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3-CARBONYL AMINO ACETIC ACID ETHYL ESTER SUBSTITUTED BENZODIAZEPINES

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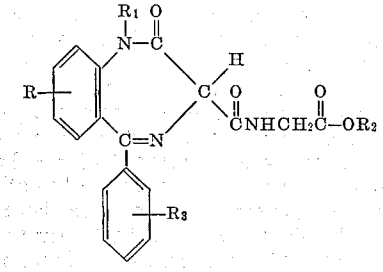
ABSTRACT OF THE DISCLOSURE

1,3-dihydro-1,4-benzodiazepin-2-ones having a carbonyl amino acetic acid ester group in the 3-position and a method for their production. These benzodiazepin-2-ones are useful as sedatives, psychosedatives, muscle relaxants and anti-convulsants.

SUMMARY

In accordance with this invention, it has been found that compounds of the formula:



(I)

wherein R is selected from the group consisting of hydrogen, halogen, nitro, trifluoromethyl and lower alkyl; R_1 is selected from the group consisting of hydrogen and lower alkyl; R_2 is lower alkyl and R_3 is selected from the group consisting of hydrogen, lower alkyl and halogen;

and pharmaceutically acceptable salts thereof are useful as sedatives, psychosedatives, muscle relaxants and anti-convulsants.

Also included within the purview of the present invention are the acid addition salts of the novel medicinally valuable 1,4-benzodiazepin-2-ones of Formula I above. More particularly, the compounds of Formula I above, form acid addition salts with pharmaceutically acceptable organic and inorganic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, acetic acid, succinic acid, maleic acid, p-toluene sulfonic acid, formic acid and the like.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "lower alkyl" includes both straight and branched chain alkyl groups having from 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, and the like. As used herein, the term "halogen" includes bromine, chlorine, fluorine and iodine.

In the preferred embodiment of the 1,4-benzodiazepin-2-ones of Formula I above, R is a substituent in the 7-position and is either halogen, trifluoromethyl or nitro. When R is a halogen in the 7-position, the preferred halogens are chlorine and bromine. When R_1 is a lower alkyl radical, the preferred radicals are methyl and ethyl.

In the preferred embodiment of the benzodiazepin-2-ones of Formula I above, R_2 is methyl or ethyl. In the most preferred embodiment R, which is a substituent on the 7-position, is halogen, advantageously chlorine, R_2 is methyl or ethyl, and R_1 and R_3 are hydrogen. When R_3 is other than hydrogen, such as a lower alkyl, which is preferably methyl or ethyl, it is preferentially joined to the 5-phenyl ring of the compound of Formula I above at the 2-position.

The benzodiazepin-2-ones of Formula I above, demonstrate a high degree of activity and are useful as sedatives, muscle relaxants, anti-convulsants, and psychosedatives. The compounds of Formula I above, as well as their pharmaceutically acceptable acid addition salts are used in the form of conventional pharmaceutical preparations which contain said compounds in connection with conventional pharmaceutical organic or inorganic materials suitable for internal administration. The pharmaceutical compositions containing the compounds of Formula I as well as their pharmaceutically acceptable acid addition salts, can be administered parenterally or orally. Dosages can be adjusted to individual requirements, for example, these compounds can be administered in dosages of from about 0.01 mg./kg. to about 10.0 mg./kg. per day. These dosages can be administered in a single dosage form or in divided dosage forms. The pharmaceutical compositions can contain conventional organic or inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, Vaseline or the like. The pharmaceutical preparations can be in conventional solid dosage forms such as tablets, dragees, suppositories, capsules or in conventional liquid dosage forms such as solutions, suspensions or emulsions. The pharmaceutical compositions can be submitted to conventional pharmaceutical expedients such as sterilization and/or can contain pharmaceutical additives such as preservatives, stabilizing agents, wetting agents, emulsifying agents, salts for adjusting the osmotic pressure, buffers or the like. They also can contain other therapeutically useful materials.

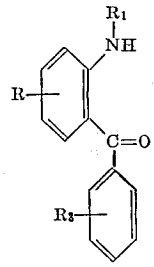
The compounds of Formula I above, are extremely effective and active as sedatives and muscle relaxants. This can be seen by the fact that dosages from below 0.1 mg./kg. to 10.0 mg./kg. and above, administered orally to cats, produce muscle relaxation. For example, a compound such as 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin - 3 - yl - carbonyl-aminoacetic acid ethyl ester has a minimum effective dose of 2 mg./kg. as measured by the unanesthesized cat test whereas the minimum effective dose of meprobamate, a conventional sedative and muscle relaxant, measured by the unanesthesized cat test, is 50 mg./kg.

