLE 1



Preparation	R	M.P. °C	Salt
13	2—$CONH_2$	173—75	CH_3SO_3H—
14	3—CF_3	123—25	[1]$C_6H_{11}NHSO_3H$
15	2—CF_3	154—56	HCl
16	3—$CONH_2$	160—63	—
17	4—$CONH_2$	187—88	$(COOH)_2$

[1]N-cyclohexylsulphamate.

The analytical data of Preparations 13 to 17 are shown in Table 2.

TABLE 2

Analytical Data on Preparations 13 to 17

Preparation	Empirical Formula	Calculated			Found		
		C	H	N	C	H	N
13	$C_{11}H_{16}N_2O_5S$	45.42	5.59	9.72	45.48	5.65	9.45
14	$C_{16}H_{23}F_3N_2O_4S$	48.48	5.85	7.07	48.08	5.94	6.97
15	$C_{10}H_{11}ClF_3NO$	47.35	4.37	5.52	47.12	4.32	5.45
16	$C_{10}H_{12}N_2O_2$	62.49	6.29	14.57	62.06	6.13	13.98
17	$C_{12}H_{14}N_2O_6$	51.07	5.00	9.93	51.39	5.22	9.56

Preparation 18

When in the procedure of Preparation 12 the following are substituted for 3-[4-(trifluoromethyl)-phenoxy]-1-(α-methylbenzyl)azetidine:

3-[4-(methyl)phenoxy]-1-(α-methylbenzyl)azetidine,
3-[4-(methoxy)phenoxy]-1-(α-methylbenzyl)azetidine,
3-[3,5-(dimethoxy)phenoxy]-1-(α-methylbenzyl)azetidine,
3-[3-(fluoro)phenoxy]-1-(α-methylbenzyl)azetidine, and
3-[4-(acetyl)phenoxy]-1-(α-methylbenzyl)azetidine,

there are obtained:

3-[4-(methyl)phenoxy]azetidine oxalate,
3-[4-(methoxy)phenoxy]azetidine oxalate,
3-[3,5-(dimethoxy)phenoxy]azetidine oxalate,
3-[3-(fluoro)phenoxy]azetidine oxalate, and
3-[4-(acetyl)phenoxy]azetidine oxalate.

Preparation 19

3-[3-(Trifluoromethyl)phenoxy]-1-azetidinecarboxamide.

To a solution of 2.2 g (0.01 mole) of 3-[3-(trifluoromethyl)phenoxy)azetidine in 45 ml of methylene chloride and 45 ml of absolute ethyl alcohol was added 7 g (0.066 mole) of nitrourea and the mixture was stirred at room temperature for 48 hr. The mixture was filtered. The filtrate was evaporated to dryness and the residue was partitioned between 75 ml methylene chloride and 75 ml water. The water layer was

extracted three times with 50 ml of methylene chloride. The methylene chloride extracts were combined and evaporated to dryness. The residue was treated (washed) with a mixture of 1 ml methylene chloride and 20 ml of toluene and filtered. The precipitate was recrystallized from ethanol-water to give pale yellow crystals. The crystals were mixed with 2 ml of methylene chloride and 20 ml toluene and the mixture was heated on a steam bath for 2 hrs. The mixutre was stored in a refrigerator for approximately 72 hrs. and filtered to give 1.2 g of the product as white crystalline needles, m.p. 151—152°C.

Analysis: Calculated for $C_{11}H_{11}N_2O_2F_3$: C, 50.77; H, 4.26; N, 10.77
Found: C, 50.72; H, 4.25; N, 10.74

Preparation 20

3-[3-(Trifluoromethyl)phenoxy]-1-azetidinecarboxamide.

A mixture of 30.6 g (0.141 mole) of 3-[3-trifluoromethyl)phenoxy]azetidine and 42 g (0.321 mole) of nitrourea (80%) in 500 ml of acetone was stirred for 5 days (5 days not required, but convenient) at room temperature. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was partitioned between 150 ml of water and 100 ml of ethyl acetate and the layers separated. The aqueous layer was washed with 100 ml of ethyl acetate. The ethyl acetate layers were washed with 75 ml of 5% aqueous sodium hydroxide solution followed by 75 ml of water, dried over sodium sulphate and concentrated *in vacuo*. The residual oil was crystallized from ethyl alcohol-ethyl acetate to give 22 g (60%) substantially the title compound. Recrystallization twice from ethyl alcohol gave 9.9 g of white crystalline solid, m.p. 151—152.5°C.

