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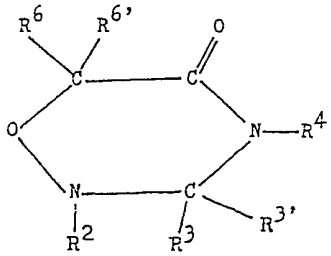
(54) Substituted tetrahydro-1,2,4-oxadiazin-5-one derivatives

(57) The invention relates to new tetrahydro-1,2,4-oxadiazin-5-one derivatives of the formula



(I)

in which

R^2 is hydrogen, alkylcarbonyl (having 1 to 12 carbon atoms in the alkyl moiety and optionally substituted by halogen), formyl, benzoyl (optionally substituted by methoxy, halogen or trifluoromethyl), ethoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, optionally N-substituted carbamoyl or N-benzyloxycarbonylglycyl;

R^3 is alkyl having 1 to 5 carbon atoms, optionally substituted phenyl, naphthyl, thienyl or nitrofuryl, and $R^{3'}$ is hydrogen; or

R^3 and $R^{3'}$ together form a pentamethylene group;

R^4 is hydrogen or acetyl;

R^6 is hydrogen, alkyl having 1 to 5 carbon atoms, phenyl or benzyl and $R^{6'}$ is hydrogen or

R^6 and $R^{6'}$ each represent a phenyl group.

The invention also provides processes for preparing these compounds and pharmaceutical compositions containing them.

The compounds possess interesting anticonvulsive activity.

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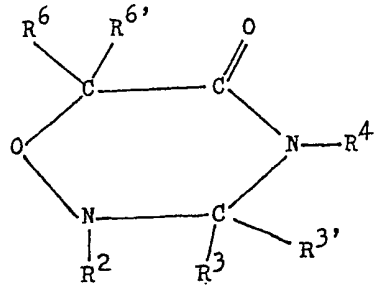
SPECIFICATION

Substituted tetrahydro-1,2,4-oxadiazin-5-one derivatives

The invention relates to new tetrahydro-1,2,4-oxadiazin-5-one derivatives having a CNS activity. More particularly, the invention concerns new substituted tetrahydro-1,2,4-oxadiazin-5-one derivatives of the general formula (I)



(I)

wherein

R^2 is hydrogen, alkylcarbonyl (having 1 to 12 carbon atoms in the alkyl moiety and optionally substituted by halogen), formyl, benzoyl (optionally substituted by methoxy, halogen or trifluoromethyl), ethoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, optionally N-substituted carbamoyl or N-benzyloxycarbonylglycyl;

R^3 is alkyl having 1 to 5 carbon atoms, optionally substituted phenyl, naphthyl, thienyl or nitrofuryl, and R^3 is hydrogen; or

R^3 and $R^{3'}$ together form a pentamethylene group;

R^4 is hydrogen or acetyl;

R^6 is hydrogen, alkyl having 1 to 5 carbon atoms, phenyl or benzyl and $R^{6'}$ is hydrogen or

R^6 and $R^{6'}$ each represent a phenyl group.

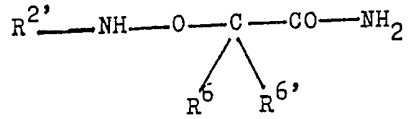
The compounds possess anticonvulsive activity. According to another aspect of the invention there are provided processes for preparing these compounds. A still further aspect of the invention is a pharmaceutical composition, which comprises as active ingredient a pharmaceutically effective amount of a compound of formula (I) with at least one pharmaceutically acceptable carrier or diluent.

Substituted derivatives of tetrahydro-1,2,4-oxadiazine have only lately become known in the art. The synthesis of such compounds was first reported by Calcagno et al (J. Org. Chem. *39*, 162(1974)]. The authors prepared 4-aroyl-tetrahydro-1,2,4-oxadiazine by cycloaddition of a nitrone and a corresponding 1-aroyl-aziridine. Recently F. G. Riddel et al. [Heterocycles *9*, 267 (1978); Tetrahedron *35*, 1391 (1979)] have prepared a tetrahydro-1,2,4-oxadiazine skeleton by condensing an N-alkyl-O-(methylamino)-ethyl-hydroxylamine with formaldehyde. The biological activity of those compounds was not reported nor were there described tetrahydro-1,2,4-oxadiazine derivatives containing an oxo group in the 5-position.

We have surprisingly found that the compounds of the formula (I), in which R^2, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as hereinabove described, possess valuable pharmacological properties, in particular show an excellent CNS activity.

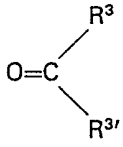
We have further found that the new tetrahydro-1,2,4-oxadiazin-5-one derivatives of the formula (I) may be obtained by

(i) condensing an α-aminooxy-carboxylic acid amide of the formula (II)



(II)

wherein $R^{2'}$ has the same meaning as R^2 defined hereinabove, except hydrogen and R^6 and $R^{6'}$ are as defined above, with an oxo-compound of the formula (III)



(III)

wherein R^3 and $R^{3'}$ are as defined above, in a protic or aprotic medium, in the presence of an acid, to prepare compounds of the formula (I), in which R^2 is other than hydrogen and R^4 is hydrogen; or

(ii) treating a compound of the formula (I), in which R^2 is benzyloxycarbonyl and R^4 is hydrogen — R^3, $R^{3'}$, R^6 and $R^{6'}$ are as defined above — with catalytically activated hydrogen, to afford compounds of the formula (I), in which R^2 and R^4 are hydrogen; or

(iii) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ have the same meaning as defined above, with an acyl halide or carboxylic acid anhydride of the formula (IV)

$$R^{2'}—X \qquad (IV)$$

wherein

$R^{2'}$ is as defined above under (i) and

X is halogen or an acyloxy group of the formula $R^{2'}—O—$, in which $R^{2'}$ is as defined above, to give compounds of the formula (I), in which

R^2 is as defined above, other than hydrogen.

(iv) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with formic acid, in the presence of a condensing agent, to give compounds of the formula (I), in which R^2 is formyl; or

(v) reacting a compound of the formula (I), in which R^4 is hydrogen, R^2, R^3, $R^{3'}$, R^6 and $R^{6'}$ are as defined above, with acetyl chloride or acetic anhydride under reactive conditions to give compounds of the formula (I), in which R^4 is acetyl; or

(vi) reacting a compound of the formula (I), in which R^2 is phenoxycarbonyl, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with ammonia or a primary or secondary amine to give compounds of the formula (I), in which R^2 is an optionally N-substituted carbamoyl group; or

(vii) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with an alkyl isocyanate of the formula (V)

$$R—N=C=O \qquad (V)$$

wherein

R is alkyl having 1 to 6 carbon atoms, to give compounds of the formula (I), in which R^2 is N-alkylcarbamoyl.

The term "alkyl" alone or in alkyl-containing groups is used herein to refer to straight or branched chained saturated hydrocarbon groups. The R^3 and R^6 alkyl groups contain 1 to 5, preferably 1 to 4, more preferably 1 or 2 carbon atoms. In the definition of R^2 the alkyl moiety of alkylcarbonyl group contains 1 to 12, preferably 1 to 6, more preferably 1 to 4 carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

In the definition of R^4 the term "acyl" preferably refers to alkanoyl groups having 1 to 6, preferably 1 to 4 carbon atoms. The acetyl group is preferred.