The unanesthesized cat test utilized to determine the sedative and muscle relaxant activity of a compound is performed by treating cats orally with the compound to be tested and observing the minimum dose of the compound necessary to produce ataxia.

Furthermore, the sedative and muscle relaxant properties of 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl-carbonyl aminoacetic acid ethyl ester is demonstrated by the inclined screen test in mice (Behrem,

Arch. Ex pt. Path. and Pharm. 140: 237, 1929) where this compound had a PD_{50} of 94 mg./kg. p.o. On the other hand, meprobamate, a common muscle relaxant and sedative has a PD_{50} of 256 mg./kg. p.o. as measured by this test.

Compounds of Formula I can be prepared, in accordance with this invention, by any of two different methods. The first of these is by reacting a 2-amino benzophenone of the formula:



(II)

wherein R, R_1 and R_3 are as above,

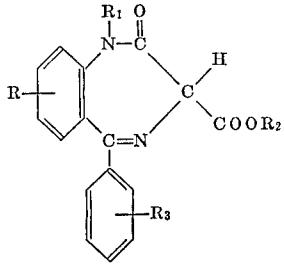
with a diester of an amino substituted dibasic acid of the formula:

$$NH_2CH(COO—R_2)_2 \quad \text{(III)}$$

wherein R_2 is as above,

and thereafter separating the compound of Formula I from the reaction medium by any conventional technique.

The second method for producing the compound of Formula I, in accordance with this invention, is by reacting a compound of the formula:



(IV)

wherein R_1, R_2 and R_3 are as above,

with the compound of Formula III above.

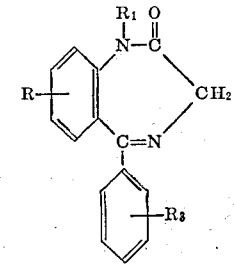
Illustrative of compounds within the genus encompassed by Formula III are dipropyl aminomalonate, dimethyl aminomalonate and most preferably, diethyl aminomalonate. Such compounds are advantageous provided in the reaction zone in both methods of preparing the compounds of Formula I in their salt form.

In the method step of preparing the compound of Formula I above, via the reaction of a compound of the Formula II above, with a compound of Formula III above, the compound of the Formula II above is reacted with the compound of Formula III above in the presence of an inert organic solvent. Any conventional inert organic solvent can be utilized in carrying out this reaction step. Representative of inert organic solvents suitable for employment as the reaction medium in the present invention are tetrahydrofuran, N,N-dimethylformamide, and organic bases such as pyridine, picoline, quinoline and the like. When the compound of Formula III above, is utilized in its salt form, an organic base such as, particularly, pyridine, is advantageously employed due to its capability to serve both as a neutralizing agent and as the reaction medium.

Temperatures and pressure are not critical factors in the conversion of compounds of Formula II above, to compounds of the Formula I above. Thus, the conversion can be effected at room temperature and atmospheric pressure or above room temperature. In the most advantageous aspect of the present invention, such reaction is conducted at elevated temperatures, most suitable, at about the reflux temperature of the reaction medium in

which the starting materials of the Formulae II and III above find themselves.

The reaction of the compounds of the Formula II above, with compounds of the Formula III above, form as reaction products in addition to the compounds of the Formula I above, compounds of the Formula IV above, and compounds of the formula:



(V)

wherein R, R_1 and R_3 are as above.

The compounds of Formulae I, IV and V above, can be easily separated from each other by conventional separating methods due to the solubility differences of these compounds in various inert organic solvents and to the differences in the adsorption rates of these compounds on various adsorbents. Therefore, the compounds of Formulae I, IV and V above, can be separated from each other by any conventional solvent separating means, such as fractional crystallization, etc. utilizing conventional inert organic solvents.

Furthermore, due to the differences in the adsorption rates of the compounds of Formulae I, IV and V above, these compounds can be separated from each other by any convention adsorbing procedure such as chromatography. This procedure can utilize any conventional adsorbing means, such as silica, alumina, florosil, etc.

In forming compounds of the Formula I above, by the reaction of benzophenone compounds of the Formula II above, with diesters of aminomalonic acids of the Formula III above, the benzophenone compounds of the Formula II above, can be reacted with a molar equivalent of the aminomalonic ester compound of the Formula III above. However, generally it is preferred to utilize two or more molar equivalents of the aminomalonic acid ester of Formula III above, per molar equivalent of the benzophenone compounds of Formula II above, in carrying out this reaction.

