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1,022,642

PATENT SPECIFICATION

NO DRAWINGS

1,022,642

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Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

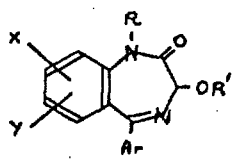
Benzodiazepine Compounds

We, AMERICAN HOME PRODUCTS CORPORATION, a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 685, Third Avenue, New York, 17, New York, United States of America, (Assignee of STANLEY CHARLES BELL), 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:—

This invention relates to processes for producing 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - ones having at the 3 - position a hydroxy, alkoxy or acyloxy group; or acid addition salts thereof. The invention also relates to certain of such compounds, to pharmaceutical preparations containing them and also to processes for producing such preparations in which a compound of the invention is put into medicinally acceptable form.

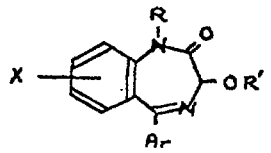
The compounds of the invention have anticonvulsant and/or muscle-relaxing properties. Some of them exhibit sedative properties and some are tranquillizers without being sedative. Certain of them have useful disinhibiting properties and increase libido.

The compounds in accordance with the invention are those having the general formula:



where X and Y are hydrogen, chlorine, bromine, nitro, trifluoromethyl or methylsulphonyl (particularly where X is hydrogen or a substituent at the 7-position and Y is hydrogen); R is hydrogen or a hydrocarbon radical, for instance alkyl or alkenyl, particularly lower alkyl (e.g. methyl, ethyl or propyl), lower alkenyl (e.g. allyl or methallyl), or lower aralkyl (e.g. benzyl or phenethyl), Ar is a monocyclic aromatic radical, e.g. phenyl, thienyl or phenyl substituted by chlorine or fluorine, methoxy, methyl or trifluoromethyl (hereinafter designated "monocyclic aryl"); and R^1 is hydrogen, lower alkyl or an acyl (e.g. lower acyl) radical of a carboxylic acid which can be substituted or unsubstituted; and their acid addition salts.

In particular the invention provides compounds having the general formula:



where X is hydrogen, chloro, bromo, nitro or trifluoromethyl; R is hydrogen, alkyl or alkenyl; Ar is phenyl or phenyl substituted by chlorine or fluorine or trifluoromethyl and R^1 is hydrogen, alkyl, or an acyl radical of a carboxylic acid.

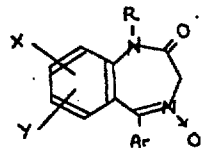
Examples of unsubstituted acyl radicals are acetyl, propionyl, caproyl, benzoyl, toluyl, phenacetyl, β-phenylpropionyl and cinnamoyl. Examples of substituted acyl radicals are haloacyl radicals (e.g. chloroacetyl, chlorobenzoyl and bromobenzoyl) and aminoacyl radicals (e.g. aminoacetyl, aminobenzoyl and morpholinoacetyl).

Preferably, R is hydrogen or methyl, Ar is phenyl or chlorophenyl, Y is hydrogen and X

is a 7-chloro-substituent and R^1 is hydrogen. Compounds where R and R^1 are hydrogen, Ar is phenyl or *o*-chlorophenyl and X is a 7-chloro-substituent and their acid addition salts are claimed *per se*, together with pharmaceutical preparations containing them, in co-pending Application No. 37788/65 (Serial No. 1022644) while a compound where R is methyl, R^1 is hydrogen, Ar is phenyl and X is a 7-chloro-substituent and its acid addition salts are claimed *per se*, together with pharmaceutical preparations containing them, in co-pending Application No. 37789/65 (Serial No. 1022645).

By lower alkyl, lower alkenyl, lower aralkyl and lower acyl is meant such groups having up to 9 carbon atoms.

Surprisingly, it has been found, in accordance with the invention, that by gently warming a 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide (some of these N-oxides are claimed *per se* in Specification No. 972,968), for example one having the formula:



in which R, X, Y and Ar are as recited above, with an organic carboxylic acylating agent, e.g. an organic carboxylic acid halide or acid anhydride, there is obtained in high yield a 3 - acyloxy - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one which, if desired, may be isolated as an acid addition salt.

The term "organic carboxylic acylating agent" requires an organic residue to be attached to its carbonyl group by a carbon - carbon bond between the organic group and the carbonyl group and thereby does not include alkyl haloformates which do not act as acylating agents in this reaction and whose use leads to the corresponding 3 - halo - compounds.

