

PATENT SPECIFICATION

(11) 1 222 294

1 222 294

NO DRAWINGS

- (21) Application No. 41548/69 (22) Filed 20 Aug. 1969
 (31) Convention Application No. 760963 (32) Filed 19 Sept. 1968
 (31) Convention Application No. 811224 (32) Filed 27 March 1969 in
 (33) United States of America (US)
 (45) Complete Specification published 10 Feb. 1971
 (51) International Classification C 07 d 99/02
 (52) Index at acceptance

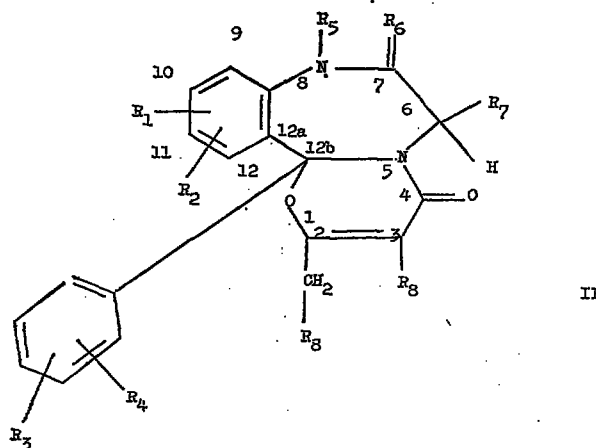


C2C 174—192—284 1E6K4 1E6K6 1E6K7 1E7E1 1E7F1
 1E7H1 1E7H2 1E7N5 1K2A1 1K2C3 1Q11J 1Q2
 1Q4 1Q5 1Q6C 1Q7A 1Q8A 1Q8B 1Q8C 1Q9B
 1Q9G 1Q9K 213 214 220 226 22Y 255 25Y 305
 30Y 313 314 315 31Y 326 332 337 338 351
 352 364 36Y 372 37Y 3A12A4C 3A12B7 3A12C5
 3A14B3C 3A14B8C 621 624 634 666 669 671 676
 679 761 790 79Y JA MD ML RQ

(54) OXAZINOBENZODIAZEPINE DERIVATIVES

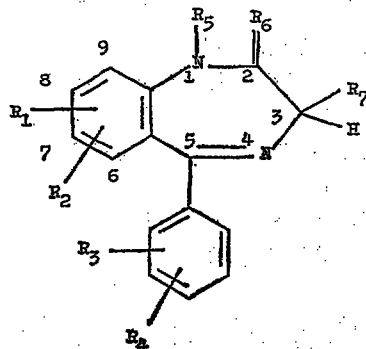
(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new organic compounds and more particularly with novel oxazinobenzodiazepines of the general formula:—



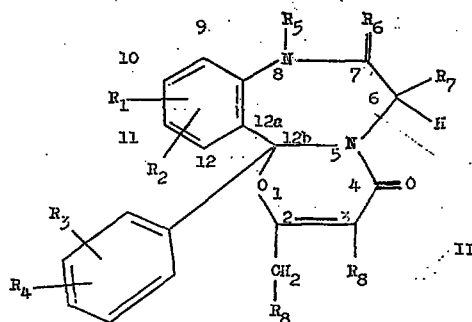
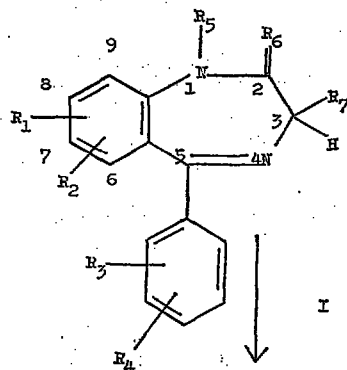
wherein R_1 , R_2 , R_3 and R_4 are hydrogen, lower-alkyl, lower-alkoxy, halogen, $-\text{CF}_3$, $-\text{NO}_2$ or $-\text{CN}$, wherein R_5 is hydrogen, lower-alkyl, cyclopropylmethyl or benzyl, wherein R_6 is oxygen or sulphur, wherein R_7 is hydrogen, lower-alkyl or lower-alkoxy, and wherein R_8 is hydrogen, lower-alkyl or phenyl.

The novel compounds of Formula II are prepared by reacting 5-phenyl-3H-1,4-benzodiazepin-2(1H)-ones of Formula I:



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are as defined above, with an acyl halide in the presence of a base or with a diketene. The new products are essentially sedatives and tranquilizers useful for treatment of mammals.

The novel compounds and the process of production thereof can be illustratively represented by the following formulae:—



wherein R_1 , R_2 , R_3 and R_4 are selected from the group consisting of hydrogen, alkyl and alkoxy of 1 to 6 carbon atoms, inclusive, halogen, $-\text{CF}_3$, $-\text{NO}_2$ and $-\text{CN}$; wherein R_5 is selected from the group consisting of hydrogen, alkyl defined as above, and benzyl; wherein R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$; wherein R_7 is selected from the group consisting of hydrogen, alkyl defined as above, and alkoxy as defined above; and wherein R_8 is selected from the group consisting of hydrogen, alkyl defined as above, and phenyl.

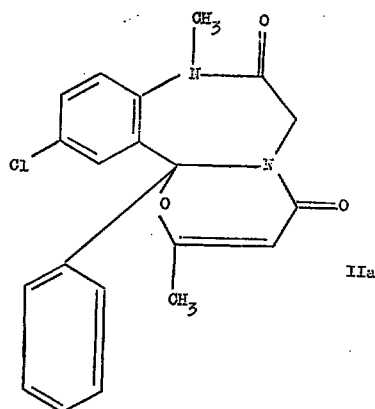
Examples of alkyl of 1 to 6 carbon atoms, inclusive, are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.butyl, pentyl, 2-methylbutyl, neopentyl, hexyl, 2-methylpentyl, 3-methylpentyl, and the like.

Examples of alkoxy of 1 to 6 carbon atoms, inclusive, are methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec.butoxy, pentyloxy, hexyloxy, and the like.