Analysis: Calculated for $C_{11}H_{11}N_2O_2F_3$: C, 50.77; H, 4.26; N, 10.76
Found: C, 50.90; H, 4.29; N, 10.71

Preparation 21

When in the procedure of Preparation 20 the following are substituted for 3-[3-(trifluoromethyl)phenoxy]azetidine,

3-(phenoxy)azetidine,
3-[4-(trifluoromethyl)phenoxy]azetidine,
3-[2-(trifluoromethyl)phenoxy]azetidine,
3-[4-(methyl)phenoxy]azetidine,
3-[4-(methoxy)phenoxy]azetidine,
3-[3,5-(dimethoxy)phenoxy]azetidine,
3-[3-(fluoro)phenoxy]azetidine,
2-(3-azetidinyloxy)benzamide,
3-(3-azetidinyloxy)benzamide,
4-(3-azetidinyloxy)benzamide, and
3-[4-(acetyl)phenoxy]azetidine,

there are obtained:

3-(phenoxy)-1-azetinecarboxamide,
3-[4-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
3-[2-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
3-[4-(methyl)phenoxy]-1-azetidinecarboxamide,
3-[4(methoxy)phenoxy]-1-azetidinecarboxamide,
3-[3,5-(dimethoxy)phenoxy]-1-azetidinecarboxamide,
3-[3-(fluoro) phenoxy]-1-azetidinecarboxamide,
3-[2-(carboxamido)phenoxy]-1-azetidinecarboxamide,
3-[3-(carboxamido)phenoxy]-1-azetidinecarboxamide,
3-[4-(carboxamido)phenoxy]-1-azetidinecarboxamide, and
3-[4-(aceto)phenoxy]-1-azetidinecarboxamide.

Example 1

N-Formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide.

A mixture of 0.524 g (0.002 mole) of 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide and 1.5 ml of formic acetic anhydride (prepared by reacting sodium formate and acetyl chloride in ether at 23—27°C. for 5.5 hr, filtering and evaporating off the ether) was stirred at room temperature for about 54 hr. The mixture was evaporated to dryness and the residue was partitioned between 7 ml methylene chloride and 2 ml water. The methylene chloride layer was separated, dried over sodium sulphate and evaporated to dryness. The residue was triturated with ether and the mixture subjected to filtration to give a solid white filter cake weighing 0.398 g after drying. The solid was stirred with more ether for 10 minutes and the mixture filtered to give 0.350 g (61%) white powder, m.p. 117.5—119°C.

Analysis: Calculated for $C_{12}H_{11}N_2O_3F_3$: C, 50.00; H, 3.84; N, 9.72.
Found: C, 49.94; H, 3.85; N, 9.68

17

Example 2

When in the procedure of Example 1, the following are substituted for 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide:

3-(phenoxy)azetidinecarboxamide,
3-[4-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
3-[2-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide.
3-[4-(methyl)phenoxy]-1-azetidinecarboxamide,
3-[3,5-(dimethoxy)phenoxy]-1-azetidinecarboxamide,
3-[3-(fluoro)phenoxy]-1-azetidinecarboxamide, and
3-[4-(aceto)phenoxy]-1-azetidinecarboxamide,

there are obtained:

N-formyl-3-(phenoxy)azetidinecarboxamide,
N-formyl-3-[4-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
N-formyl-3-[2-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
N-formyl-3-[4-(methyl)phenoxy]-1-azetidinecarboxamide,
N-formyl-3-[3,5-(dimethoxy)phenoxy]-1-azetidinecarboxamide,
N-formyl-3-[3-(fluoro)phenoxy]-1-azetidinecarboxamide, and
N-formyl-3-[4-(aceto)phenoxy]-1-azetidinecarboxamide.

Example 3

When in the procedure of Example 1, the following are substituted for 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide and the amount of acetic formic anhydride is doubled:

3-[2-(carboxamido)phenoxy]-1-azetidinecarboxamide,
3-[3-(carboxamido)phenoxy]-1-azetidinecarboxamide, and
3-[4-(carboxamido)phenoxy]-1-azetidinecarboxamide,

there are obtained:

N-formyl-3-[2-(N-formylcarboxamido)phenoxy]-1-azetidinecarboxamide,
N-formyl-3-[3-(N-formylcarboxamido)phenoxy]-1-azetidinecarboxamide, and
N-formyl-3-[4-(N-formylcarboxamido)phenoxy]-1-azetidinecarboxamide.