Where R^2 represents a substituted carbamoyl group, the substituent on the nitrogen atom may be for example a C_{1-8} alkyl group optionally substituted, e.g. by an amino or alkyl substituted amino group.

Where R^3 represents a substituted phenyl group the sbustituent may for example be a halo, nitro, carboxy, hydroxy, amino or alkyl substituted amino group or an alkoxy, e.g. methoxy group.

Preferred representatives of compounds of the formula (I) are as follows:
2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one, 2-acetyl-3-phenyl-6-methyl-tetrahydro-1,2,4-oxadiazin-5-one and optical isomers and mixtures thereof, 2,4-diacetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one and 2-acetyl-3-thienyl-tetrahydro-1,2,4-oxadiazin-5-one.

The process variant (i) defined hereinabove may be performed in aprotic or protic solvents. As an aprotic solvent preferably hydrocarbons, e.g. benzene or toluene are used. The solubility of the reactants may be improved by adding a small amount of butyl acetate to the reaction medium. The reaction is catalysed by a catalytic amount of acids, preferably mineral acids, e.g. sulfuric acid, preferably camphor-10-sulfonic acid. (Camphor-10-sulfonic acid has not been suggested before for a similar purpose.) To eliminate the solvent formed during the reaction the reaction is preferably performed at a temperature about the boiling point of the reaction mixture and water formed is continuously eliminated by a suitable water separator.

As a protic solvent in process variant (i) for example a 1:1 mixture of acetic acid and acetic anhydride may be employed, optionally in the presence of a mineral acid and camphor-10-sulfonic acid. In this case the reaction can successfully be performed even at room temperature.

The reaction is preferably monitored by thin layer chromatography. As soon as the reaction is complete, the solvent is eliminated in a conventional manner and the residue is recrystallized from a suitable solvent.

The α-aminooxycarboxylic acid amides of the general formula (II) used as starting compounds in process variant a) are known in the art [see e.g. A. Frank and K. Riedl, Mh. Chem. *92,* 725 (1961); Blaser et al. Helv. Chim. Acta *1969,* 569; M. Bellando et al. Il. Farm. Ed. Sci. *1976,* 31 (3), 169], which can be

prepared by methods disclosed in the cited literature or by reacting acethydroxamic acid with a corresponding α-halocarboxylic acid amide.

In process variant (ii) compounds of the formula (I), in which R^2 is benzyloxycarbonyl and R^4 is hydrogen, prepared according to process variant (i) are employed as starting materials. From these compounds the R^2 benzyloxycarbonyl group is split off by catalytic hydrogenation. The hydrogenation is performed in a suitable organic solvent or solvent mixture, e.g. methanol or ethyl acetate, preferably under atmospheric pressure, preferably using palladium-on-charcoal as a catalyst. To avoid the formation of by-products the progress of the reaction is preferably monitored by thin layer chromatography. The reaction is terminated as soon as according to the thin layer chromatogram the reaction is devoid of the starting compounds and at the same time the amount of by-products is negligible. Thereafter the catalyst is filtered off, the filtrate is evaporated and the residue is triturated with an inert solvent and/or is recrystallized.

According to process variant (iii) the compounds of formula (I), in which R^2 is hydrogen (which may be prepared for example by process variant (ii) are converted into compounds of formula (I), in which R^2 represents an acyl group. The acylation is carried out by means of compounds of formula (IV), which contain the desired aceyl moiety. Compounds of the formula (IV) are either acyl halides or carboxylic acid anhydrides. The reaction is accomplished by conventional N-acylation methods, under conventional reaction conditions. Preferably to a solution of the starting compound in a dry organic solvent a cooled solution of the corresponding acyl halide, preferably acyl chloride in an organic solvent is added at 0°C, in the presence of an acid binding agent. If a carboxylic acid anhydride of the formula (IV) is employed as an acylating agent, this agent may serve as a reaction medium as well.

The starting compounds of process variant (iii) may contain an exchangable hydrogen atom in both the 2- and 4-positions. However, under the reaction conditions described hereinabove the 2-nitrogen is always acylated selectively. If, however, the compounds of formula (I) in which R^2 and R^4 are both hydrogen are acylated with acetyl chloride or acetic anhydride under drastic reaction conditions (e.g. in the presence of an excess amount of acylating agent, under boiling), the corresponding 2,4-diacetyl compound is obtained as a reaction product. Similarly, compounds having an acyl group in the 2-position and having hydrogen in the 4-position may be acylated in the 4-position according to process variant (v) under the reaction conditions described hereinabove, to produce 4-acetyl compounds.

The elimination of the 2-benzyloxycarbonyl group according to process variant (ii) and the acylation of the compound obtained, according to process variant (iii) may be performed also simultaneously, if an acid anhydride corresponding to the acyl group to be introduced into the 2-position is employed as a reaction medium in the step of catalytic hydrogenation. In this case parallel with splitting off the 2-benzyloxycarbonyl group the acylation in the 2-position also takes place.

Compounds of the formula (I) containing a formyl group in place of R^2 may be prepared according to process variant (iv) by treating a compound of the formula (I), in which R^2 is hydrogen with formic acid in a dry organic solvent, for example dry tetrahydrofuran, in the presence of a condensing agent, e.g. dicyclohexylcarbodiimide. The reaction is preferably carried out at a temperature between 0 and −10°C.

Compounds of the formula (I) prepared e.g. by process variant (iii) in which R^2 represents a phenoxycarbonyl group can be converted into compounds of the formula (I), in which R^2 is an optionally N-substituted carbamoyl group by process variant (vi). The reaction is performed by reacting compounds of the formula (I), in which R^2 is phenoxycarbonyl with a corresponding organic amine or, if N-substituted carbamoyl derivatives are to be prepared, with an aqueous ammonium hydroxide solution, in an inert organic solvent, e.g. chloroform or tetrahydrofuran. Accordingly, the reaction with organic amines takes place in a homogeneous reaction medium, while the reaction with an aqueous ammonium hydroxide solution proceeds in a heterogenous system. The phenol formed during the reaction may be bound by the excess of the amine reactant or by an organic tertiary amine, e.g. triethylamine. At room temperature the reaction may take several days but at reflux temperature the reaction is complete in a few hours. The reaction product can be isolated from the reaction mixture by conventional techniques.

Compounds of the formula (I), in which R^2 is an N-alkylcarbamoyl group may also directly be prepared by reacting corresponding compounds of formula (I), in which R^2 is hydrogen with an alkylisocyanate of the formula (V). This reaction is performed in a dry organic solvent, e.g. dry tetrahydrofuran, under conditions conventionally employed for carrying out such acylating reactions and the product may be isolated from the reaction mixture by conventional preparative techniques.