Halogen herein defined consists of fluorine, chlorine, bromine and iodine.

The process of this invention comprises: treating a selected 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one of formula I with a diketene, either by direct addition or produced in situ, i.e., by the addition of acyl halides, e.g., acyl chloride, acyl bromide or less desirably, acyl iodide and a strong base, e.g., triethylamine. In general, higher yields are obtained by the acyl halide and base method.

The novel compounds of formula II have anti-convulsive, anti-anxiety and tranquilizing properties. Illustratively, in mice, 2 mg/kg of 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione IIa (II in which R₁, R₃, R₄, R₇, and R₈ are hydrogen; R₂ is chlorine at C₁₁; R₆ is oxygen; and R₅ is methyl):



protects the mice from convulsions induced by administration of 85 mg/kg pentylene tetrazole. Monkeys at a dosage of 10 mg/kg of IIa have sharply decreased wakefulness. Cats at a dosage of 1.6 mg/kg of IIa have incoordinated muscular movement (ataxia) and at a dosage of 2 mg/kg of IIa are completely relaxed.

The novel compounds II in dosages of 0.5 to 20 mg/kg act as good tranquilizers, sedatives and anti-convulsants and can be used in birds and mammals when needed, e.g., for minor veterinary operations, tranquilization during transport of animals by airplane, ship, train, truck and so on. Administration to cattle, horses, dogs, cats or the like, or zoo animals on long voyages, in a quantity between 0.5 to 20 mg/kg of body weight produces sedation and tranquilization and thereby reduces losses of valuable animals due to anxiety, overexcitement and fighting among the caged animals.

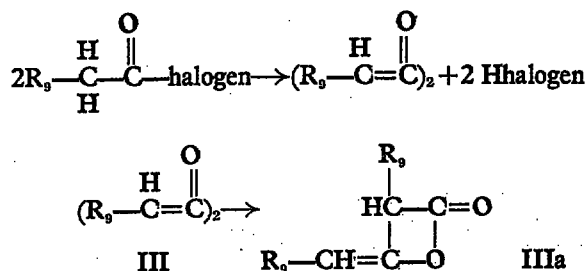
The novel compounds of formula II can be administered to mammals and birds by both oral and parenteral routes in order to produce their pharmacological effects. For oral administration, unit dosage forms such as tablets, capsules, powders, granules, syrups, elixirs and the like containing the appropriate amount for treatment are used. For tablets, common pharmaceutical carriers such as starch, lactose, kaolin, dicalcium phosphate and the like are employed. Powders may also be used in gelatin capsules with or without carriers such as methylcellulose, magnesium stearate, calcium stearate, talc and the like. For fluid preparations, these compounds may be dissolved or suspended in aqueous alcoholic vehicles with or without buffering agents and with flavoring mixtures.

Accordingly the present invention provides a therapeutic composition comprising as the active ingredient one of the novel compounds of the invention together with a pharmaceutically acceptable carrier.

Starting materials of formula I and the preparation thereof are disclosed particularly in U.S. Patents 3,371,085 and 3,296,249, and in L. H. Sternback et al., "Drugs Affecting the Central Nervous System", Medicinal Research Series, Vol. 2, Chapter 6, p. 237-264, 1968, Dekker. Representative starting materials comprise:

- 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
- 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
- 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
- 7-bromo-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
- 7,8-dimethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
- 7-chloro-5-(p-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;

- 7,9-dimethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7,9-dichloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-bromo-5-(p-tolyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-3-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 5 6-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 5-(p-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 6-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 9-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-hexyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 10 8-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-(m-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 1-benzyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-phenyl-3-methoxy-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-1-ethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 15 9-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-(p-fluorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-phenyl-3-methyl-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-(m-tolyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-fluoro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 20 7-chloro-1-methyl-5-(p-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-3-butoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-3-pentyloxy-5-(m-tolyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-3-hexyloxy-5-(p-trifluoromethylphenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-3-ethoxy-5-(p-methoxyphenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 25 7-bromo-3-methoxy-5-(p-chlorophenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-(m-methoxyphenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 7-nitro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-cyano-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-butoxy-1-benzyl-5-(p-hexyloxyphenyl)-3H-1,4-benzodiazepin-2(1H)-one;
 30 7-trifluoromethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-nitro-1-isopentyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-nitro-1-methyl-3-propoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-thione;
 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-thione;
 35 7-cyano-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-isopropoxy-1-benzyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one;
 7-chloro-1-benzyl-3-methoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one, and the like.
- In carrying out the process of this invention by the acyl halide method, a selected
 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one of formula I in an inert organic solvent is
 40 treated with a selected acyl halide in the presence of a base capable of accepting
 hydrogen halide. As an inert organic solvent ether (preferred), tetrahydrofuran,
 methylene chloride, chloroform and the like is used. As a base, organic bases, soluble
 in the selected solvent, are preferably used, e.g., triethylamine, tributylamine, 1-
 45 methylpiperidine or the like. However, inorganic bases, e.g., zinc oxide, barium oxide
 can also be used. The reaction is generally carried out between 0 and 35°C., usually
 at about room temperature (24—26°C.) or slightly below, at 18—20°C. The time
 to complete the reaction is between 10 and 30 hours. As acyl halides, the bromides
 and chlorides of alkanolic acids of 2 to 8 carbon atoms, inclusive, and also phenyl-
 50 substituted alkanolic acids of 8 to 10 carbon atoms, inclusive, are used providing
 that these acyl chlorides or bromides have at least two hydrogen atoms at the 2-
 position in order to be able to form a diketene, thus:



wherein R₉ is selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, inclusive, phenyl, phenyl methyl and phenylethyl. Such acyl halides include the

acetyl, phenylacetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, isovaleryl and 3-phenylpropionyl chlorides and bromides. In the preferred embodiment of this invention, to achieve high yields, the molar ratio of formula I 5-phenyl-3H-benzodiazepin-2(1H)-one to acyl halide to organic base ranges from 1:10:20 to 1:30:60.

