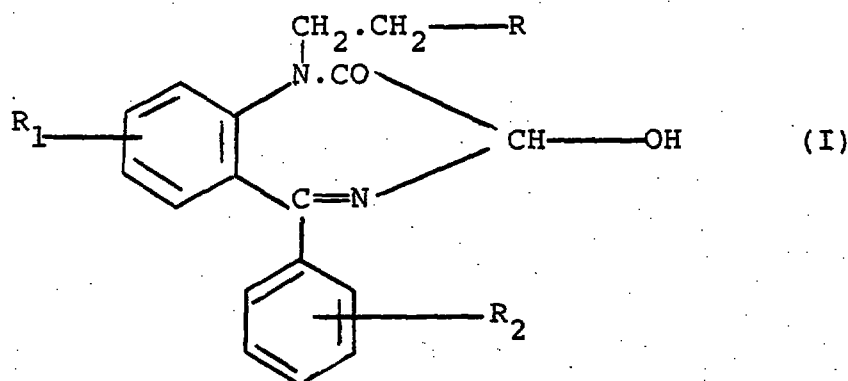


This invention relates to new 3-hydroxy-1,4-benzodiazepine-2-ones and process for the production thereof, and compositions containing them.

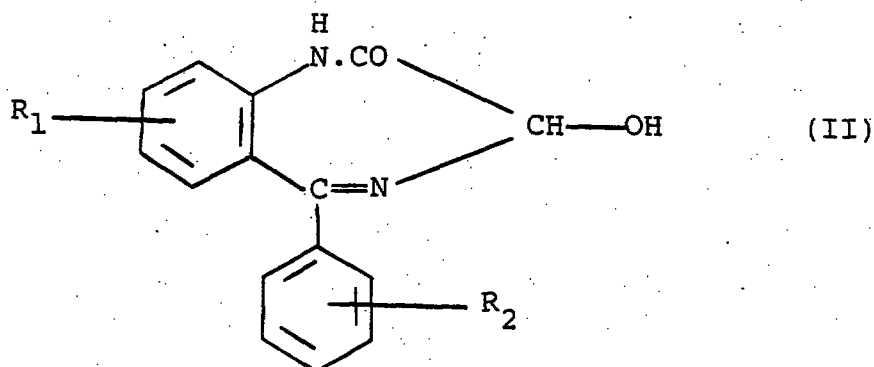
The present invention provides 3-hydroxy-1,4-benzodiazepine-2-ones of the general formula



15 in which R represents a nitrile group, R_1 represents hydrogen, halogen, trifluoromethyl or nitro and R_2 represents hydrogen or halogen.

20 We have found that such compounds have a highly sedative and sleep prolonging activity as well as a hexobiarbital potentiating activity while exhibiting a low toxicity. They may also be used as intermediates in the production of new pharmaceuticals.

25 The compounds according to the invention may be prepared by the selective substitution of 3-hydroxy-1,4-benzodiazepine-2-ones of the general formula



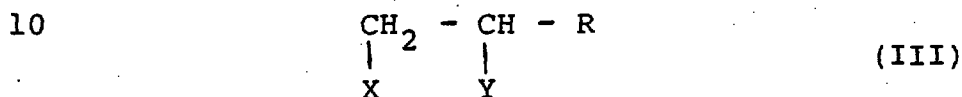
in which R_1 and R_2 have the above stated meanings, at the NH-group, the group OH in positions 3 remaining unaffected.

The compounds according to the invention are new compounds. Compounds of formula I in which R has a meaning other than nitrile are obtained usually by routes via the 4-oxide substituted in position 1, the Polonovsky-rearrangement thereof to give the 3-acyloxy derivative and subsequent saponification (German Offenlegungs-schrift 2,237,211 (U.K. Patent No. 1,393,286), *Arzneim. Forsch.* 25, 720 (1975)).

Compounds of general formula (II) have been known since 1962. Nevertheless the possibility of a selective substitution at the group NH has hardly been utilized up to now. By the process of the invention it is possible to obtain from easily available compounds, such as e.g. oxazepam, lorazepam etc. (see Austrian patent specification 309,436) in a one-step reaction new, highly active

sleeping drugs.

According to the process of the invention 3-hydroxy-1,4-benzodiazepine-2-ones of general formula (II) or alkali compounds thereof are reacted, if desired, with use of basic additions and/or with addition of phase transfer catalysts, such as quaternary ammonium or phosphonium salts or crown ethers and optionally alkali metal iodides, with compounds of the general formula



in which R has the meaning given above, X is a reactive radical, such as a halogen atom or the sulfonyloxy group and Y is hydrogen or X may together with Y form a second atomic bond.

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Reactants of general formula (III) include for example acrylonitrile as well as 3-chloropropionitrile or 3-bromopropionitrile.

The alkali metal compounds of the starting products of general formula (II), which also have not been described before, may be obtained easily, e.g. by reaction of these compounds with one equivalent potassium-tert.butylate in absolute water-free solvents,

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such as dimethylformamide or dioxan. In such a reaction first the starting product is dissolved and then the potassium compound is precipitated or it may be obtained by precipitation with ethers.