Example 4

N-Hydroxymethyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide.

A mixture of 0.639 g (0.0024 mole) of 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide amd 6 ml of 37% formaldehyde solution were heated on a water bath at 65°C. for 1 hr, at which time dissolution was complete. The solution was stirred at room temperature for approximately 60 hr. The reaction mixture was divided into two 15 ml centrifuge tubes each extracted three times with ether. The combined extracts were dried over magnesium sulphate, decolourised with charcoal and evaporated to dryness. The residue weighing about 1.5 g was dissolved in ether, washed 5 times with 3 ml of water each time. The ether layer was again dried over magnesium sulphate and evaporated to dryness. The residue was triturated with hexane and ether to give 0.213 g (30.5%) of white powder, m.p. 113—115°C.

Analysis: Calculated for $C_{12}H_{13}N_2O_3F_3$: C, 49.66; H, 4.51; N, 9.65
Found: C, 49.59; H, 4.52; N, 9.54

Example 5

When in the procedure of Example 4, the following are substituted for 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide:

3-(phenoxy) azetidinecarboxamide,
3-[4-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
3-[2-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
3-[4-(methyl)phenoxy]-1-azetidinecarboxamide,
3-[3,5-(dimethoxy)phenoxy]-1-azetidinecarboxamide,
3-[3-(fluoro)phenoxy]-1-azetidinecarboxamide, and
3-[4-(aceto)phenoxy]-1-azetidinecarboxamide,

there are obtained:

N-hydroxymethyl-3-(phenoxy)azetidinecarboxamide,
N-hydroxymethyl-3-[4-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
N-hydroxymethyl-3-[2-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide,
N-hydroxymethyl-3-[4-(methyl)phenoxy]-1-azetidinecarboxamide,
N-hydroxymethyl-3-[3,5-(dimethoxy)phenoxy]-1-azetidinecarboxamide,
N-hydroxymethyl-3-[3-(fluoro)phenoxy]-1-azetidinecarboxamide, and
N-hydroxymethyl-3-[4-(aceto)phenoxy]-1-azetidinecarboxamide.

Example 6

When in the procedure of Example 4, the following are substituted for 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide and the amount of formaldehyde is doubled:

3-[2-(carboxamido)phenoxy]-1-azetidinecarboxamide,
3-[3-(carboxamido)phenoxy]-1-azetidinecarboxamide, and
3-[4-(carboxamido)phenoxy]-1-azetidinecarboxamide,
there are obtained:
N-hydroxymethyl-3-[2-(N-hydroxymethylcarboxamido)phenoxy]-1-azetidinecarboxamide,
N-hydroxymethyl-3-[3-(N-hydroxymethylcarboxamido)phenoxy]-1-azetidinecarboxamide, and
N-hydroxymethyl-3-[4-(N-hydroxymethylcarboxamido)phenoxy]-1-azetidinecarboxamide.

Pharmacology: Procedure for Determining Anticonvulsant Activity

Anticonvulsant activity of a compound of the invention is determined in mice using Metrazole as the convulsant by the method of Swinyard (see above citation) as follows:

Adult female mice are randomly assigned to dosage groups according to the method of Steel, R. G. D. and Torrie, J. H. (1960) in "Principles and Procedures of Statistics," McGraw-Hill Book Company, Inc., pp. 99—100, pp. 428—31. Each mouse is identified with a colour code on its tail. The test compounds are administered as suspensions in 10 ml/kg mouse body weight of 0.5% aqueous methylcellulose within 15 minutes of preparation of the suspension. Metrazole (pentylenetetrazol) is prepared as a solution in physiological saline. The mice are not fasted prior to the test. Eight mice are tested at each level.

Each mouse receives one dose of the test drug in the 0.5% aqueous methylcellulose or the control article (0.5% aqueous methylcellulose alone) intraperitoneally. One-half hour after administration of the test compound, Metrazole (80 mg/kg S.C. in saline) is then given in a loose fold of skin on the back of the neck. Injections are given with a 1-ml glass tuberculin syringe with appropriate size hypodermic needle (27 gauge for solutions; 23 gauge for suspensions). All injections are given in a volume of 10 ml/kg mouse body weight. Each mouse is observed for 30 minutes following Metrazole injection. Failure of the animals to exhibit a threshold seizure (a single episode of clonic spasms at least 5 seconds in duration) is defined as protection.