After the reaction is terminated the obtained oxazinobenzodiazepine is isolated and purified by conventional methods such as extraction, evaporation, trituration, chromatography and crystallization, and the like.

In carrying out the method using a diketene as described above, as reactant, the selected 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one is refluxed with an excess of the diketene in an inert organic solvent, for example, acetone, benzene, chloroform, and the like. The diketene is defined by formula III or IIIa above. In the preferred embodiment of this invention, the diketene is used in an excess of 5—15 molar equivalents compared to 1 molar equivalent of the formula I benzodiazepin-2(1H)-one selected. The reaction is generally carried out at the reflux temperature of the mixture during a period of 1 to 10 hours. The product is isolated and purified by convention procedures such as extraction, chromatography, trituration, crystallization and recrystallization, and the like.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1

11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione

A solution of 78.5 g. (1 mole) of acetyl chloride in 400 ml. of ether was added over a period of 45 minutes to a solution of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (28.4 g.; 0.1 mole) and 200 g. (2 moles) of triethylamine in 2 l. of ether while keeping the temperature at 20°C. The mixture was then stirred at room temperature (about 23—25°C.) for a period of 18 hours. It was cooled in ice and 800 ml. each of water and methylene chloride was added. The organic layer was separated and the aqueous layer was extracted once with ether, and the ether washings combined with the organic layer. The total organic extracts were washed twice with water and then with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at 40°C. in vacuo. The resulting yellow solid was washed with water and then triturated with 50 ml. of ice-cold methanol, filtered, washed with two 20-ml. portions of ice-cold methanol, followed by 100 ml. of ether, to give an almost colorless solid (33.3 g.). A 31-g. portion of this solid was recrystallized from 180 ml. of chloroform and 600 ml. of ether to give 22 g. of 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]-oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione of melting point 182—183.5°C. (sintering at 170°C.).

U.V.: λ max. 202 (40,600); sh 241 (18,400).

Anal. Calcd. for $C_{20}H_{17}ClN_2O_3$:

C, 65.13; H, 4.65; Cl, 9.61; N, 7.60.

Found: C, 64.85; H, 4.62; Cl, 9.61; N, 7.58.

In the same manner given in Example 1, using 3.05 g. of acetyl bromide, 0.7 g. of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one and 5 g. of triethylamine gave 0.4 g. of 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione, identical with the product of Example 1.

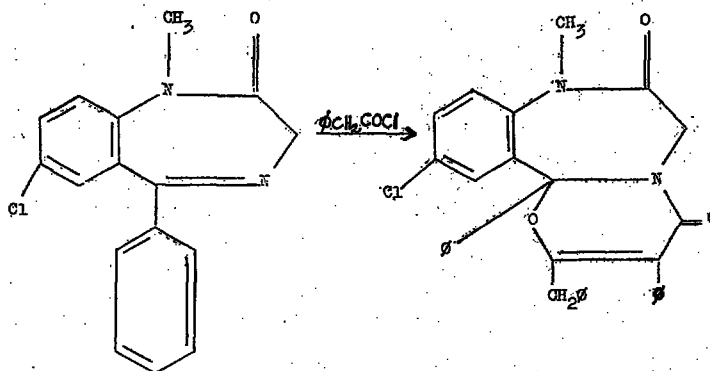
EXAMPLE 2

11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d]-[1,4]benzodiazepine-4,7(6H)-dione

A 0.70 g. (0.0025 mole) portion of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was added to 5 g. of a 50% (by weight) solution of diketene in acetone and the mixture was refluxed for 18 hours. The solution was then evaporated in vacuo at 45°C. and the resulting crude product was triturated with 10 ml. of ethyl acetate and filtered to give 0.58 g. of 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione, identical with the product of Example 1.

EXAMPLE 3

11-Chloro-8,12b-dihydro-2-benzyl-3,12b-diphenyl-8-methyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione



A solution of 3.85 g. (0.025 mole) of phenylacetyl chloride in 10 ml. of ether was added during 10 minutes to a solution of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepine-2(1H)-one (0.7 g.; 0.0025 mole) and 5 g. (0.05 mole) of triethylamine in 50 ml. of ether, keeping the temperature between 10–15°C. The mixture was then stirred for a period of 18 hours at room temperature (about 23–25°C.), cooled in ice, and 20 ml. of water and 10 ml. of methylene chloride were added. The organic layer was separated, washed with saturated salt solution, dried over anhydrous magnesium sulfate and evaporated. The resulting residue (1.3 g.) was dissolved in 25 ml. of a mixture of 60% (volume) of ethyl acetate and 40% cyclohexane and chromatographed over 130 g. of silica gel using the same solvent mixture as eluant and collecting 150-ml. fraction. Fractions 3 and 4 were combined and evaporated, and the residue was crystallized from ether to give 0.53 g. of a precipitate in crystalline form. This precipitate was 11-chloro-8,12b-dihydro-2-benzyl-3,12b-diphenyl-8-methyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione of melting point 203–207°C.

U.V.: λ max. 244 (21,650); sh 277 (4,550).

Anal. Calcd. for $C_{32}H_{25}ClN_2O_3$:

C, 73.77; H, 4.84; Cl, 6.81; N, 5.38.

Found: C, 73.69; H, 4.96; Cl, 6.58; N, 5.56.

EXAMPLE 4

11-Chloro-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

A. 11-Chloro-8,12b-dihydro-8-benzyl-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1-benzyl-7-chloro-5-phenyl-3H-1,4-benzodiazepine-2(1H)-one was treated with acetyl chloride in the presence of triethylamine to give 11-chloro-8,12b-dihydro-8-benzyl-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

B. 11-Chloro-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

The thus-obtained 11-chloro-8,12b-dihydro-8-benzyl-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione was dissolved in ethyl acetate and hydrogenated at 50 p.s.i. hydrogen pressure in the presence of a 10% palladium-on-charcoal catalyst for a period of 6 hours. The reaction mixture was then filtered and evaporated to give 11-chloro-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

EXAMPLE 5

11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-(p-chlorophenyl)-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1-methyl-7-chloro-5-(p-chloro-

phenyl) - 3H - 1,4 - benzodiazepin - 2(1H) - one in ether solution was treated with acetyl chloride in the presence of triethylamine to give 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (p - chlorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione hemihydrate of melting point 181—183°C. (effervescence; sintering 170°C.).