5 The possibility of the selective cyanoethylation of compounds of formula (II) at the amide-nitrogen (position 1) is surprising, because acetanilide, which corresponds to the present structure, is found to react with acrylonitrile only at 90 to 100°C,

10

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whereas the reaction thereof with secondary alcohols occurs already at room temperature or even at a lower temperature (Org. Reactions 5, 88, 89 (1949)).

According to the process of the present invention the
5 reaction at the amide-nitrogen of product (II) starts even at room temperature without a simultaneous substitution at the OH-group, although acrylonitrile is present in great excess as reaction medium.

The substitution of the radicals $-\text{CH}_2\text{CH}_2-\text{R}$
10 at the amide-nitrogen may be proved by the peaks of the CH-OH -coupling in the n.m.r. spectra of the derivatives obtained and by the esterification of the OH-group which remained free.

The following examples illustrate the invention.

15

Example 1

1 g of triethylbenzylammoniumchloride ("Teba") was added to a suspension of 10 g of 7-chloro-3-hydroxy-5-(2'-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one
20 in 50 ml acrylonitrile. Then 8 drops of a 40% methanolic solution of benzyltrimethyl ammonium hydroxide (Reg. Trade Mark (Triton/B")) were added with stirring. After stirring for 8 hours at room temperature the reaction mixture was left overnight at 4°C. Then the precipitate was filtered off with
25 suction, washed with acetone and crystallized from ethanol.

The 1-(2-cyanoethyl)-7-chloro-3-hydroxy-5-(2'-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one thus obtained had a melting point of 190 to 193 °C. Without addition of Teba the disubstituted 1-(2-cyanoethyl)-7-chloro-3-(2-cyanoethoxy)-5-(2'-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one was also formed. This melted after recrystallization from acetonitrile at 204 to 207 °C.

In order to distinguish the mono- and disubstituted products from the starting chromatography on thin layer kieselgel 60 F 254 using as liquid phase a mixture of benzenes dioxan; glacial acetic acid (90 : 25 : 4 parts by volume) is suitable.

Example 2

15 1 g Teba and 8 drops of a 40% methanolic solution of Triton B was added to a suspension of 10 g of 7-chloro-3-hydroxy-5-(2'-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one ("Lorazepam") in 50 ml of acrylonitrile and was stirred for 24 hours at room temperature. Then
20 the reaction mixture is cooled to 4 °C, the precipitate was filtered off with suction and recrystallized from ethyl acetate. 1-(2-Cyanoethyl)-7-chloro-3-hydroxy-5-(2'-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one, m.p. 198 to 202 °C, was obtained. Without
25 addition of Teba the disubstituted 1-(2-cyanoethyl)-7-

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chloro-3-(2-cyanoethoxy)-7-chloro-3-(2-cyanoethoxy)-
5-(2'-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-
2-one, m.p. 210 to 213°C (from acetonitrile), was
also obtained.

Example 3

3 ml of a 40 % methanolic solution of Triton B were added dropwise to a suspension of 20 g of Oxazepam in 240 ml of acrylonitrile with stirring. Then it was
5 heated for one hour to 50°C to produce an orange solution. After standing overnight the reaction was complete. The solution was concentrated in vacuo and upon cooling the concentrate a precipitate was obtained, which was recrystallized from CHCl_3 . It melted at 192 to 194°C
10 and consisted of 1-(2-cyanoethyl)-7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

If the reaction mixture was heated for 2 hours to 50°C the disubstituted 1(2-cyanoethyl)-7-chloro-3-(2-cyanoethoxy)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-
15 2-one was also formed, which was practically insoluble in CHCl_3 . After recrystallization from acetonitrile it melted at 215 to 218°C.

Example 4

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0.1 g of Teba and 1 ml of triethylamine were added to a suspension of 2 g of Lorazepam in 20 ml of acrylonitrile and then heated with stirring to 50°C. A yellowish solution resulted, from which gradually a precipitate was formed. After 3 hours the mixture was concentrated in vacuo and the concentrate was allowed to crystallize overnight at a temperature of 4°C. The precipitate was filtered off with suction and recrystallized from ethyl acetate. It was identical with the monosubstitution product obtained according to Example 2 (melting point 198 to 202°C).

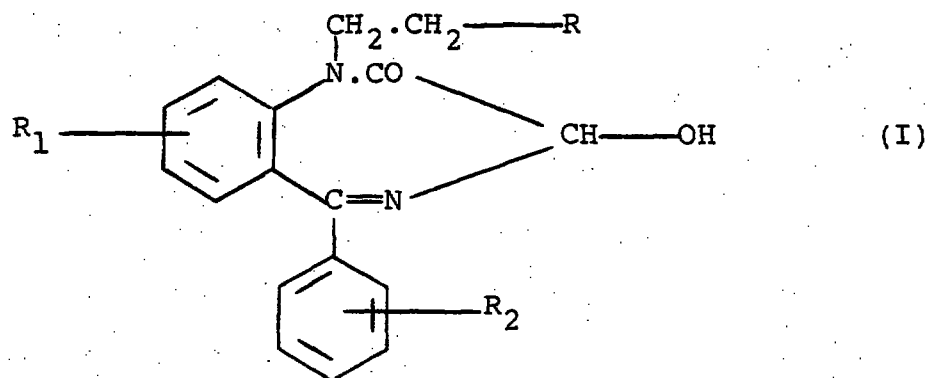
By following the procedure of the above examples, the following compounds were prepared.