The compounds of Formula I above, can be prepared in accordance with another embodiment of this invention by reacting a compound of the Formula IV above, with an aminomalonic acid ester of the Formula III above, generally in the presence of an inert organic solvent. Any conventional inert organic solvent can be utilized in carrying out this reaction. Representative of inert organic solvents suitable for employment as the reaction medium in the present invention are tetrahydrofuran, N,N-dimethylformamide, an organic base such as pyridine, picoline, quinoline, and the like. Generally, it is preferred to utilize pyridine as the reaction medium.

Temperature and pressure are not critical factors in the conversion of compounds of Formula IV above, to compounds of the Formula I above. Thus, this conversion can be effected at room temperature and atmospheric pressure or above room temperature. In the most advantageous aspect of the present invention, this reaction is conducted at elevated temperatures most suitable at about the reflux temperature of the reaction medium in which the starting materials of Formulae IV and III above, find themselves.

The following examples are illustrative of the claimed invention. All temperatures given in the examples are stated in degrees centigrade.

Example 1

7 - chloro - 1,3 - dihydro - 2 - oxo - 5 - phenyl - 2H - 1,4-benzodiazepin-3-yl-carbonylaminoacetic acid ethyl es-

ter.—A solution of 46.4 g. (0.2 M) of 2-amino-5-chlorobenzophenone in 250 ml. of pyridine was treated with 125 g. 0.59 M) of diethylaminomalonate hydrochloride. The solution was heated under reflux for 18 hrs., and then pyridine was removed under vacuum. The residual oil was dissolved in 300 ml. of dichloromethane which was then washed with 3× 100 ml. of water, 100 ml. of a saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness. The oil was next triturated with 2× 500 ml. of boiling hexane, which was decanted and the remaining oil was crystallized from ethanol to yield 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepine-3-carboxylic acid ethyl ester.

The filtrate thus obtained from crystallization was evaporated, and the residue was dissolved in 100 ml. of benzene and chromatographed over a column containing 300 g. of "Woelm" Grade I neutral alumina. The column was eluted with 500 ml. of benzene (discarded) and then 1 l. of ether (discarded). Using ethyl acetate as the eluant and after removal of the solvent a mixture of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one and 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl-carbonylaminoacetic acid ethyl ester was obtained. This mixture was recrystallized from methanol which removed the unwanted 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one and the filtrates were evaporated to dryness and recrystallized first from benzene and then from methanol to yield 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl-carbonylaminoacetic acid ethyl ester as white prisms.

Example 2

7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl-carbonylaminoacetic acid ethyl ester.—A solution of 0.5 g. (0.00125 M) of 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepine-3-carboxylic acid ethyl ester in 30 ml. of pyridine was treated with 2 g. of diethylaminomalonate hydrochloride and the solution was heated under reflux for 36 hrs. Solvent was removed under reduced pressure and the residual oil was dissolved in 50 ml. of dichloromethane, which was then washed with water (2× 40 ml.), a saturated solution of brine (40 ml.), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in 5 ml. of benzene and filtered through a sintered glass funnel containing 50 g. of alumina. Elution with ethyl acetate removed starting material and other by-products. Using methanol as the eluant a mixture of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one and the product was obtained. The product was separated from the mixture by recrystallization from methanol as in Example 1. A pure product was obtained.

Example 3

	Per tablet (mg.)
7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl-carbonylaminoacetic acid ethyl ester	25.00
Dicalcium phosphate dihydrate, unmilled	175.00
Corn starch	24.00
Magnesium stearate	1.00
Total weight	225.00

A 225 mg. tablet was prepared from the above ingredients as follows:

7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl-carbonylaminoacetic acid ethyl ester and corn starch were mixed together and passed through a No. 00 screen in Model "J" Fitz with hammers forward. This premix was then mixed with dicalcium phosphate and one-half of the magnesium stearate, passed through a No. 1A screen in Model "J" Fitz with knives forward and slugged. The slugs were passed through a No. 2A screen in a Model "D" Fitz at slow speed with knives forward, and the remaining magnesium stearate was added. The mixture was mixed and compressed.

Example 4

	Per cc.
7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl-carbonylaminoacetic acid ethyl ester ---mg---	0.5
Propylene glycol ---cc---	0.4
Benzyl alcohol (benzaldehyde free) ---cc---	0.015
Ethanol 95 percent U.S.P. ---cc---	0.10
Sodium benzoate ---mg---	48.8
Benzoic acid ---mg---	1.2
Water for injection q.s. ---cc---	1.0

A 10,000 cc. parenteral formulation was prepared from the above ingredients as follows:

The 5 gm. of 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl-carbonylaminoacetic acid ethyl ester were dissolved in 150 cc. of benzyl alcohol; 4,000 cc. of propylene glycol and 1,000 cc. of ethanol were added. The 12 gm. of benzoic acid were dissolved in the above. The 488 gm. of sodium benzoate dissolved in 3,000 cc. of water for injection were added. The solution was brought up to final volume of 10,000 cc. with water for injection. The solution was filtered through an 02 Selas candle, filled into suitable size ampules, gassed with N_2 and sealed. It was then autoclaved at 10 p.s.i. for 30 minutes.