U.V.: λ max. 233 (26,000).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O_3 \cdot 0.5H_2O$:

C, 58.26; H, 4.16; Cl, 17.20; N, 6.80.

Found: C, 58.69; H, 4.04; Cl, 17.68; N, 6.57.

The hemihydrate was heated at 100°C. and a pressure of 15 mm. of mercury for 72 hours to obtain anhydrous 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (p - chlorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione.

EXAMPLE 6

11-Trifluoromethyl-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1 - methyl - 7 - trifluoromethyl - 5 - phenyl - 3H - 1,4 - benzodiazepin - 2(1H) - one was treated with acetyl chloride in the presence of triethylamine to give 11 - trifluoromethyl - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione of melting point 134—136°C. (effervescence).

U.V.: λ max. 203 (36,200); sh 243 (14,750).

Anal. Calcd. for $C_{21}H_{17}F_3N_2O_3$:

C, 62.68; H, 4.26; F, 14.17; N, 6.96.

Found: C, 62.61; H, 4.43; F, 13.38; N, 7.02.

EXAMPLE 7

11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepin-4(6H)-one-7-thione

In the manner given in Example 1, 1 - methyl - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine - 2(1H) - thione was treated in ether solution with acetyl chloride in the presence of triethylamine to give 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2-d][1,4]benzodiazepin - 4(6H) - one-7 - thione of melting point 197°C. (dec.).

Anal. Calcd. for $C_{20}H_{17}ClN_2O_2S$:

C, 62.41; H, 4.45; Cl, 9.21; N, 7.28.

Found: C, 62.66; H, 4.53; Cl, 9.21; N, 7.32.

EXAMPLE 8

11-Cyano-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1-methyl-7-cyano-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was treated in ether solution with acetyl chloride in the presence of triethylamine to give 11 - cyano - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2-d][1,4]benzodiazepine - 4,7(6H) - dione of melting point 152—154°C.

U.V.: sh 227 (22,900); sh 260.5 (16,900); λ max. 265 (17,400); 269.5 (16,450).

Anal. Calcd. for $C_{21}H_{17}N_3O_3$:

C, 70.18; H, 4.77; N, 11.69.

Found: C, 69.99; H, 5.01; N, 11.83.

EXAMPLE 9

11-Nitro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 2, 7.4 g. of 1-methyl-7-nitro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was treated with 100 g. of diketene at 95°C. for 19 hours to give 11 - nitro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione of melting point 196—198°C.

Anal. Calcd. for $C_{20}H_{17}N_3O_5$:

C, 63.32; H, 4.52; N, 11.08.

Found: C, 63.05; H, 4.65; N, 11.09.

EXAMPLE 10

5 11-Chloro-8,12b-dihydro-3-ethyl-8-methyl-2-propyl-12b-phenyl-4H-
[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione 5

In the manner given in Example 1, 1-methyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one in ether solution was treated with butyryl chloride in the presence of triethylamine to give 11-chloro-8,12b-dihydro-3-ethyl-8-methyl-2-propyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione of melting point 154—157°C.

U.V. λ max. 203 (39,450); 244 (19350); sh 280 (3,150).

Anal. Calcd. for $C_{24}H_{25}ClN_3O_3$:

C, 67.83; H, 5.93; Cl, 8.34; N, 6.59.

15 Found: C, 67.88; H, 6.13; Cl, 8.07; N, 6.22. 15

EXAMPLE 11

11-Chloro-8,12b-dihydro-2-ethyl-3,8-dimethyl-12b-phenyl-4H-
[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

20 In the manner given in Example 1, 1-methyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one in ether solution was treated with propionyl chloride in the presence of triethylamine to give 11-chloro-8,12b-dihydro-2-ethyl-3,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione of melting point 197—201°C.

U.V.: 203 (38,550); 243 (19,050); sh 275; sh 285.

Anal. Calcd. for $C_{22}H_{21}ClN_3O_3$:

C, 66.58; H, 5.33; Cl, 8.93; N, 7.06.

25 Found: C, 66.52; H, 5.41; Cl, 9.15; N, 6.60. 25

EXAMPLE 12

8,12b-Dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]-oxazino[3,2-d]-
[1,4]benzodiazepine-4,7(6H)-dione

30 In the manner given in Example 1, 1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one in ether solution was treated with acetyl chloride in the presence of triethylamine to give 8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]-oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione of melting point 161—167°C. (dec.). 35

EXAMPLE 13

11-Methoxy-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino-
[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

40 In the manner given in Example 1, 7-methoxy-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one in ether solution was treated with acetyl chloride in the presence of triethylamine to give 11-methoxy-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

EXAMPLE 14

11-Bromo-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino-
[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

45 In the manner given in Example 1, 1-methyl-7-bromo-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was treated with acetyl chloride in the presence of triethylamine to give 11-bromo-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,4]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione.

EXAMPLE 15

11-Iodo-8,12b-dihydro-2-hexyl-3-pentyl-8-methyl-12b-phenyl-
4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

50 In the manner given in Example 1, 1-methyl-7-iodo-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was treated with heptanoyl chloride in the presence of triethylamine to give 11-iodo-8,12b-dihydro-2-hexyl-3-pentyl-8-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione. 55

EXAMPLE 16

11-Fluoro-8,12b-dihydro-2-ethyl-3,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepine-4,7(6H)-dione

In the manner given in Example 2, 1-methyl-7-fluoro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one was treated with bis-(methylketene) ($\text{CH}_3-\text{C}=\text{C}=\text{O}$)₂ in acetone

to give 11 - fluoro - 8,12b - dihydro - 2 - ethyl - 3,8 - dimethyl - 12b - phenyl-4H - [1,4]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione.