Anticonvulsant data are calculated in terms of percent protection, i.e.,

$$\frac{\text{No. mice protected}}{\text{No. mice tested}} \times 100 = \text{percent protected}$$

The ED_{50} and (95% confidence limits) and potency ratio if desired are ascertained by the computer-based probit analysis ascribed to Fenney, D. J. (1964) "Statistical Method in Biological Assay.," 2nd Ed., New York, Hafner Publishing Co.

Formulation and Administration

The pharmacologically active N-formyl and N-hydroxy-methyl-3-phenoxy-1-azetidinecarboxamides of this invention are effective in the treatment of both petit mal epilepsy and grand mal epilepsy. Effective quantitites of these compounds may be administered to a living animal body orally as in capsules, tablets or elixirs employing the usual pharmaceutical carriers. It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosage as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

Based upon a comparison with known anticonvulsant compounds, daily dosages appear to preferably range from about 0.5 to 1.5 milligrams per kilogram of body weight in the treatment of petit mal epilepsy and about 25 to 35 milligrams per kilogram of body weight in the treatment of grand mal epilepsy. Very small quantities of the active materials of the present invention, even as low as 0.1 milligrams, are effective when minor therapy is involved. Unit dosages are usually 5 milligrams or above and preferably 25, 50 or 100 milligrams per unit dose. The active ingredients of the invention may be combined with other pharmacologically active agents or with buffers, antacids or the like for administration and the proportion of the active agent in the composition may be varied widely.

Capsules

Capsules of 5 mg., 25 mg., and 50 mg. of active ingredient per capsule are prepared; with higher amounts of ingredient reduction may be made in the amount of lactose.

Typical blend for encapsulation	Per Capsule. mg.
Active ingredient	5.0
Lactose	296.7
Starch	129.0
Magnesium stearate	4.3
Total	435.0 mg.

Uniformly blend the selected active ingredient with lactose, starch and magnesium stearate and encapsulate the blend.

Additional capsule formulations preferably contain a higher dose of active ingredient and are as follows:

Ingredients	100 mg. per Capsule	250 mg. per Capsule	500 mg. per Capsule
Active ingredient	100.0	250.0	500.0
Lactose	231.5	126.5	31.1
Starch	99.2	54.2	13.4
Magnesium stearate	4.3	4.3	5.5
Total, mg.	435.0	435.0	550.0

Tablets

A typical formulation for a tablet containing 5.0 mg. of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

Ingredients	Per Tablet, mg.
(1) Active ingredient	5.0
(2) Corn Starch	13.6
(3) Corn Starch (paste)	3.4
(4) Lactose	79.2
(5) Dicalcium phosphate	68.0
(6) Calcium Stearate	0.9
Total	170.1 mg.

Uniformly blend 1, 2, 4 and 5. Prepare 3 as a 10 percent paste in water. Granulate the blend with the starch paste and pass the wet mass through a number eight mesh screen. The wet granulation is dried and passed through a number twelve mesh screen. The dried granules are blended with calcium stearate and compressed.

Additional tablet formulations preferably contain a higher dosage of the active ingredient and are as follows.

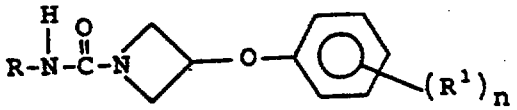
50 mg. Tablet

Ingredients	Per Tablets, mg.
Active ingredient	50.0
Lactose	90.0
Milo starch	20.0
Corn starch	38.0
Calcium Stearate	2.0
Total	200.0

Uniformly blend the active ingredient, lactose, milo starch and corn starch. The blend is granulated, using water as a granulating medium. The wet granules are passed through an eight mesh screen and dried at 60 to 70 degrees Celcius (140 to 160 degrees Fahrenheit) overnight. The dried granules are passed through a number ten mesh screen and blended with the proper amount of calcium stearate and this blend is then converted into tablets on a suitable tablet press.