The compounds of formula (I), for example those in which R^6 is other than hydrogen and $R^{6'}$ is hydrogen, may contain an asymmetric carbon atom, and therefore these compounds may be present in the form of optionally active isomers or mixtures thereof, including racemates. The invention includes the preparation both of optically active compounds of the formula (I) and mixtures, including racemic mixtures. Optically active compounds of the formula (I) may be prepared by starting from corresponding optically active starting materials in the above-described reactions, e.g. from compounds in which R^6 is other than hydrogen and $R^{6'}$ is hydrogen.

The pharmaceutical activity of the new compounds according to the invention was tested by conventional animal tests. Tests were performed on CFLP (LATI) mice of both sexes weighting 18 to 22

g. each, in groups of 10. Test compounds were suspended in a 5% aqueous "Tween 80" solution and the suspension was administered orally, through a probe. When testing anticonvulsive activity 20 mg./kg. doses, while in the tests concerning neurotoxic activity 80 mg/kg. doses were employed. The induced effect was measured one hour after administration by the following methods:

1. Test of anticonvulsive activity

a. Maximum electroshock (MES):

According to the method of E. A. Swinyard et al. [J. Pharmacol. *106,* 319 (1952)] test animals were shocked by a corneal electrode (20 mA, 0.2 sec.). On the stimulation 100% of the control animals reacted by a tonic, extensor spasm of the lower limbs. Absence of this phenomenon was considered a protection due to the treatment.

b. Inhibition of spasm induced by pentetrazole (PPT)

According to the method of Cr. N. Everett and R. K. Richards [J. Pharmacol. Exp. Therap. *81,* 402 (1944)] 125 mg./kg. of pentatrazole (pentamethylene tetrazole) were administered to the animals subcutaneously. One hour after administration the animals were observed. Absence of the clonic spasm (Kl) and the tonic, extensor spasm of lower limbs (TE) was considered a protection due to the administration of test compounds.

2. Test of neurotoxic activity

Muscle coordination (RR) on mice

Change of the coordinated muscular movement was tested according to W. J. Kinnard and C. F. Carr [Brit. J. Pharmacol. *121,* 354 (1957)], on a rotating rod (diameter: 20 mm., frequency: 12/min.). Normal trained animals are able to remain on the rotating rod for about 120 seconds. One hour after administration it was examined, how many percent of the test animals showed muscle incoordination, i.e. the number of animals falling down from the rotating rod within 120 seconds was determined and expressed in percentage of the control animals.

3. Acute toxicity

Toxicity of the animals was examined by administration of various single doses. Evaluation was made 14 days after administration. The LD_{50}-values were calculated on the basis of the number of animals having died in 14 days by probite analysis, by means of a TPA/101 computer.

As a reference substance in the above tests diphenyl hydantoin and 3-methyl-5-ethyl-5-phenylhydantoin were used. The results obtained are shown in the following table.

Compounds of formula (I)				Inhibition (%)			Muscle incoordination (%)	LD_{50} mg./kg. p.o.
				MES	PTT			
R^2	R^3	R^4	R^6		TE	Cl		
H	4-HO–C_6H_4–	H	H	40	20	ϕ	20	800
H	2,5-di-CH_3O–C_6H_3–	H	H	ϕ	20	ϕ	ϕ	1000
CH_3CO–	C_6H_5–	H	H	70	90	ϕ	20	1188
n-C_4H_9–CO–	C_6H_5–	H	H	ϕ	20	ϕ	ϕ	1000
i-C_3H_7–CO–	C_6H_5–	H	H	ϕ	20	ϕ	ϕ	1000
t-C_4H_9–CO–	C_6H_5–	H	H	20	20	ϕ	ϕ	1000
CCl_3–CO–	C_6H_5–	H	H	ϕ	20	ϕ	ϕ	1000
C_2H_5–O–CO–	C_6H_5–	H	H	ϕ	20	ϕ	ϕ	1000
4-F_3C–C_6H_4–CO–	C_6H_5–	H	H	20	ϕ	ϕ	ϕ	1000
CH_3CO–	–$(CH_2)_5$–	H	H	40	ϕ	ϕ	ϕ	1000
CH_3CO–	4-HOOC–C_6H_4–	H	H	40	ϕ	ϕ	ϕ	1000
CH_3CO–	4-F–C_6H_4–	H	H	40	40	ϕ	ϕ	800
CH_3CO–	4-Br–C_6H_4–	H	H	40	ϕ	ϕ	ϕ	800
CH_3CO–	–naphthyl–	H	H	40	ϕ	ϕ	ϕ	800
CH_3CO–	2-thienyl-	H	H	20	40	ϕ	20	800
CH_3CO–	C_6H_5–	CH_3CO–	H	60	40	ϕ	20	1000
CH_3CO–	C_6H_5–	H	(DL)CH_3–	20	50	ϕ	ϕ	1000
CH_3CO–	C_6H_5–	H	(D)CH_3–	20	20	ϕ	ϕ	800
CH_3CO–	C_6H_5–	H	(L)CH_3–	40	60	ϕ	20	800
CH_3CO–	C_6H_5–	H	(DL)Bzl–	ϕ	20	ϕ	40	1000
CH_3CO–	C_6H_5–	H	(L)Bzl–	ϕ	20	ϕ	20	1000
Diphenyl-hydanroin				90	80	ϕ	70	279
3-Methyl-5-ethyl-5-phenylhydantoin				10	50	ϕ	50	476

MES: maximum electroshock
TE: tonic extensor spasm
PTT: pentetrazole spasm inhibiting activity
Cl: clonic spasm

From the data of the above table it can be concluded that the compounds of the formula (I) show excellent anticonvulsive activity, their neurotoxic activity can be neglected, they are lethal only in very high doses and accordingly, their therapeutic application is considerably more extensive than that of known compounds having similar activity. The new compounds of the formula (I), due to their excellent pharmaceutical properties, can advantageously be used for treating epileptic diseases and in this field provide better results than the hydantoin derivatives widely used for this purpose.

The compounds of the formula (I) can be used in therapy in the form of pharmaceutical compositions containing an effective amount of these active ingredients in admixture with organic or inorganic carriers or diluents suitable for enteral or parenteral administration. The compositions may be provided as tablets, injections, dilute or concentrated suspensions or emulsions or other conventional formulations. These formulations may be prepared by conventional techniques of the pharmaceutical industry.

The pharmaceutical compositions according to the invention generally contain about 30 to 100 mg. of active ingredient per dose unit. Their administration in human therapy includes oral or parenteral administration, preferably in the form of intravenous injections. The actual doses depend on the disease to be treated, on the condition of the patient, route of administration and the desired effect. Generally daily doses between 200 and 600 mg. are employed.

Further details of the invention are illustrated by the following non-limiting examples. The abbreviations used in the examples are entirely in line with the IUPAC rules.

The melting points of the compounds disclosed in the examples were determined in an apparatus by dr. Tottoli (Büchi). The thin layer chromatograms were prepared on "Kieselgel G" (Merck) silica gel plates according to Stahl, which are sensitized to ultraviolet radiation. For preparing the chromatograms the following solvent mixtures were used:

(A): 1:1 mixture of benzene and acetone
(B): 3:1 mixture of chloroform and methanol
(C): 30:4:2:1 mixture of ethyl acetate, acetic acid, water and pyridine
(D): 1:4:8 mixture of *n*-hexane, acetic acid and chloroform
(E): 63:4:2:1 mixture of ethyl acetate, acetic acid, water and pyridine.