When the reagent employed is an organic carboxylic acid anhydride, for example acetic anhydride, the product is largely a 3 - acyloxy - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one. When the reagent is an organic carboxylic acid halide, for example acetyl chloride, the product is ordinarily a mixture of a 3 - acyloxy - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and a 3 - halo - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with the former normally predominating. The latter compounds are the subject of copending application No. 5679/65 (Serial No. 1022643).

The 3 - acyloxy or 3 - halo - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - ones can be hydrolysed to give the corresponding hydroxy compounds, in the case of the 3 - acyloxy compounds e.g. by alkaline hydrolysis and in the case of the 3 - chloro compounds e.g. by warming with water and a mutual solvent, such as acetone and, if desired the product can be isolated as an acid addition salt.

The 3 - haloacyloxy (e.g. 3 - chloroacetyloxy) - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - ones can be converted by reaction with an amine, e.g. morpholine, to 3 - aminoacyloxy (e.g. 3 - morpholinoacetyloxy) - 5 - ~~monocyclicaryl~~ - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - ones and, if desired, the product can be isolated as an acid addition salt.

Compounds which are unsubstituted at position 1 can, if desired, be converted to compounds having a hydrocarbon radical at position 1 by treatment with an alkylating agent (using this term in the wide sense of an agent which introduces a hydrocarbon, e.g. an alkyl, alkenyl or aralkyl, group) such as dimethyl sulphate, ~~diethylsulphate~~, methyl iodide, allyl bromide or benzyl chloride in the presence of an alkali such as sodium hydroxide or potassium hydroxide.

The 3 - alkoxy - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - ones of the invention can be prepared by reacting a 3 - halo - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with an alcohol and, if desired, the product can be isolated as or converted to an acid addition salt. The 3 - halo - starting materials, preferably the 3 - chloro - compounds, can be prepared by reaction of 5 - ~~monocyclicaryl~~ - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxides with an alkyl haloformate or by reaction of 3 - hydroxy - 5 - monocyclic-aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepines with a thionyl halide in accordance with copending application No. 5679/65. (Serial No. 1022643) In addition these starting materials are in some instances co-produced during acid chloride acylation of the 2 - one - 4 - oxides as above mentioned and as shown in Example 8 where the 3 - halo compound formed is converted to the corresponding 3 - ethoxy compound.

The compounds of the invention can be administered parenterally or orally as pharmaceutical preparations containing the compound and a pharmaceutically acceptable carrier, for instance diluents, solvents, suspending agents, fillers, excipients, adhesives, colouring and flavouring materials, as desired for preparation of convenient dosage forms.

The following examples illustrate the preparation of the compounds of the invention:

EXAMPLE 1

A suspension of 10 g. of 7 - chloro - 1,3 -

dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide in 150 ml. of acetic anhydride was warmed on a steam bath with stirring until all the solid had dissolved. Upon cooling there was filtered off crystalline, analytically pure 3 - acetoxy - 7 - chloro -1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 242—3°C. Analysis, calcd. for $C_{17}H_{13}ClN_2O_3$: C, 62.09; H, 3.98; N, 8.52. Found: C, 62.06; H, 4.13; N. 8.30.

EXAMPLE 2

3 - Acetoxy - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 229—31°C, was prepared from 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1. Analysis, calcd. for $C_{17}H_{14}N_2O_3$: C, 69.39; H, 4.80; N, 9.51. Found: C, 69.30; H, 4.91; N, 9.64.

EXAMPLE 3

3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 262—3°C, was prepared from 7 - chloro - 1,3 - dihydro - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example I. Analysis, calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17; Cl, 10.34. Found: C, 63.16; H, 4.57; N, 8.22; Cl, 10.25.

EXAMPLE 4

3 - Acetoxy - 7 - bromo - 5 - (*p* - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 256—7°C, was prepared from 7 - bromo - 5 - (*p* - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1. Analysis, calcd. for $C_{17}H_{12}BrClN_2O_3$: C, 50.07; H, 2.97; N, 6.86; Cl, 8.70; Br, 19.60. Found: C, 50.08; H, 3.08; N, 6.77; Cl, 8.51; Br. 19.18.

EXAMPLE 5

3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 5 - (2 - thienyl) - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 269°C, was prepared from 7 - chloro - 1,3 - dihydro - 5 - (2 - thienyl) - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1. Analysis, calcd. for $C_{15}H_{11}ClN_2O_3S$: C, 53.80; H, 3.31; N, 8.37. Found: C, 53.95; H, 3.41; N, 8.17.