Claims for the contracting states: BE FR DE IT LU NL SE CH LI GB

1. A compound characterized by the formula:



wherein

R represents formyl or hydroxymethyl;

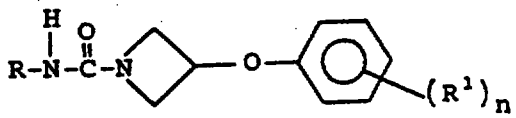
R^1 represents hydrogen, fluoro, $(C_1—C_8)$ alkyl, $(C_1—C_8)$ alkoxy trifluoromethyl, acetyl, N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different.

2. A compound as claimed in claim 1, wherein n is 1 and R^1 represents 3-trifluoromethyl.

3. N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidine-carboxamide or N-hydroxymethyl-3 3-(trifluoromethyl)-phenoxy-1-azetidinecarboxamide.

4. N-formyl and N-hydroxymethyl-3-phenoxy-1-azetidinecarboxamides having the formula:



wherein

R represents formyl or hydroxymethyl;

R^1 represents hydrogen, fluoro, $(C_1—C_8)$ alkyl, $(C_1—C_8)$ alkoxy, trifluoromethyl, acetyl N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different for use in medicine.

5. N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide or N-hydroxymethyl-3-[3-(trifluoromethyl) phenoxy]-1-azetidinecarboxamide as claimed in claim 3 for use in medicine.

6. A pharmaceutical composition comprising a) an effective amount of a compound according to claim 1 and b) a pharmaceutically acceptable carrier therefor.

7. A pharmaceutical composition comprising N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidine-carboxamide or N-hydroxymethyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide as claimed in claim 3 and a pharmaceutically acceptable carrier therefor.

8. A process for the preparation of a compound as defined in Claim 1, which process comprises reacting a compound having the formula:

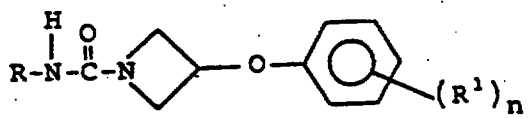
50 mg. Tablet

Ingredients	Per Tablets, mg.
Active ingredient	50.0
Lactose	90.0
Milo starch	20.0
Corn starch	38.0
Calcium Stearate	2.0
Total	200.0

Uniformly blend the active ingredient, lactose, milo starch and corn starch. The blend is granulated, using water as a granulating medium. The wet granules are passed through an eight mesh screen and dried at 60 to 70 degrees Celcius (140 to 160 degrees Fahrenheit) overnight. The dried granules are passed through a number ten mesh screen and blended with the proper amount of calcium stearate and this blend is then converted into tablets on a suitable tablet press.

Claims for the contracting states: BE FR DE IT LU NL SE CH LI GB

1. A compound characterized by the formula:



wherein

R represents formyl or hydroxymethyl;

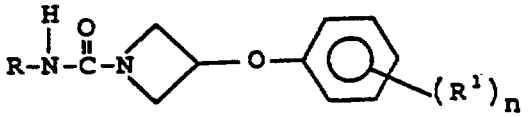
R^1 represents hydrogen, fluoro, (C_1—C_8) alkyl, (C_1—C_8) alkoxy trifluoromethyl, acetyl, N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different.

2. A compound as claimed in claim 1, wherein n is 1 and R^1 represents 3-trifluoromethyl.

3. N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidine-carboxamide or N-hydroxymethyl-3 3-(trifluoromethyl)-phenoxy-1-azetidinecarboxamide.

4. N-formyl and N-hydroxymethyl-3-phenoxy-1-azetidinecarboxamides having the formula:



wherein

R represents formyl or hydroxymethyl;

R^1 represents hydrogen, fluoro, (C_1—C_8) alkyl, (C_1—C_8) alkoxy, trifluoromethyl, acetyl N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different for use in medicine.

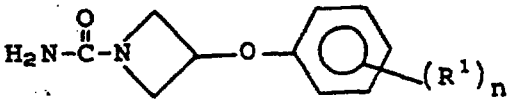
5. N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide or N-hydroxymethyl-3-[3-(trifluoromethyl) phenoxy]-1-azetidinecarboxamide as claimed in claim 3 for use in medicine.

6. A pharmaceutical composition comprising a) an effective amount of a compound according to claim 1 and b) a pharmaceutically acceptable carrier therefor.

7. A pharmaceutical composition comprising N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidine-carboxamide or N-hydroxymethyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide as claimed in claim 3 and a pharmaceutically acceptable carrier therefor.