The thin layer chromatograms were developed by one or more of the following methods:

1. u.v. irradiation at 254 nm
2. treatment with iodine vapour
3. tolidine/potassium iodide spray, after chlorination

The structure of the compounds prepared was analyzed by elementary analysis, and on the basis of the IR and NMR spectra. The IR spectra were determined on a "Perkin-Elmer 257" equipment and the NMR spectra were recorded on a "Varian EM—60" apparatus.

The evaporation of the reaction mixture was carried out on a "Rotavapor R" (Büchi) vacuum evaporator at a temperature not exceeding 50°C.

If the NMR spectra were taken in a water-immiscible solvent, e.g. deuterochloroform, the spectra were recorded also after shaking with heavy water, when the signal of the protons easily replaceable by deuterium disappeared from the spectrum (these signals are marked with asterisks) and the multiplicity of the protons attached to them was simplified.

This has also been marked in the text. For example the sign "d→s" shows that a doublet was converted into a singulet.

EXAMPLE 1

2-Benzyloxycarbonyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (method a)

In a flask equipped with a Marcusson water separator a mixture of 10.1 g. (45 mmoles) of benzyloxycarbonylaminooxy-acetamide, 5.05 ml. (50 mmoles) of freshly distilled benzaldehyde and 1.0 g. dl-camphor-sulfonic acid in 200 ml. of benzene is boiled for 8 to 10 hours. The progress of the reaction is monitored by thin layer chromatography. The reaction mixture is then evaporated to dryness and the residue is recrystallized from 80 ml. of ethanol. 10.2 g. of 2-benzyl-oxycarbonyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (76%) are obtained, melting at 130°C to 133°C; $R_f^A = 0.7$.

Analysis for $C_{17}H_{16}N_2O_4$ (molecular weight: 312.33):

calculated:	C 65.38%,	H 5.16%,	N 8.97%;
found:	C 65.11%,	H 5.43%,	N 8.55%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 1740 (C=O, Z), 1685 (C=O, amide), 1412, 824 (ring), 1583, 748, 698 (aromatic).
NMR spectrum (DMSO—D_6+$CDCl_3$, TMS) ppm: 4.48 AB quadruplet (—CH_2—C_6H_5), 6.55 broad, singlet (1OH, aromatic), 8.90 broad (—NH—).

EXAMPLE 2

2-Acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (method b)

A mixture of 1.32 g. (0.01 moles) of acetylaminooxaacetamide, 1.1 ml. (1.06 g., 0.01 moles) of benzaldehyde, 0.2 g. of camphor-10-sulfonic acid, 10 ml. of toluene and 10 ml. of butyl acetate is refluxed for one hour. To the reaction mixture 0.5 ml. of benzaldehyde are added and boiling is continued for a further one hour. The product precipitating upon cooling is filtered off and washed with two 10-ml. portions of ether. 1.12 g. of 2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (55%) are obtained, melting at 167 to 168°C; $R_f^b = 0.7$. .

Analysis for $C_{11}H_{12}N_2O_3$ (molecular weight: 220.23):

calculated:	C 59.99%,	H 5.49%,	N 12.72%;
found:	C 60.12%,	H 5.92%,	N 12.73%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 1690, 1668 (C=O, amide), 1412, 790 (ring), 740, 700 (aromatic).
NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS) ppm: 2.13 singlet (—CH_3), 4.56 A^B quadruplet (—CH_2—), 6.70 broad, singlet (—CH—), 7.45 singlet (5H, aromatic), 9.2 broad (—NH—).

EXAMPLE 3

2-Acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one
(*in situ* preparation of the starting compound)

34.75 g. (0.5 moles) of hydroxylamine hydrochloride are dissolved in 500 ml. of methanol and 55 g. (0.52 moles) of anhydrous sodium carbonate and 75.5 ml. (0.78 moles) of ethyl acetate are added to the solution. The mixture is refluxed for 5 hours and allowed to stand overnight. To the reaction mixture (which contains the obtained acethydroxamic acid), 46.7 g. (0.5 moles) of chloroacetamide are added and the mixture is refluxed for 5 hours, with stirring. The reaction mixture is cooled and the solvent is evaporated under reduced pressure. As a residue crude N-acetylaminooxyacetic amide is obtained contaminated with a certain amount of inorganic salts. This crude product can be used in the next reaction step without further purification. If desired, however, the product can be purified by chromatography on an ion exchange column. The pure product melts at 88 to 90°C.

The crude N-acetylaminooxyacetic amide obtained above is suspended in a mixture of 500 ml. of acetic acid and 61.5 ml. of acetic anhydride. 61.5 g. (0.67 moles) of benzaldehyde are added followed by the addition of 25 ml. of concentrated sulfuric acid taking care that the temperature of the reaction mixture should not exceed 30°C. The mixture is stirred at room temperature for one hour. 140 g. of crystalline sodium acetate are added whereupon it is stirred for 10 minutes and the solvent is evaporated under reduced pressure. The residue is dissolved in one litre of ethyl acetate. The solution is shaken with 250 ml. of water and dried over anhydrous sodium acetate. The solution is evaporated to dryness and the solid residue is crystallized from 100 ml. of ethanol. 28 g. of 2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (yield for hydroxylamine: 25.4%) are obtained, melting at 165 to 166°C; $R_f^B = 0.7$. The IR and NMR spectra of the product are identical with the spectra given in Example 2.

EXAMPLE 4

2-Benzyloxycarbonyl-3-n-propyl-tetrahydro-1,2,4-oxadiazin-5-one (method c)

A mixture of 45 g. (0.2 moles) of α-(benzyloxycarbonylaminooxy)-acetic amide, 23 ml. (20.2 g., 0.28 moles) of butyraldehyde, 200 ml. of acetic acid, 26 ml. of acetic anhydride and 10 ml. of concentrated sulfuric acid is allowed to stand at room temperature for 24 hours. Thereafter further 5 ml. of butyraldehyde are added to the reaction mixture which is then allowed to stand at room temperature for additional two days. 56 g. of sodium acetate trihydrate are added and the reaction mixture is decoloured with activated carbon, filtered and the filtrate is evaporated. The residue is admixed with a mixture of 100 ml. of water and 100 ml. diisopropyl ether, the solid is filtered off and washed alternately with water and diisopropyl ether several times. 32 g. of 2-benzyl-oxycarbonyl-3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one (57%) are obtained, melting at 105 to 106°C.

Analysis for $C_{14}H_{18}N_2O_4$ (molecular weight: 278.31):

calculated:	C 60.42%,	H 6.52%,	N 10.07%;
found:	C 60.69%,	H 6.60%,	N 9.83%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 1730 (C=O, Z), 1680 (C=O, amide), 1422, 790 (ring), 755, 695 (aromatic).
^1H—NMR spectrum (CMSO-d_6 + $CDCl_3$, TMS) ppm: 0.8—2.2 multiplet (—C_3H_7), 4.30 *AB* quadruplet (—CH_2—C = = O), 5.27 singlet (—CH_2—C_6H_5), 7.44 singlet (5H, aromatic), 8.80 broad (—NH—).