EXAMPLE 17

11-Chloro-8,12b-dihydro-8-benzyl-2-methyl-12b-(3,4-dimethylphenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1-benzyl-7-chloro-5-(3,4-dimethylphenyl)-3H-1,4-benzodiazepin-2(1H)-one was treated with acetyl chloride in the presence of triethylamine to give 11 - chloro - 8,12b - dihydro - 8 - benzyl - 2 - methyl - 12b-(3,4 - dimethylphenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H)-dione.

EXAMPLE 18

11-Chloro-8,12b-dihydro-2,8,9-triethyl-3-methyl-12b-(3-bromo-4-butylphenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 1, 1,9-diethyl-7-chloro-5-(3-bromo-4-butylphenyl)-3H-1,4-benzodiazepine-2(1H)-one was treated with propionyl chloride in the presence of triethylamine to give 11 - chloro - 8,12b - dihydro - 2,8,9 - triethyl-3 - methyl - 12b - (3 - bromo - 4 - butylphenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]-benzodiazepine - 4,7(6H) - dione.

EXAMPLE 19

10-Chloro-8,12b-dihydro-2-methyl-12b-(p-fluorophenyl)-4H-[1,3]oxazino[3,2-d][1,4]-benzodiazepin-4(6H)-one-7-thione

In the manner given in Example 1, 1-benzyl-8-chloro-5-(p-fluorophenyl)-3H-1,4-benzodiazepine-2(1H)-thione was treated with acetyl chloride in the presence of triethylamine to give 10 - chloro - 8,12b - dihydro - 8 - benzyl - 2 - methyl - 12b-(p - fluorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepin - 4(6H) - one-7 - thione.

In the manner given in Example 4B, the thus-produced 10 - chloro - 8,12b-dihydro - 8 - benzyl - 2 - methyl - 12b - (p - fluorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepin - 4(6H) - one - 7 - thione was hydrogenated in ethyl acetate in the presence of 10% palladium-on-charcoal catalyst to give 10 - chloro-8,12b - dihydro - 2 - methyl - 12b - (p - fluorophenyl) - 4H - [1,3]oxazino[3,2-d]-[1,4] - benzodiazepin - 4(6H) - one - 7 - thione.

EXAMPLE 20

11-Nitro-8,12b-dihydro-2,8-dimethyl-12b-(o-fluorophenyl)-4H-[1,3]-oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

A mixture of 0.78 g. (2.5 mmoles) of 5-(o-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one and 10 g. of diketene was heated on the steambath for 1 hour. The reaction mixture was poured on a silica gel column (100 g.) and eluted with 50% ethyl acetate-cyclohexane:

Fraction No.	ml.	Product
1	100	—
2	50	diketene
3 and 4	25 each	diketene
5—7	25 each	—
8—11	25 each	0.432 g. of starting material
12	25 each	—
13—16	25 each	0.255 g. of desired product

Fractions 13—16 gave 0.255g. of 11 - nitro - 8,12b - dihydro - 2,8 - dimethyl-12b - (o - fluorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione of melting point 199°C. (efferv.).

U.V.: sh 225 (19,800); sh 259 (7400); λ max. 265 (8000); 271 (8400); 301 (10,450).

Anal. Calcd. for $C_{29}H_{19}FN_5O_5$:

C, 60.45; H, 4.06; F, 4.78; N, 10.58.

Found: C, 60.48; H, 4.45; F, 4.27; N, 10.40.

EXAMPLE 21

11-Chloro-8,12b-dihydro-2-isobutyl-3-isopropyl-8-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

A solution of 9 g. (0.075 mole) of isovaleryl chloride in 20 ml. of ether was added during 20 minutes to a solution of 0.7 g. (2.5 mmole) of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one and triethylamine (15 g., 0.15 mole) in 50 ml. of ether, keeping the temperature at 20°C. The mixture was stirred at room temperature overnight. It was cooled in ice, 20 ml. of water was added, the organic layer was separated and washed with water (3×25 ml.), 25 ml. of saturated salt solution, dried over anhydrous magnesium sulfate and evaporated to give a residue. The residue (5.3 g.) was chromatographed on 100 g. of silica gel using 40% ethyl acetate-cyclohexane as the eluant; 20-ml. fractions were collected. Fractions 1—6 were discarded. Fractions 7—9 were combined (0.965 g.) and rechromatographed on 100 g. of silica gel exactly as described above. Fractions 7—10 were combined to give 0.74 g. (66%) of 11-chloro-8,12b-dihydro-2-isobutyl-3-isopropyl-8-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione as an oil.

U.V.: λ max. 224 (18,400); sh 272 (4450).

Anal. Calcd. for $C_{26}H_{23}ClN_2O_3$:

C, 68.94; H, 6.45; Cl, 7.83; N, 6.19.

Found: C, 68.86; H, 6.81; Cl, 7.75; N, 6.00.

EXAMPLE 22

11-Chloro-8-(cyclopropylmethyl)-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

A mixture of 0.81 g. (2.5 mmoles) of 7-chloro-1-(cyclopropylmethyl)-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one and 10 g. of diketene was heated at 95°C. for 45 minutes. The solution was evaporated *in vacuo*, and the resulting oily solid was triturated with 10 ml. of cold methanol. The solid was filtered, washed with 2 ml. of cold methanol, then with ether (2×5 ml.) to give 0.668 g. (66%) of 11-chloro-8-(cyclopropylmethyl)-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione of melting point 185—186°C. (dec.), having tranquilising properties.

U.V.: λ max. 243 (17,150).

Anal. Calcd. for $C_{23}H_{21}ClN_2O_3$:

C, 67.56; H, 5.18; Cl, 8.67; N, 6.85.

Found: C, 67.64; H, 5.22; Cl, 8.69; N, 6.59.