EXAMPLE 6

7 - Chloro - 3 - (α - chloroacetoxy) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 230—1°C, was prepared from 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide and α - chloroacetic anhydride according to the procedure of Example 1. Analysis, calcd. for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.06; H, 3.32; N, 7.70; Cl, 19.47. Found: C, 56.08; H, 3.42; N, 7.43; Cl, 19.40.

EXAMPLE 7

7 - Chloro - 3 - (α - chloroacetoxy) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one was prepared by the action of chloroacetyl chloride on 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide. This compound was the same as that prepared in Example 6.

EXAMPLE 8

(a) A suspension of 5.0 g. of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide in 20 ml. of benzoyl chloride was warmed until all the solid dissolved. Addition of cyclohexane precipitated a solid which was suspended in warm ethanol and the white crystalline 3 - benzoyloxy - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 251—2°C, was collected. Analysis, calcd, for $C_{22}H_{15}ClN_2O_3$: C, 67.63; H, 3.87; N, 7.17; Cl 9.07. Found: C, 67.57; H, 4.05; N, 6.93; Cl, 9.05.

(b) To the above alcohol filtrate was added water and the solid that precipitated was collected and recrystallised from acetonitrile giving 7 - chloro - 1,3 - dihydro - 3 - ethoxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 225—7°C. Analysis, calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90; Cl, 11.25. Found: C, 64.45; H, 4.69; N, 8.88; Cl, 11.20.

EXAMPLE 9

To a slightly warm suspension of 3.0 g. of 3 - acetoxy - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 150 ml. of ethanol was added 4 ml. of 4*N* sodium hydroxide solution with stirring. All the solid dissolved and soon a thick white solid precipitated out. The solid was filtered, washed well with water and recrystallised from ethanol, giving 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 203°C. Analysis, calcd for $C_{15}H_{11}ClN_2O_2$: C, 62.81; H, 3.84; N, 9.27; Cl, 12.37. Found: C, 62.57; H, 3.98; N, 9.59; Cl, 12.30.

EXAMPLE 10

To a suspension of 3.4 g. of 3 - acetoxy - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 80 ml. of alcohol was added 6 ml. of 4*N* sodium hydroxide. After complete solution had taken place a solid precipitated that redissolved upon the addition of 80 ml. of water. The solution was acidified with acetic acid to give white crystals. After recrystallisation from alcohol the compound melted at 203—204°C, and is identical with the product of Example 9.

EXAMPLE 11

3,7 - Dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one was dissolved in warm ethanol. After a few minutes water was added, precipitating crude 7 - chloro - 3 - ethoxy - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, which was filtered off, dried, and recrystallised from acetonitrile. The product melted

at 224—225°C, and was the same as described in Example 8b.

EXAMPLE 12

One gram of 3,7 - dichloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one was dissolved in 20 ml. of 50% aqueous acetone and warmed in a water bath until, after a few minutes, a solid precipitated. This material was recrystallised from alcohol to afford 7 - chloro - 3 - hydroxy - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, identical with the product of Examples 9 and 10.

EXAMPLE 13

A solution of 3.0 g. of 7 - chloro - 3 - (α - chloroacetoxy) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, 2.2 ml. of morpholine and 75 ml. of ethanol was refluxed for two hours. After cooling, the solution was acidified with alcoholic hydrogen chloride. The white 7 - chloro - 1,3 - dihydro - 3 - (morpholino - acetoxy) - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride, m.p. 223—4°C, was filtered off and washed with ethanol. Analysis, calcd. for $C_{21}H_{20}Cl_2N_3O_4$: N, 9.33; Cl, 15.75. Found: N, 9.02; Cl, 15.70.

EXAMPLE 14

7 - Chloro - 1,3 - dihydro - 3 - hydroxy - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 119—121°C, was prepared from 3 - acetoxy - 7 - chloro - 1,3 - dihydro - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and one equivalent of sodium hydroxide according to the procedure of Example 10. Analysis, calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.92; H, 4.36; N, 9.32. Found: C, 63.78; H, 4.64; N, 9.26.

EXAMPLE 15

A mixture of 3.4 g. of ~~17~~ - chloro - 3 - hydroxy - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, 4 ml. of 4*N* - sodium hydroxide and 1.4 ml. of dimethyl sulphate in 200 ml. of 50% alcohol was stirred for 2 hours and evaporated to dryness *in vacuo*. Water and ether were added and the ether layer was separated. The solvent was removed and the residue was recrystallised from cyclohexane to give 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 119—121°C.