EXAMPLE 5

3-Phenyl-tetrahydro-1,2,4-oxadiazin-5-one (method d)

To a solution of 6.8 g. (21.8 moles) of 2-benzyloxy-carbonyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one in a mixture of 100 ml. of methanol and 125 ml. of ethyl acetate 1.0 g. of a 5% palladium on activated carbon catalyst is added and hydrogen gas is bubbled through the solution. The progress of the reaction is monitored by thin layer chromatography. When the reaction is complete, i.e. no further starting compound is present, the catalyst is filtered off and the filtrate is evaporated to dryness. The residue is recrystallized from a mixture of 10 ml. of ethyl acetate and 30 ml. of *n*-hexane. 3.0 g. (77%) of 3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained, melting at 118 to 119°C. $R_f^A = 0.35$.

Analysis for $C_9H_{10}N_2O_2$ (molecular weight: 178.19):

calculated:	C 60.66%,	H 5.66%,	N 15.72%;
found:	C 60.33%,	H 5.57%,	N 15.94%.

IR spectrum (KBr): 3160 (—NH—), 1670 (>C=O), 1420, 806 (ring), 700 (aromatic).
NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS) ppm: 4.22 singlet (—CH_2—), 5.33 d→S, J = 6.5 Hz (>CH—), 7.02 d*, I = 6.5 Hz (—NH—), 7.47 singlet (5H, aromatic), 8.80 broad* (—NH—).

EXAMPLE 6

2-Acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (method e)

38.5 g. (216 mmoles) of 3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one in 190 ml. of acetic anhydride are stirred for one hour. The initial suspension quickly dissolves followed by the precipitation of the product. When the reaction is complete, the solvent is evaporated under reduced pressure and the residue is recrystallized from 150 ml. of ethanol. 36.3 g. (81%) of 2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained, melting at 167 to 168°C. $R_f = 0.7$.

Analysis for $C_{11}H_{12}N_2O_3$ (molecular weight: 220.23):

calculated:	C 59.99%,	H 5.49%,	N 12.72%;
found:	C 60.12%,	H 5.92%,	N 12.73%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 1690, 1668 (>C=O, amide), 1412, 790 (ring), 740, 700 (aromatic),
NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS): ppm: 2.13 s (—CH_3), 4.56 *AB* quadruplet (—CH_2—), 6.70 (broad singlet) (>CH—), 7.45 (singlet) (5H, aromatic), 9.2 broad* (—NH—).

EXAMPLE 7

2-Acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (method f)

6.28 g. (20 mmoles) of 2-benzyloxycarbonyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are dissolved in 50 ml. of acetic anhydride. 0.5 g. of a 5% palladium-on-activated carbon catalyst are added and hydrogen is bubbled through the solution. The progess of the reaction is monitored by thin layer chromatography. When the reaction is complete, the catalyst is filtered off, the filtrate is evaporated to dryness and the residue is recrystallized from 15 ml. of ethanol. 3.55 g. (80%) of 2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained. The physical constants of the compounds obtained are identical with those of the product of Example 2.

EXAMPLE 8

2,4-Diacetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one

1.1 g. (5 mmoles) of 2-acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are dissolved in 10 ml. of dry tetrahydrofuran. To the solution 1.5 ml. of triethylamine are added, the solution is cooled to 0°C and 0.8 ml. (11 mmoles) of acetyl chloride are added. The reaction mixture is then refluxed for 20 hours. After cooling the triethylamine salt precipitate is filtered off and the filtrate is evaporated to dryness. The residue is passed through a silica gel column using a 1:1 mixture of benzene and acetone for the elution.

Fractions containing the desired product are evaporated and subsequently recrystallized from a mixture of 2 ml. of ethyl acetate and 6 ml. of *n*-hexane. 0.3 g. (23%) of 2,4-diacetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained, melting at 104 to 106°C. $R_f^A = 0.8$.

Analysis for $C_{13}H_{14}N_2O_4$ (molecular weight: 262.27):

calculated:	C 59.54%,	H 5.38%,	N 10.68%;
found:	C 59.30%,	H 5.12%,	N 10.84%.

IR spectrum (KBr) cm^{-1}: 1710, 1680, 1648 (>C=O), 1585, 755, 700 (aromatic).
NMR spectrum (DMSO-d_6 + $CDCl_3$ + TMS) ppm: 2.13 singlet (—CH_3), 2.56 singlet (—CH_3), 4.8 *AB* quadruplet (—CH_2—), 7.36 singlet (5H, aromatic), 7.5 singlet (>CH—).

EXAMPLE 9

2-Phenoxycarbonyl-3-n-propyl-tetrahydro-1,2,4-oxadiazin-5-one (method g)

11.25 ml. (13.9 g., 89 mmoles) of phenoxycarbonyl chloride are dissolved in 75 ml. of dry tetrahydrofuran, the solution is cooled to a temperature below 0°C and at this temperature a solution of 10.8 g. (75 mmoles) of 3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one in a mixture of 150 ml. of dry tetrahydrofuran, and 11.4 ml. of dry triethylamine is added dropwise. After the addition the mixture is heated up to room temperature and stirred for 3 hours. The triethylamine hydrochloride precipitate is filtered off, the filtrate is evaporated under reduced pressure, the residue is triturated with a mixture of water and ether and filtered. 14.7 g. (80%) of 2-phenoxycarbonyl-3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained, melting at 106 to 107°C.

Analysis for $C_{13}H_{16}N_2O_4$ (molecular weight: 264.28):

calculated:	C 59.08%,	H 6.10%,	N 10.60%;
found:	C 59.31%,	H 5,70%,	N 10.70%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 1735 (>C=O, Z), 1680 (>C=O, amide), 1210 (>C—O—C<), 1592, 690, 742 (aromatic).
NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS) ppm: 0.95 (—CH_3), 1.44 multiplet (—CH_2—CH_3), 2.10 multiplet (>CH—CH_2—), 4.5 AB quadruplet (>CH_2—CO—), 5.3 miltiplet → triplet (>CH—), 7.5 multiplet (5H, aromatic), 9.0 doublet* (—NH—).

EXAMPLE 10

2-Carbamoyl-3-n-propyl-tetrahydro-1,2,4-oxadiazin-5-one (method h)

7.94 g. (30 mmoles) of 2-phenoxycarbonyl-3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one in a mixture of 75 ml. of chloroform and 75 ml. of a concentrated ammonium hydroxide solution are vigorously stirred at room temperature until in a sample taken from the organic phase the starting compound cannot be traced any more by thin layer chromatography (about 1 to 2 days). When the reaction is complete, the precipitated product is separated by filtration, washed with water and susequently ether and dried.