EXAMPLE 23

11-Chloro-8,12b-dihydro-6-methoxy-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

A mixture of 0.7 g. (0.00227 mole) of 7-chloro-1-methyl-3-methoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one [S. C. Bell et al., J. Med., Chem. 11, 457 (1968)] and 10 g. of diketene was heated at 96°C. for 1.5 hours to give 130 mg. of 11-chloro-8,12b-dihydro-6-methoxy-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione of melting point 158—160°C.

U.V.: λ max. 244 (18,500).

Anal. Calcd. for $C_{21}H_{23}ClN_2O_4$:

C, 63.24; H, 4.80; Cl, 8.89; N, 7.03.

Found: C, 63.21; H, 5.16; Cl, 8.86; N, 6.61.

EXAMPLE 24

11-Chloro-8,12b-dihydro-2-methyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

A mixture of 0.675 g. (2.5 mmoles) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one and 10 g. of diketene was heated on the steam bath for 1 hour to give

0.252 g. of 11 - chloro - 8,12b - dihydro - 2 - methyl - 12b - phenyl - 4H - [1,3]-oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione of melting point 173°C. with effervescence.

U.V.: λ max. 204 (35,850); 243 (17,800); sh 290 (1650); sh 305 (663).

Anal. Calcd. for $C_{19}H_{16}ClN_2O_3$:

C, 64.32; H, 4.26; Cl, 9.99; N, 7.90.

Found: C, 64.79; H, 4.90; Cl, 9.81; N, 7.37.

EXAMPLE 25

11-Chloro-12b-(o-fluorophenyl)-8,12b-dihydro-2,8-dimethyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 2, but in the absence of solvent, 0.85 g. of 7 - chloro - 1,3 - dihydro - 5 - (o - fluorophenyl) - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was treated with 10 g. of diketene on the steam bath under nitrogen for 2 hours to give 0.32 g. (30%) of 11 - chloro - 12b - (o - fluorophenyl) - 8,12b-dihydro - 2,8 - dimethyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H)-dione of melting point 175—177°C.

U.V.: (Ethanol): 203 (38,550); sl. sh 228 (18,000); 238 (17,850); sl. sh 263 (7,000); sh 269 (4,600).

Anal. Calcd. for $C_{20}H_{16}ClFN_2O_3$:

C, 62.10; H, 4.17; N, 7.24; Cl, 9.16; F, 4.91.

Found: C, 62.01; H, 4.71; N, 7.14; Cl, 9.17; F, 4.54.

EXAMPLE 26

11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-(o-chlorophenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione

In the manner given in Example 2, but in the absence of solvent, 0.80 g. of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was reacted with 10 g. of diketene on the steam bath under nitrogen for 19 hours to give 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (o-chlorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

In the manner given in the preceding examples, other oxazinobenzodiazepinones of formula II can be prepared from the corresponding benzodiazepinones by treating such benzodiazepinones with a diketene or a diketene-producing reagent (acyl halide and triethylamine). Representative compounds of this type include:

11-chloro-8,12b-dihydro-2-pentyl-3-butyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

9-methoxy-11-iodo-8,12b-dihydro-2-heptyl-3-hexyl-12b-(3,4-dimethylphenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

12-chloro-8,12b-dihydro-2-methyl-8-propyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

10-trifluoromethyl-8,12b-dihydro-2,8-dimethyl-12b-(p-bromophenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

9-bromo-8,12b-dihydro-2,8-diethyl-3-methyl-12b-(p-tolyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

10-nitro-8,12b-dihydro-2-propyl-3-ethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

11-nitro-8,12b-dihydro-2,8-dibutyl-3-propyl-12b-(p-trifluoromethyl)phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

9-methyl-10-nitro-8,12b-dihydro-2-methyl-8-benzyl-12b-(3,4-diethoxyphenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

12-bromo-9-butoxy-8,12b-dihydro-2-hexyl-3-pentyl-8-benzyl-12b-(p-propylphenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

11-chloro-12-nitro-8,12b-dihydro-6-methoxy-2-methyl-12b-(m-bromophenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

11-bromo-8,12b-dihydro-6-ethoxy-2-propyl-3-ethyl-8-benzyl-12b-(p-chlorophenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

9-methyl-8,12b-dihydro-2,6,8-triethyl-3-methyl-12b-(p-iodophenyl)-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione;

10-cyano-8,12b-dihydro-2-methyl-6,8-dibutyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4(6H)-one-7-thione;

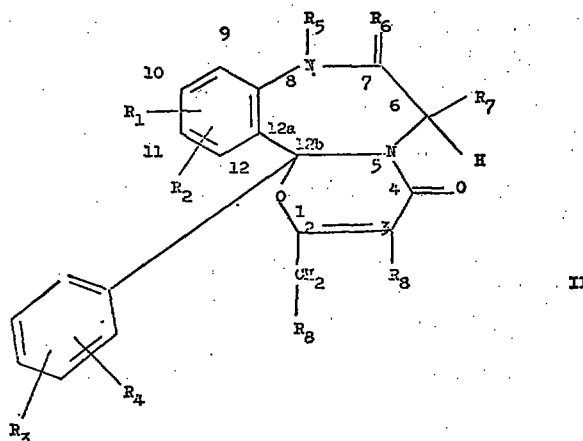
9-cyano-8,12b-dihydro-2-butyl-3-propyl-8-benzyl-12b-(m-butylphenyl)-4H-[1,3]-oxazino[3,2-d][1,4]benzodiazepin-4(6H)-one-7-thione;
11-fluoro-8,12b-dihydro-2-pentyl-3-butyl-8-methyl-12b-(m-trifluoromethylphenyl)-4H [1,3]oxazino[3,2-d][1,4]benzodiazepin-4(6H)-one-7-thione, and the like.