8. A process for the preparation of a compound as defined in Claim 1, which process comprises reacting a compound having the formula:

* C L M S *



wherein R^1 and n are as defined in claim 1, the carboxamido group of R^1 being unsubstituted with a reagent selected from

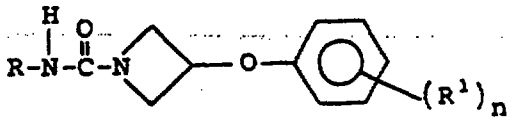
a) formaldehyde
b) formic acid or a salt thereof
c) methyl orthoformate
d) ethyl orthoformate, and
e) acetic-formic anhydride.

9. A process according to claim 8 for the preparation of N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide comprising reacting 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide with acetic formic anhydride.

10. A process according to claim 8 for the preparation of N-hydroxymethyl-3-[3-(trifluoromethyl)-phenoxy]-1-azetidinecarboxamide comprising reacting 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide with formaldehyde.

Claims for the contracting state: AT

1. A process for the preparation of a compound selected from those having the formula:



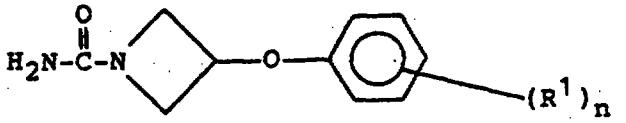
wherein

R represents formyl or hydroxymethyl;

R^1 represents hydrogen, fluoro, (C_1—C_8) alkyl, (C_1—C_8) alkoxy, trifluoromethyl, acetyl, N-formylcarboxamido or N-hydroxymethylcarboxamido;

n is an integer from 1 to 3 inclusive and when n is 2 or 3 R^1 may be the same or different,

which process comprises reacting a compound having the formula:



wherein R^1 and n are as defined above, the carboxamido group of R^1 being unsubstituted with a reagent selected from

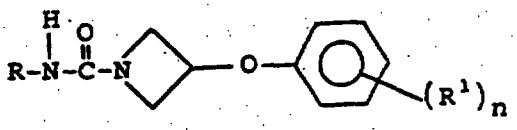
a) formaldehyde
b) formic acid or a salt thereof
c) methyl orthoformate
d) ethyl orthoformate, and
e) acetic-formic anhydride.

2. A process according to claim 1 for the preparation of N-formyl-3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide comprising reacting 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide with acetic formic anhydride.

3. A process according to claim 1 for the preparation of N-hydroxymethyl-3-[3-(trifluoromethyl)-phenoxy]-1-azetidinecarboxamide comprising reacting 3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide with formaldehyde.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Eine Verbindung der Formel



worin

R Formyl oder Hydroxymethyl,

* C L M S *

R^1 Wasserstoff, Fluor, (C_1—C_8) Alkyl, (C_1—C_8)Alkoxy, Trifluormethyl, Acetyl, N-Formylcarboxamid oder N-Hydroxymethylcarboxamid

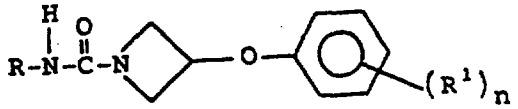
bedeuten und

n eine ganze Zahl von 1—3 ist, und falls n 2 oder 3 bedeutet, dann ist R^1 gleich oder voneinander verschieden.

2. Verbindung nach Anspruch 1, worin n gleich ist 1 und R^1 3-Trifluormethyl bedeutet.

3. N-Formyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid der N-Hydroxymethyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid.

4. N-Formyl und N-Hydroxymethyl-3-phenoxy-1-azetidincarboxamide der Formel:



worin

R Formyl oder Hydroxymethyl,

R^1 Wasserstoff, Fluor, (C_1—C_8)Alkyl, (C_1—C_8)Alkoxy, Trifluormethyl, Acetyl, N-Formylcarboxamid oder N-Hydroxymethylcarboxamid bedeuten und

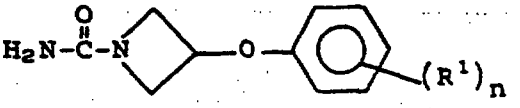
n eine ganze Zahl von 1—3 ist, und falls n gleich ist 2 oder 3 bedeutet, dann ist R^1 gleich oder voneinander verschieden, zur Verwendung in der Medizin.

5. N-Formyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid oder N-Hydroxymethyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid gemäß Anspruch 3 zur Verwendung in der Medizin.