1-(cyanoethyl)-7-nitro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one, m.p. 185 to 188°C;
1-(2-cyanoethyl)-7-nitro-3-hydroxy-5-(2'-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one, m.p. 191 to 194°C;
1-(2-cyanoethyl)-7-nitro-3-hydroxy-5-(2'-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one, m.p. 183 to 186°C.



CLAIMS

1. 3-Hydroxy-1,4-benzodiazepine-2-ones of the formula



10 in which R represents nitrile, R_1 represents hydrogen, halogen, trifluoromethyl or nitro and R_2 represents hydrogen or halogen.

- 15 2. 1-(2-Cyanoethyl)-7-chloro-3-hydroxy-5-(2'-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

3. 1-(2-Cyanoethyl)-7-chloro-3-hydroxy-5-(2'-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

- 20 4. 1-(2-Cyanoethyl)-7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

5. 1-(2-Cyanoethyl)-7-nitro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

- 25 6. 1-(2-Cyanoethyl)-7-nitro-3-hydroxy-5-(2'-chloro-



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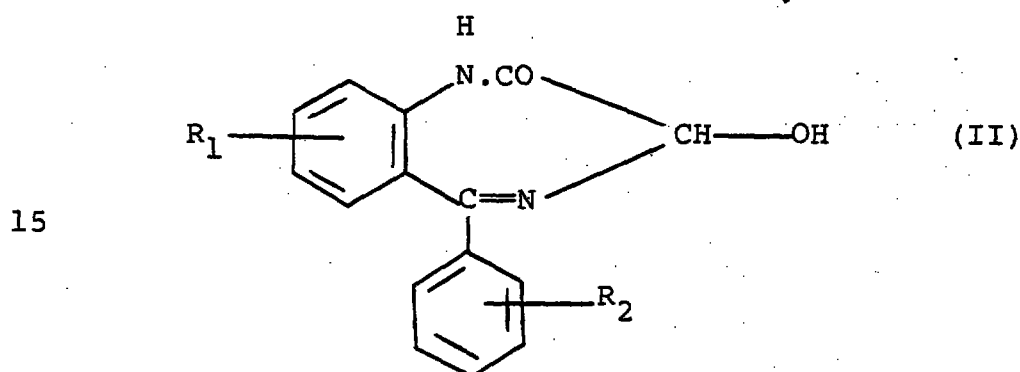
phenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

7. 1-(2-Cyanoethyl)-7-nitro-3-hydroxy-5-(2'-fluoro-phenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

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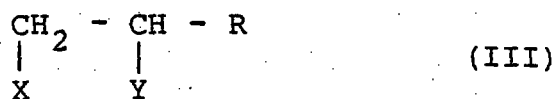
8. Compounds as claimed in claim 1 substantially as herein described with reference to the Examples.

9. A process for the preparation of compounds as
10 claimed in claim 1 which comprises selectively substituting compounds of the general formula



20 in which R_1 and R_2 have the meanings given in claim 1, at the 1-position to introduce a group $-CH_2CH_2-R$ in which R has the meaning given in claim 1.

10. A process as claimed in claim 9 which comprises
25 reacting a compound of formula II or an alkali derivative thereof with a compound of the general formula



in which R has the meaning given in claim 1, X is a reactive radical and Y is hydrogen or X may together with Y form a second bond.

11. A process as claimed in claim 10 in which the process is carried out in the presence of a base.

12. A process as claimed in claim 10 or claim 11 in which the process is carried out in the presence of a phase transfer catalyst.

13. A process as claimed in claim 12 in which the phase transfer agent is a quaternary ammonium or phosphonium salt or a crown ether.

14. A process as claimed in any of claims 10 to 13 in which the process is carried out in the presence of an alkali metal iodide.

15. A process as claimed in any of claims 10 to 14 in which the compound of formula III is used as a reaction medium optionally diluted with an inert solvent.

16. A process as claimed in any of claims 10 to 15



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in which the reaction component of formula (III) is
3-chloropropionitrile or 3-bromopropionitrile.

17. A process as claimed in any of claims 10 to 15
5 in which the reaction component of formula (III) is
acrylonitrile.

18. A process as claimed in claim 9 substantially
as herein described with reference to the Examples.

10

19. Compounds as claimed in claim 1 when prepared
by a process as claimed in any of claims 9 to 18.

20. Pharmaceutical compositions comprising a compound
15 as claimed in any one of claims 1 to 8 or 19 together
with a pharmaceutically acceptable carrier.

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