From the filtrate the organic phase is separated, dried with anhydrous sodium sulfate and evaporated. The evaporation residue is triturated with ether and filtered off. The second crop obtained is combined with the product of the previous step. Thus 4.6 g. of 2-carbamoyl-3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one (82%) are obtained, melting at 189°C.

EXAMPLE 11

2-(n-Butylcarbamoyl)-3-n-propyl-tetrahydro-1,2,4-oxadiazin-5-one

3.0 g. (20.8 mmoles) of 3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one are dissolved in 40 ml. of dry tetrahydrofuran. The solution is cooled to a temperature below 5°C and at this temperature a solution of 2.5 ml (2.2 g., 22.5 mmoles) of *n*-butyl-isocyanate in 20 ml. of dry tetrahydrofuran is added dropwise. The mixture is stirred at room temperature for four days. When the spot corresponding to the starting compound is not present any more on the thin layer chromatogram, the reaction mixture is evaporated to dryness in *vacuo*, the residue is trituated with *n*-hexane, filtered and recrystallized from a mixture of ethyl acetate and *n*-hexane. 4.23 g. (87%) of 2-(*n*-butylcarbamoyl)-3-*n*-propyl-tetrahydro-1,2,4-oxadiazin-5-one are obtained, melting at 105 to 106°C.

Analysis for $C_{11}H_{21}N_3O_3$ (molecular weight: 243.31%):

calculated:	C 54.30%,	H 8.70%,	N 17.27%;
found:	C 54.68%,	H 8.77%,	N 17.54%.

IR spectrum (KBr) cm^{-1}: 3320, 3180 (—NH—), 1690 (>C=O, carbamoyl-), 1660 (>C=O, amide), 1441, 820 (ring).

^1H—NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS) ppm: 0.7—1.9 multiplet (14H, aliphatic), 3.15 quadruplet → triplet (—NH—CH_2—), 4.21 quadruplet (—O—CH_2—), 5.30 multiplet → triplet (CH—), 7.13 doublet*, J=6 Hz (—NH—), 8.70 doublet J=3 Hz (—NH—).

EXAMPLE 12

2-Formyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one

5.4 g. (30 mmoles) of 3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one (prepared according to Example 1) and 10.5 g. (51 mmoles) of dicyclohexyl carbodiimide are dissolved in 50 ml. of absolute tetrahydrofuran. The solution is cooled to a temperature below —5°C and at this temperature 2.3 ml. (2.35 g., 51 mmoles) of formic acid are added dropwise. The mixture is stirred for 30 minutes at —5°C, whereupon the dicyclohexyl carbamide precipitate is filtered off. The filtrate is evaporated to dryness *in vacuo*, the oily residue is dissolved in hot water, the insoluble substances are filtered off and the filtrate is evaporated to dryness *in vacuo*. Recrystallization of the residue from ethyl acetate affords 1.52 g. (24%) of 2-formyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one, melting at 115 to 116°C, $R_f^D = 0.4$.

Analysis for $C_{10}H_{10}N_2O_3$ (molecular weight: 206.20):

calculated:	C 58.25%,	H 4.89%,	N 13.59%;
found:	C 58.30%,	H 4.69%,	N 13.59%.

IR spectrum (KBr) cm^{-1}: 3180 (—NH—), 3050, 1700 (—CHO), 1670 (C=O, amide), 1585, 755, 702 (aromatic).

^1H—NMR spectrum (DMSO-d_6 + $CDCl_3$, TMS) ppm: 4.5 AB quadruplet (—CH_2—C—O), 6.5 broad, singlet (CH—) 7.3 broad (5H, aromatic), 8.5 singlet (—CHO), 9.2 broad* (NH—).

The compounds of the general formula (I) listed in the following table can be prepared in an analogeous way. In the table the method used for the preparation of these compounds, their physical constants, the yields and the solvents used for recrystallization are also set forth. Different reaction media or other differences in comparision with the detailed examples are given where appropriate as "Remarks".

Compounds of formula (I) R^2	R^3	R^4	R^6	M.p. (°C)	R_f	Method	Yield	Solvent used recrystallization
acetyl	4-fluorophenyl	H	H	162–163	0.4/A	a	5.8	ethanol
acetyl	4-bromophenyl	H	H		0.4/A	a	20	ethylacetate
acetyl	α-naphthyl	H	H	218–220	0.8/B	a	28	ethanol
acetyl	2-thienyl	H	H	176–177	0.8/B	c /1/	20	ethanol
acetyl	4-nitrophenyl	H	H	200	0.7/B	a /2/	10	methanol
acetyl	2-carboxyphenyl	H	H	188–189	0.7/B	a /2/	17	dioxane + ethylacetate
benzoyl	phenyl	H	H	153–154	0.6/A	a	10	–
benzyloxycarbonyl	2-chlorophenyl	H	H	135–136	0.6/A	b /4/	44	ethylacetate/*n*-hexane
benzyloxycarbonyl	4-chlorophenyl	H	H	147–148	0.6/A	b /4/	46	ethylacetate/*n*-hexane
benzyloxycarbonyl	2-bromophenyl	H	H	140–141	0.6/A	b /4/	30	–
benzyloxycarbonyl	3-bromophenyl	H	H	122–123	0.4/A	b /4/	47	–
benzyloxycarbonyl	4-bromophenyl	H	H	158–160	0.5/A	b /4/	53	ethylacetate/*n*-hexane
benzyloxycarbonyl	4-hydroxyphenyl	H	H	193–194	0.3/A	a	15	ethylacetate/*n*-hexane
benzyloxycarbonyl	4-carboxyphenyl	H	H	205–210	0.8/C	a	61	–
benzyloxycarbonyl	2-carboxyphenyl	H	H	166–168	0.6/B	a	64	–
benzyloxycarbonyl	4-nitrophenyl	H	H	144–145	0.3/A	b /3/	46	ethanol
benzyloxycarbonyl	4-dimethylaminophenyl	H	H	124–127	0.7/A	b /3/	20	–
benzyloxycarbonyl	2,5-dimethoxyphenyl	H	H	98–100	0.5/A	b /4/	42	–
benzyloxycarbonyl	2,4-dinitrophenyl	H	H	186–187	0.8/A	b /4/	17	–
benzyloxycarbonyl	3,4,5-trimethoxyphenyl	H	H	152–153	0.7/A	a	88	–