6. Eine pharmazeutische Zubereitung, enthaltend a) eine wirksame Menge einer Verbindung nach Anspruch 1 und b) einen pharmazeutische annehmbaren Träger hiefür.

7. Eine pharmazeutische Zubereitung enthaltend N-Formyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid oder N-Hydroxymethyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid nach Anspruch 3 und einen pharmazeutisch annehmbaren Träger hiefür.

8. Verfahren zur Herstellung einer Verbindung wie im Anspruch 1 definiert, dadurch gekennzeichnet, daß man eine Verbindung der Formel:



worin R^1 und n die im Anspruch 1 angegebene Bedeutung haben und die Carboxamidogruppe von R^1 unsubstituiert ist, mit einem Reagens aus der Gruppe

a) Formaldehyd

b) Ameisensäure oder ein Salz hievon

c) Methylorthoameisensäureester

d) Äthylorthoameisensäureester und

e) Essigsäure-Ameisensäureanhydrid

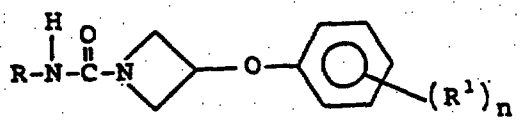
umsetzt.

9. Verfahren nach Anspruch 8 zur Herstellung von N-Formyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid, dadurch gekennzeichnet, daß man 3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid mit Essigsäure-Ameisensaureanhydrid umsetzt.

10. Verfahren nach Anspruch 8 zur Herstellung von N-Hydroxymethyl-3-[3-(triofluormethyl)phenoxy]-1-azetidincarboxamid, dadurch gekennzeichnet, daß man 3-[3-(Trifluormethyl)phenoxy]-1-azetidincarboxamid mit Formaldehyd umsetzt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel:



worin

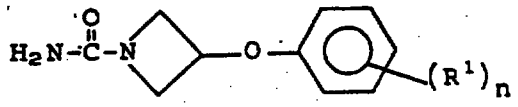
R Formyl oder Hydroxymethyl,

R^1 Wasserstoff, Fluor, (C_1—C_8)Alkyl, (C_1—C_8)Alkoxy, Trifluormethyl, Acetyl, N-Formylcarboxamid oder N-Hydroxymethylcarboxamid

bedeuten und

* C L M S *

n eine ganze Zahl von 1—3 ist, und falls n 2 oder 3 bedeutet, dann kann R^1 gleich oder voneinander verschieden sein, dadurch gekennzeichnet, daß man eine Verbindung der Formel:



worin R^1 und n die obige Bedeutung haben und die Carboxamidgruppe von R^1 unsubstituiert ist, mit einem Reagens aus der Gruppe

a) Formaldehyd
b) Ameisensäure oder ein Salz hievon
c) Methylorthoameisensäureester
d) Äthylorthoameisensäureester und
e) Essigsäure-Ameisensäureanhydrid

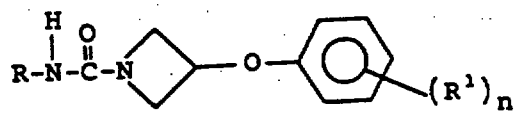
umsetzt.

2. Verfahren nach Anspruch 1 zur Herstellung von N-Formyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid, dadurch gekennzeichnet, daß man 3-[3-(Trifluormethyl)phenoxy]-1-azetidincarboxamid mit Essigsäure-Ameisensäureanhydrid umsetzt.

3. Verfahren nach Anspruch 1 zur Herstellung von N-Hydroxymethyl-3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid, dadurch gekennzeichnet, daß man 3-[3-(trifluormethyl)phenoxy]-1-azetidincarboxamid mit Formaldehyd umsetzt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé répondant à la formule:



dans laquelle:

R représente un radical formyle ou hydroxyméthyle,

R^1 représente l'hydrogène, le fluor, un alkyle en C_1—C_8, un alcoxy en C_1—C_8, un trifluorométhyle, un acétyle, un N-formylcarbamoyle ou un N-hydroxyméthyl-carbamoyle,

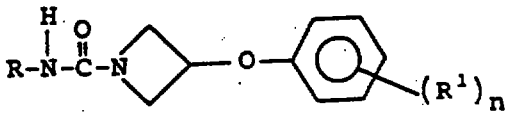
et

n représente un nombre entier égal à 1, à 2 ou à 3, les radicaux R^1 pouvant être identiques ou différents lorsque n est égal à 2 ou à 3.