Example 5

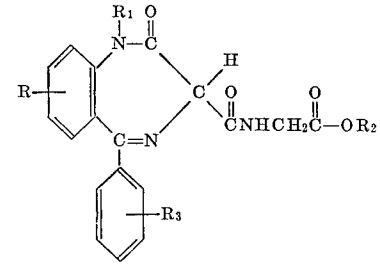
	Per capsule mg.
7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl carbonylaminoacetic acid ethyl ester	10
Lactose, U.S.P.	165
Corn starch, U.S.P.	30
Talc, U.S.P.	5
Total weight	210

A 210 mg. capsule was prepared from the above ingredients as follows:

7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepin-2-yl-carbonylaminoacetic acid ethyl ester, lactose and corn starch were mixed in a suitable mixer. The mixture was further blended by passing through a Fitzpatrick comminuting machine with a No. 1A screen with knives forward. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into No. 4 hard shell gelatin capsules on a Parke Davis capsulating machine.

We claim:

1. A compound selected from the group consisting of compounds of the formula:



wherein R is selected from the group consisting of hydrogen, halogen, nitro, trifluoromethyl and lower alkyl; R_1 is selected from the group consisting of hydrogen and lower alkyl; R_2 is lower alkyl and R_3 is selected from the group consisting of hydrogen, lower alkyl and halogen;

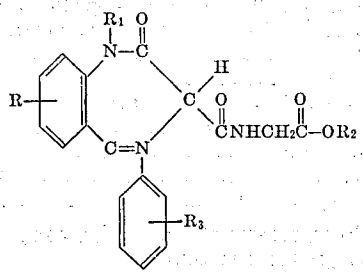
and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R is a halogen.

3. The compound of claim 2, wherein said compound is 7-chloro-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-

benzodiazepin-3-yl-carbonylaminoacetic acid ethyl ester.

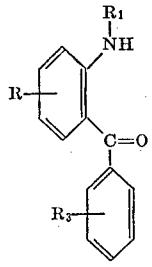
4. A process for preparing a benzodiazepine compound of the formula:



wherein R is selected from the group consisting of hydrogen, halogen, nitro, trifluoromethyl and lower alkyl; R_1 is selected from the group consisting of hydrogen and lower alkyl; R_2 is lower alkyl and R_3 is selected from the group consisting of hydrogen, lower alkyl and halogen;

comprising:

(a) reacting a compound of the formula:



wherein R, R_2 and R_3 are as above,

in an inert organic reaction medium containing an organic base with a compound of the formula:

$$NH_2CH(COO—R_2)_2$$

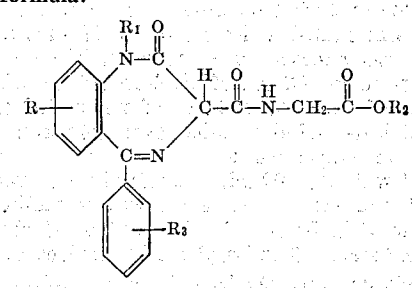
wherein R_2 is as above,

to form said benzodiazepine compound and

(b) separating said benzodiazepine compound from said reaction medium.

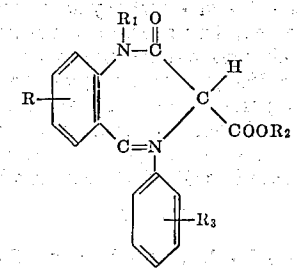
5. The process of claim 4, wherein said inert organic medium is pyridine.

6. A process for preparing a benzodiazepine compound of the formula:



wherein R is selected from the group consisting of hydrogen, halogen, nitro, trifluoromethyl and lower alkyl; R_1 is selected from the group consisting of hydrogen and lower alkyl; R_2 is lower alkyl and R_3 is selected from the group consisting of hydrogen, lower alkyl and halogen;

comprising reacting in an inert organic medium containing an organic base compounds of the formula:



wherein R, R_1, R_2 and R_3 are as above

with aminomalonic acid ester of the formula:

$$NH_2CH(COO—R_2)_2$$

wherein R_2 is as above.

7. A process of claim 6, wherein said inert organic medium is pyridine.

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