Compounds of formula (I) R^2	R^3	R^4	R^6	M.p. (°C)	R_f	Method	Yield	Solvent used for recrystallization
benzyloxycarbonyl	phenyl	H	ethyl	127–128	0.5/A	a	81	ethanol
benzyloxycarbonyl	4-chlorophenyl	H	ethyl	118–121	0.5/A	b /4/	65	ethylacetate/*n*-hexane
benzyloxycarbonyl	2-bromophenyl	H	ethyl	136–138	0.6/A	b /4/	49	–
benzyloxycarbonyl	3-bromophenyl	H	ethyl	121–124	0.6/A	b /4/	50	–
benzyloxycarbonyl	4-bromophenyl	H	ethyl	140–143	0.5/A	b /4/	68	–
benzyloxycarbonyl	2,5-dimethoxyphenyl	H	ethyl	141–146	0.5/A	b /4/	45	–
benzyloxycarbonyl	phenyl	H	phenyl	179–180	0.8/A	a	65	ethanol
benzyloxycarbonyl	2,5-dimethoxyphenyl	H	phenyl	160–163	0.7/A	a	70	ethanol
benzyloxycarbonyl	phenyl	H	diphenyl	162–164	0.8/A	b /3/	19	–
benzyloxycarbonyl	pentamethylene	H	H	158–160	0.6/A	a	33	ethanol
benzyloxycarbonyl	5-nitro-2-furyl	H	H	152–153	0.7/A	c	19	ethanol
benzyloxycarbonyl	phenyl	H	methyl-(DL)	168–170	0.7/A	a	68	ethanol
benzyloxycarbonyl	phenyl	H	benzyl-(DL)	155	0.7/A	a	72	ethanol $/\alpha/_D^{20}$
acetyl	4-bromophenyl	H	methyl-(D)	160–172	0.4/A	b /3/	26	+ 14.4°
benzoyl	phenyl	H	methyl-(D)	151–153	0.7/A	b /3/	76	+134.0°
benzoyl	4-fluorophenyl	H	methyl-(D)	105–108	0.6/A	b /3/	55	+175.0°
benzyloxycarbonyl	4-chlorophenyl	H	methyl-(D)	155–159	0.5/A	b /4/	25	+ 5.8°
benzyloxycarbonyl	2-bromophenyl	H	methyl-(d)	122–124	0.5/A	b /4/	23	+ 85.8°
benzyloxycarbonyl	4-nitrophenyl	H	methyl-(D)	145–147	0.5/A	b /4/	17	+ 2.3°
benzyloxycarbonyl	4-nitrophenyl	H	benzyl-(D)	145–147	0.5/A	b /4/	37	+144.0°

Compounds of formula (I) R^2	R^3	R^4	4^6	M.p. (°C)	R_f	Method	Yield	Solvent used for recrystallization
benzyloxycarbonyl	2,5-dimethyloxyphenyl	H	methyl-(D)	165–174	0.5/A	b /4/	59	+ 5.8°
benzyloxycarbonyl	2,5-dimethoxyphenyl	H	benzyl-(D)	126–128	0.6/A	b /4/	33	+ 42.9°
benzyloxycarbonyl	5-nitro-2-furyl	H	methyl-(D)	–	0.5/A	b /4/	25	+ 75.4°

Remarks:

/1/ : 1:1 mixture of acetic acid and acetic anhydride.

/2/ : reaction medium 1:1 mixture of benzene and butylacetate.

/3/ : reaction medium : toluene.

/4/ : reaction medium : toluene; catalyst: cc. sulfuric acid.

Compounds of formula (I) R^2	R^3	R^4	R^6	M.p. (°C)	R_f	Method	Yield /%/	Solvent used for recrystallization	Remarks
H	2,5-di-CH_3O–C_6H_3–	H	H	149–150	0.45/A	d	91	ethanol	Rk : dioxane
H	4-HO–C_6H_4–	H	H	186–187	0.20/A	d	80	ethanol	Rk : dioxane + methanol
H	n-C_3H_7–	H	H	98–97	0.30/A	d	80	ethanol /hexane	–
H	4-$(CH_3)_2N$–C_6H_4–	H	H	146–147	0.70/E	d	30	ethanol	Rk : methanol + DMF
H	4-HOOC–C_6H_4	H	H	170	0.20/D	d	60	–	Rk : methanol + DMF
H	C_6H_5–	H	C_2H_5–(DL)	107–110	0.40/A	d	77	–	–
H	3,4,5-tri-CH_3O–C_6H_5	H	H	150–151	0.20/A	d	72	ethanol	–
H	C_6H_5–	H	C_6H_5	143–144	0.50/A	d	70	ethanol	Rk : ethyl acetate + DMF
H	2,5-di-CH_3O–C_6H_5	H	C_6H_5	158–160	0.6/A	d	91	–	Rk : ethyl acetate + DMF
H	C_6H_5	H	diphenyl-	184–185	0.6/A	d	64	ethanol	Rk : dioxane
H	–$(CH_2)_5$–	H	H	172–173	0.4/A	d	68	ethyl acetate	Rk : ethyl acetate + DMF
CH_3CO–	n-C_3H_7–	H	H	102–103		g	56	$CHCl_3/C_6H_{13}$	base : pyridine
CH_3CO–	3,4,5-tri-CH_3O–C_6H_2	H	H	195–196	0.4/A	g	88	methanol	base : pyridine
C_6H_5		H	C_2H_5–(DL)	144–145	0.5/A	g	96	ethyl acetate	base : pyridine
CH_3CO–	C_6H_5	H	C_6H_5–	176–177	0.3/D	g	98	ethyl acetate	base ; pyridine
CH_3CO–	4-HO–C_6H_4–	H	H	204	0.2/D	e	58	ethanol	–
CH_3CO–	4-$(CH_3)_2N$–C_6H_4–	H	H	165–167	0.6/E	e	85	–	–

Compound of formula (I) R^2	R^3	R^4	R^6	M.p. (°C)	R_f	Method	Yield /%/	Solvent used for recrystallization	Remarks
$ClCH_2$–CO–	C_6H_5–	H	H	170–171	0.5/D	g	84	–	base: pyridine
Cl_2CH–CO–	C_6H_5–	H	H	170–173	0.6/D	g	80	–	base: pyridine
Cl_3C–CO–	C_6H_5–	H	H	188–190	0.6/D	g	69	–	base: pyridine
F_3C–CO–	C_6H_5–	H	H	139–140	0.6/D	e	75	–	Rk: THF
CH_3CO–	–$(CH_2)_5$–	H	H	159–160	0.6/A	e	71	–	–
CH_3CO–	4-HOOC–C_6H_4–	H	H	232–233	0.3/D	e	40	water	–
CH_3CO–	C_6H_5–	H	CH_3–(DL)	165	0.6/A	f	89	ethanol	Rk: acetic anhydride + DMF
CH_3CO–	C_6H_5–	H	CH_3–(D)	194–196	0.4/D	f	63	–	$/x/_D^{20}$ = +235°
CH_3CO–	C_6H_5–	H	CH_3–(L)	193–194	0.4/D	f	37	ethyl acetate	$/x/_D^{20}$ = –231°
CH_3CO–	C_6H_5–	H	C_6H_5–CH_2–(L)	173–174	0.7/A	f	80	ethanol	Rk: aceticanhydride + DMF
CH_3CO–	C_6H_5–	H	C_6H_5–CH_2–(D)	141–143	0.7/A	f	42	methanol	$/x/_D^{20}$ = +257°
CH_3CO–	C_6H_5–	H	C_6H_5–CH_2–(L)	146–147	0.7/A	f	51	ethanol	$/x/_D^{20}$ = –265°
n-C_4H_9CO–	C_6H_5–	H	H	56–58	0.5/D	g	60	–	base: pyridine
t-C_4H_9CO–	C_6H_5–	H	H	94–97	0.6/D	g	80	–	base: pyridine
i-C_3H_7CO–	C_6H_5–	H	H	125–126	0.5/D	g	45	–	base: pyridine
$C_{11}H_{23}CO$–	C_6H_5–	H	H	103–104	0.6/D	g	85	–	base: pyridine
C_2H_5O–CO–	C_6H_5–	H	H	125–126	0.4/D	g	78	–	base: pyridine
C_6H_5O–CO–	C_6H_5–	H	H	142–143	0.7/A	g	44	–	–
4-F_3C–C_6H_4–CO–	C_6H_5–	H	H	113–114	0.5/A	g	65		Rk: chloroform base: aqueous $NaHCO_3$