2. Composé selon la revendication 1 dans lequel n est égal à 1 et R^1 représente un radical trifluorométhyle occupant la position 3.

3. N-Formyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 ou N-hydroxyméthyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1.

4. N-Formyl et N-hydroxyméthyl phénoxy-3 azétidine-carboxamides-1 qui répondent à la formule:



dans laquelle:

R représente un radical formyle ou hydroxyméthyle,

R^1 représente l'hydrogène, le fluor, un alkyle en C_1—C_8, un alcoxy en C_1—C_8, un trifluorométhyle, un acétyle, un N-formylcarbamoyle ou un N-hydroxyméthyl-carbamoyle

et

n représente un nombre entier égal à 1, à 2 ou à 3, les radicaux R^1 pouvant être identiques ou différents lorsque n est égal à 2 ou à 3.

pour leur emploi en médecine.

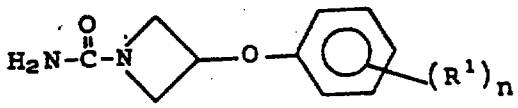
5. N-Formyl (trifluorométhyl-3 phénoxy)-3-azétidine-carboxamide-1 ou N-hydroxyméthyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 selon la revendication 3 pour leur emploi en médecine.

6. Composition pharmaceutique renfermant a) une quantité efficace d'un composé selon la revendication 1 et b) un excipient acceptable en pharmacie, pour ledit composé.

7. Composition pharmaceutique renfermant du N-formyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxyamide-1 ou du N-hydroxyméthyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 selon la revendication 3, et un excipient acceptable en pharmacie, pour ledit composé.

* C L M S *

8. Procédé préparation d'un composé selon la revendication 1, procédé caractérisé en ce qu'on fait réagir un composé répondant à la formule:



dans laquelle R^1 et n ont les significations données à la revendication 1, et la radical carbamoyle de R^1 est dépourvu de substituant avec un composé pris dans l'ensemble constitué par:

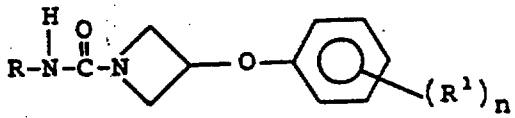
a) le formaldéhyde,
b) l'acide formique ou un sel de cet acide,
c) l'orthoformiate de méthyle,
d) l'orthoformiate d'éthyle et
e) l'anhydride acétique-formique.

9. Procédé selon la revendication 8 pour la préparation du N-formyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1, procédé caractérisé en ce qu'on fait réagir le (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 avec l'anhydride acétique-formique.

10. Procédé selon la revendication 8 pour la préparation du N-hydroxyméthyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1, procédé caractérisé en ce qu'on fait réagir le (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 avec le formaldéhyde.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé répondant à la formule:



dans laquelle:

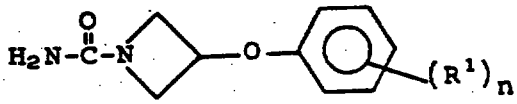
R représente un radical formyle ou hydroxyméthyle,

R^1 représente l'hydrogène, le fluor, un alkyle en C_1—C_3, un alcoxy en C_1—C_3, un trifluorométhyle, un acétyle, un N-formylcarbamoyle ou un N-hydroxyméthyl-carbamoyle,

et

n représente un nombre entier égal à 1, à 2, ou à 3, les radicaux R^1 pouvant être identiques ou différents lorsque n est égal à 2 ou à 3,

procédé caractérisé en ce qu'on fait réagir un composé répondant à la formule:



dans laquelle R^1 et n ont les significations données cidessus, et le radical carbamoyle de R^1 ne porte pas de substituant, avec un composé pris dans l'ensemble constitué par:

a) le formaldéhyde,
b) l'acide formique ou un sel de cet acide,
c) l'orthoformiate de méthyle,
d) l'orthoformiate d'éthyle et
e) l'anhydride acétique-formique.

2. Procédé selon la revendication 1 pour la préparation du N-formyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1, procédé caractérisé en ce qu'on fait réagir le (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 avec l'anhydride acétique-formique.

3. Procédé selon la revendication 1 pour la préparation du N-hydroxyméthyl (trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1, procédé caractérisé en ce qu'on fait réagir le(trifluorométhyl-3 phénoxy)-3 azétidine-carboxamide-1 avec le formaldéhyde.

* C L M S *