5

WHAT WE CLAIM IS:—

1. An oxazinobenzodiazepine of the formula II:

5



wherein R_1 , R_2 , R_3 and R_4 are selected from the group consisting of hydrogen, alkyl and alkoxy of 1 to 6 carbon atoms, inclusive, halogen, $-\text{CF}_3$, $-\text{NO}_2$, and $-\text{CN}$; wherein R_5 is selected from the group consisting of hydrogen, alkyl defined as above, cyclopropylmethyl, and benzyl; wherein R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$; wherein R_7 is selected from the group consisting of hydrogen, alkyl defined as above, and alkoxy defined as above; and wherein R_8 is selected from the group consisting of hydrogen, alkyl defined as above, and phenyl.

10

10

15

2. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - chloro - 8, 12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

15

20

3. The compound of claim 1 wherein R_1 is 11-chloro-, R_2 , R_3 , R_4 and R_7 are hydrogen, R_5 is methyl, R_6 is oxygen and R_8 is phenyl, and the compound is thus 11 - chloro - 8,12b - dihydro - 2 - benzyl - 3,12b - diphenyl - 8 - methyl - 4H - [1,3]oxazino[3,2-d][1,4]benzodiazepine - 4,7(6H) - dione.

20

25

4. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_5 , R_7 and R_8 are hydrogen and R_6 is oxygen, and the compound is thus 11 - chloro - 8,12b - dihydro - 2 - methyl - 12b - phenyl - 4H - [1,3]oxazino - [3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

25

30

5. The compound of claim 1 wherein R_1 is 11-trifluoromethyl, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - trifluoromethyl - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione.

30

35

6. The compound of claim 1 wherein R_1 is 11-chloro, R_4 is *p*-chloro, R_2 , R_3 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (*p* - chlorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

35

40

7. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is sulfur, and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepin - 4(6H) - one - 7 - thione.

40

8. The compound of claim 1 wherein R_1 is 11-cyano, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - cyano - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

9. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 and R_7 are hydrogen, R_5 is methyl, R_6 is oxygen and R_8 is ethyl, and the compound is thus



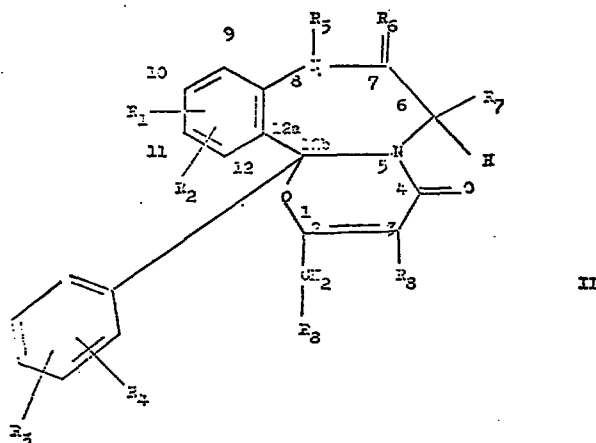
9-cyano-8,12b-dihydro-2-butyl-3-propyl-8-benzyl-12b-(m-butylphenyl)-4H-[1,3]-oxazino[3,2-d][1,4]benzodiazepin-4(6H)-one-7-thione;
11-fluoro-8,12b-dihydro-2-pentyl-3-butyl-8-methyl-12b-(m-trifluoromethylphenyl)-4H [1,3]oxazino[3,2-d][1,4]benzodiazepin-4(6H)-one-7-thione, and the like.

5

WHAT WE CLAIM IS:—

1. An oxazinobenzodiazepine of the formula II:

5



wherein R_1 , R_2 , R_3 and R_4 are selected from the group consisting of hydrogen, alkyl and alkoxy of 1 to 6 carbon atoms, inclusive, halogen, $-\text{CF}_3$, $-\text{NO}_2$ and $-\text{CN}$; wherein R_5 is selected from the group consisting of hydrogen, alkyl defined as above, cyclopropylmethyl, and benzyl; wherein R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$; wherein R_7 is selected from the group consisting of hydrogen, alkyl defined as above, and alkoxy defined as above; and wherein R_8 is selected from the group consisting of hydrogen, alkyl defined as above, and phenyl.

10

15

2. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - chloro - 8, 12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]-benzodiazepine - 4,7(6H) - dione.

20

3. The compound of claim 1 wherein R_1 is 11-chloro-, R_2 , R_3 , R_4 and R_7 are hydrogen, R_5 is methyl, R_6 is oxygen and R_8 is phenyl, and the compound is thus 11 - chloro - 8,12b - dihydro - 2 - benzyl - 3,12b - diphenyl - 8 - methyl - 4H - [1,3]oxazino[3,2-d][1,4]benzodiazepine - 4,7(6H) - dione.

25

4. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_5 , R_7 and R_8 are hydrogen and R_6 is oxygen, and the compound is thus 11 - chloro - 8,12b - dihydro - 2 - methyl - 12b - phenyl - 4H - [1,3]oxazino - [3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

30

5. The compound of claim 1 wherein R_1 is 11-trifluoromethyl, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - trifluoromethyl - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]-oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione.

35

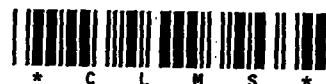
6. The compound of claim 1 wherein R_1 is 11-chloro, R_4 is *p*-chloro, R_2 , R_3 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (*p* - chlorophenyl) - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

40

7. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is sulfur, and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]-benzodiazepin - 4(6H) - one - 7 - thione.

8. The compound of claim 1 wherein R_1 is 11-cyano, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - cyano - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]-benzodiazepine - 4,7(6H) - dione.

9. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 and R_7 are hydrogen, R_5 is methyl, R_6 is oxygen and R_8 is ethyl, and the compound is thus



11 - chloro - 8,12b - dihydro - 3 - ethyl - 8 -methyl - 2 - propyl - 12b - phenyl-4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione.