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Compound of formula (I) R^2	R^3	R^4	R^6	M.p. (°C)	R_f	Method	Yield /%/	Solvent used for recrystallization	Remarks
H_2N-CO-	C_6H_5-	H	H	210–211	0.2/A	h	70	–	–
$n-C_3H_7-NH-CO-$	C_6H_5-	H	H	198–199	0.4/A	h	44	–	Rk: TRF + triethyl amine
$n-C_8H_{17}-NH-CO$	$n-C_3H_7-$	H	H	104–105	0.5/B	h	43	–	Rk: triethyl amine
$(C_2H_5)_2N-C_2H_4-NH-CO$	C_6H_5-	H	H	127–128	0.2/F	h	68	ethyl acetate/hexane	–
C_6H_5-CO-	$n-C_3H_7-$	H	H	115–117	0.5/A	g	73	–	Rk: chloroform base: aqueous $NaHCO_3$
$4-Cl-C_6H_4-CO$	C_6H_5-	H	H	125–128	0.5/A	d	79	–	Rk: chloroform base: aqueous $NaHCO_3$
3,4,5-trimethoxy-benzoyl	C_6H_5-	H	H	154	0.6/A	d	74	methanol	base: pyridine
benzyloxycarbonyl-glycyl	C_6H_5-	H	H	178–180	0.6/A	d	20	methanol	base: pyridine

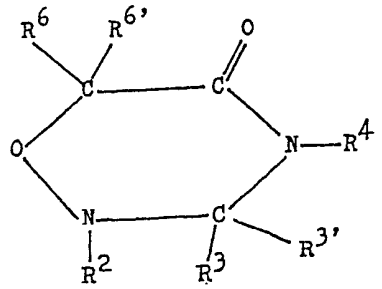
Remarks: DMF = dimethyl formamide

THF = tetrahydrofurane

DCC = dicyclohexyl carbodiimide

CLAIMS

1. Tetrahydro-1,2,4-oxadiazin-5-one derivatives of the formula (I)



(I)

in which

R^2 is hydrogen, alkylcarbonyl (having 1 to 12 carbon atoms in the alkyl moeity and optionally substituted by halogen), formyl, benzoyl (optionally substituted by methoxy, halogen or trifluoromethyl), ethoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, optionally N-substituted carbamoyl or N-benzyloxycarbonylglycyl;

R^3 is alkyl having 1 to 5 carbon atoms, optionally substituted phenyl, naphtyl, thienyl or nitrofuryl, and $R^{3'}$ is hydrogen; or

R^3 and $R^{3'}$ together form a pentamethylene group;

R^4 is hydrogen or acetyl;

R^6 is hydrogen, alkyl having 1 to 5 carbon atoms, phenyl or benzyl and $R^{6'}$ is hydrogen or

R^6 and $R^{6'}$ each represent a phenyl group

2. 2-Acetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one.

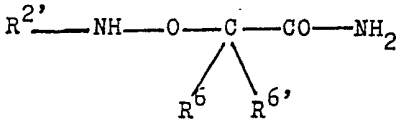
3. 2-Acetyl-3-phenyl-6-methyl-tetrahydro-1,2,4-oxadiazin-5-one (racemic or optically active).

4. 2,4-Diacetyl-3-phenyl-tetrahydro-1,2,4-oxadiazin-5-one.

5. 2-Acetyl-3-thienyl-tetrahydro-1,2,4-oxadiazin-5-one.

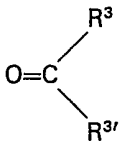
6. Process for the preparation of tetrahydro-1,2,4-oxadiazin-5-one derivatives of the formula (I) wherein R^2, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined in claim 1, which comprises

(i) condensing an α-aminooxy-carboxylic acid amide of the formula (II)



(II)

wherein $R^{2'}$ has the same meaning as R^2 defined hereinabove, except hydrogen and R^6 and $R^{6'}$ are as defined above, with an oxo-compound of the formula (III)



(III)

wherein R^3 and $R^{3'}$ are as defined above, in a protic or aprotic medium, in the presence of an acid, to prepare compounds of the formula (I), in which R^2 is other than hydogen and R^4 is hydrogen; or

(ii) treating a compound of the formula (I), in which R^2 is benzyloxycarbonyl and R^4 is hydrogen — R^3, $R^{3'}$, R^6 and $R^{6'}$ are as defined above — with catalytically activated hydrogen, to afford compounds of the formula (I), in which R^2 and R^4 are hydrogen; or

(iii) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ have the same meaning as defined above, with an acyl halide or carboxylic acid anhydride of the formula (IV)

$$R^{2'}—X \qquad (IV)$$

wherein

$R^{2'}$ is as defined above under (i) and

X is halogen or an acyloxy group of the formula $R^{2'}—O—$, in which $R^{2'}$ is as defined above, to give compounds of the formula (I), in which R^2 is as defined above, other than hydrogen; or

(iv) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with formic acid, in the presence of a condensing agent, to give compounds of the formula (I), in which R^2 is formyl; or

(v) reacting a compound of the formula (I), in which R^4 is hydrogen, R^2, R^3, $R^{3'}$, R^6 and $R^{6'}$ are as defined above, with acetyl chloride or acetic anhydride under reactive conditions to give compounds of the formula (I), in which R^4 is acetyl; or

(vi) reacting a compound of the formula (I), in which R^2 is phenoxycarbonyl, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with ammonia or a primary or secondary amine to give compounds of the formula (I), in which R^2 is an optionally N-substituted carbamoyl group; or

(vii) reacting a compound of the formula (I), in which R^2 is hydrogen, R^3, $R^{3'}$, R^4, R^6 and $R^{6'}$ are as defined above, with an alkyl isocyanate of the formula (V)

$$R—N=C=O \qquad (V)$$

wherein

R is alkyl having 1 to 6 carbon atoms, to give compounds of the formula (I), in which R^2 is N-alkylcarbamoyl.

7. Pharmaceutical compositions comprising as active ingredient a pharmaceutically effective amount of a compound of formula (I) as defined in claim 1, in association with at least one pharmaceutically acceptable carrier or diluent.

8. Compounds of formula (I) as defined in claim 1 for use in anticonvulsive therapy of the human or animal body.

9. Compounds of formula (I) as defined in claim 1 substantially as herein described in any one of the Examples.

10. Processes for the manufacture of compounds of formula (I) as defined in claim 1 substantially as herein described in any one of the Examples.

11. Compounds of formula (I) as defined in claim 1 produced by any process claimed in claim 6.

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