5 10. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 and R_5 are hydrogen, R_6 and R_8 are methyl and R_7 is oxygen, and the compound is thus 11-chloro - 8,12b - dihydro - 2 - ethyl - 3,8 - dimethyl - 12b - phenyl - 4H - [1,3]-oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 5

11. The compound of claim 1 wherein R_1 , R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and the compound is thus 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H)-dione. 10

12. The compound of claim 1 wherein R_1 is 11-nitro, R_2 , R_4 , R_7 and R_8 are hydrogen, R_3 is o-fluoro, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - nitro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (o - fluorophenyl) - 4H - [1,3]-oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 15

13. The compound of claim 1 wherein R_1 is 11-nitro, R_2 , R_3 , R_4 , R_7 and R_8 are hydrogen, R_5 is methyl, R_6 is oxygen and R_8 is phenyl, and the compound is thus 11 - nitro - 8,12b - dihydro - 2,8 - dimethyl - 12b - phenyl - 4H - [1,3]oxazino[3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione. 15

14. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 , and R_7 are hydrogen, R_5 is methyl and R_6 is oxygen, R_8 is isopropyl and the compound is thus 11 - chloro - 8,12b - dihydro - 2 - isobutyl - 3 - isopropyl - 8 - methyl - 12b-phenyl - 4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 20

15. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_4 and R_8 are hydrogen, R_5 is methyl and R_6 is oxygen, and R_7 is methoxy, and the compound is thus 11 - chloro - 8,12b - dihydro - 6 - methoxy - 2,8 - dimethyl - 12b - phenyl-4H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 25

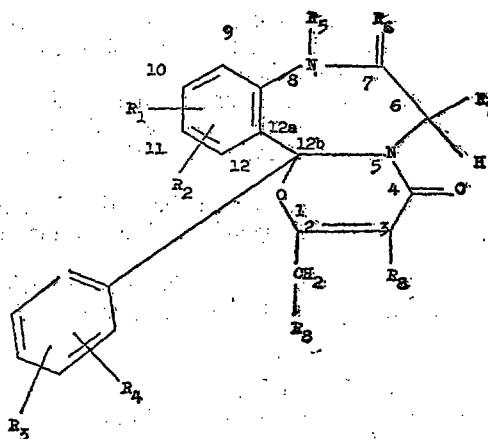
16. The compound of claim 1 wherein R_1 is 11-fluoro, R_2 , R_3 , R_4 , and R_7 are hydrogen, R_5 and R_8 are methyl, and R_6 is oxygen, and the compound is thus 11-fluoro - 8,12b - dihydro - 2 - ethyl - 3,8 - dimethyl - 12b - phenyl - 4H - [1,3]-oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 30

17. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_7 and R_8 are hydrogen, R_4 is o-fluoro, R_5 is methyl and R_6 is oxygen and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (o - fluorophenyl) - 4H-[1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 35

18. The compound of claim 1 wherein R_1 is 11-chloro, R_2 , R_3 , R_7 and R_8 are hydrogen, R_4 is o-chloro, R_5 is methyl and R_6 is oxygen, and the compound is thus 11 - chloro - 8,12b - dihydro - 2,8 - dimethyl - 12b - (o - chlorophenyl) - 4H-[1,3]oxazino[3,2 - d][1,4]benzodiazepine - 4,7(6H) - dione. 35

19. 11 - Chloro - 8 - (cyclopropylmethyl) - 8,12b - dihydro - 2 - methyl - 12b-phenyl - 4H - [1,3]oxazino - [3,2 - d][1,4] - benzodiazepine - 4,7(6H) - dione. 40

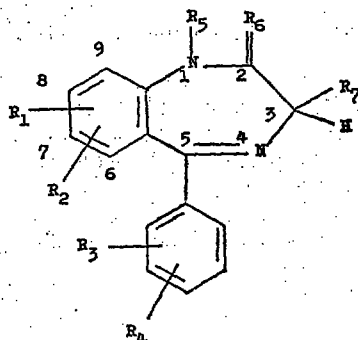
20. A process for the production of an oxazinobenzodiazepine of the formula II:



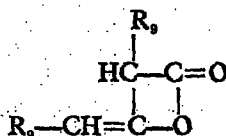
wherein R_1 , R_2 , R_3 and R_4 are selected from the group consisting of hydrogen, alkyl and alkoxy of 1 to 6 carbon atoms, inclusive, halogen, $-\text{CF}_3$, $-\text{NO}_2$ and $-\text{CN}$;



wherein R_5 is selected from the group consisting of hydrogen and alkyl defined as above, cyclopropylmethyl and benzyl; wherein R_6 is selected from the group consisting of $=O$ and $=S$; wherein R_7 is selected from the group consisting of hydrogen, alkyl defined as above, and alkoxy as defined above; and wherein R_8 is selected from the group consisting of hydrogen, alkyl defined as above, and phenyl, which comprises: treating, in an inert organic solvent, a 5-phenyl-3H-1,4-benzodiazepin-2(1H)-one of the formula I:



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are defined as above, with a diketene of the formula



wherein R_8 is selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, inclusive, phenyl, phenylmethyl and phenylethyl.

21. The process of claim 20 wherein 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one is reacted with diketene in acetone to give 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione.

22. The process of claim 20 wherein the diketene is produced *in situ* by the reaction of an acyl halide selected from the group consisting of chlorides and bromides of alkanic acids of 2 to 8 carbon atoms, inclusive, and phenylsubstituted alkanic acids of 8 to 10 carbon atoms, inclusive; which have at least two hydrogen atoms in the 2-position, with an acid acceptor.

23. The process of claim 22 wherein the acyl halide is acetyl chloride.

24. The process of claim 22 wherein the acyl halide is phenylacetyl chloride.

25. The process of claim 23 wherein 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one is reacted with acetyl chloride and triethylamine in ether to give 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione.

26. A process for the preparation of a compound as claimed in any of claims 1 to 19 substantially as herein described with reference to the Examples.

27. A compound as claimed in any of claims 1 to 19 when prepared by a process as claimed in claims 20 to 26.

28. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 19 or 27 together with a pharmaceutically acceptable carrier.

29. A method of tranquilising animals excluding humans which comprises administering to the said animals a compound as claimed in any of claims 1 to 19 or 27.

For the Applicants:—
GILL, JENNINGS & EVERY,
51/52 Chancery Lane,
London, W.C.2.