EXAMPLE 16

3 - Acetoxy - 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, m.p. 262—264°C, was prepared from 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1. Analysis, calcd. for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.21; H, 3.33; N, 7.71. Found: C, 56.21; H, 3.54; N, 7.40.

EXAMPLE 17

7 - Chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - hydroxy - 2H - 1,4 - benzodiazepin - 2 - one, was prepared from 3 - acetoxy - 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10 and was isolated as a solvate with 1 mole of ethanol. When heated, it loses the ethanol of solvation and melts at 166—168°C. Analysis, calcd. for $C_{17}H_{16}Cl_2N_2O_3$: C, 55.60; H, 4.39; N, 7.63. Found: C, 55.68; H, 4.20; N, 7.93.

EXAMPLE 18

7 - Chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - hydroxy - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was prepared from 3 - acetoxy - 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 -one according to the procedure of Example 10.

EXAMPLE 19

7 - Chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - hydroxy - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was prepared from 7 - chloro - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 3 - hydroxy - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 15, m.p. 192—194°C. Analysis, calcd. for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; N, 8.36; Cl, 21.15. Found: C, 57.42; H, 3.44; N, 8.69; Cl, 21.25.

EXAMPLE 20

1,3 - Dihydro - 3 - hydroxy - 5 - phenyl - 7 - trifluoromethyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 5 - phenyl - 7 - trifluoromethyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10. The latter compound is easily made by the process of Example 1 from 1,3 - dihydro - 5 - phenyl - 7 - trifluoromethyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide, described in British Specification No. 972,968.

EXAMPLE 21

3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 1 - ethyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 1 - ethyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1.

EXAMPLE 22

7,8 - Dichloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 -acetoxy - 7,8 - dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 23

1,3 - Dihydro - 3 - hydroxy - 5 - (*m* - fluorophenyl) - 7 - chloro - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 5 - (*m* - fluorophenyl) - 7 - chloro - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 24

1,3 - Dihydro - 3 - hydroxy - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10. The latter can be made by the process of Example 1 from the 4 - oxide described in British Specification No. 972,968.

EXAMPLE 25

1 - Allyl - 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and allyl bromide according to the procedure of Example 15.

EXAMPLE 26

1,3 - Dihydro - 3 - hydroxy - 7 - chloro - 5 - (*o* - tolyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - chloro - 5 - (*o* - tolyl) - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 27

1,3 - Dihydro - 3 - hydroxy - 7 - methylsulphonyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - methylsulphonyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 28

1,3 - Dihydro - 3 - hydroxy - 7 - chloro - 5 - (*p* - trifluoro - methylphenyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - chloro - 5 - (*p* - trifluoromethyl - phenyl) - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 29

3 - Acetoxy - 7,9 - dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 one can be prepared from 7, 9- dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1.

EXAMPLE 30

6 - Chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 6 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

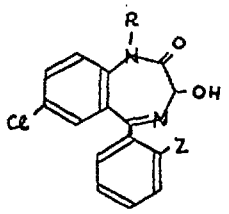
EXAMPLE 31

1 - Benzyl - 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and benzyl bromide according to the procedure of Example 15.

EXAMPLE 32

3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 5 - (*p* - methoxyphenyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 5 - (*p* - methoxyphenyl) - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1.

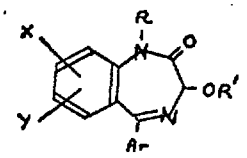
In this specification we make no *per se* claim to compounds of formula



where R is hydrogen and Z is hydrogen or a chlorine atom or to their acid addition salts or pharmaceutical compositions containing them as these are claimed in copending Application No. 37788/65 (Serial No. 1022644); also we make no *per se* claim to the compound where Z is hydrogen and R is a methyl group or to its acid addition salts or pharmaceutical compositions containing them as these are claimed in copending Application No. 37789/65 (Serial No. 1022645).

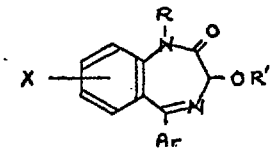
Subject to the above disclaimers WHAT WE CLAIM IS:—

1. A compound having the formula



where X and Y are hydrogen, chlorine, bromine, nitro, trifluoromethyl or methylsulphonyl; R is hydrogen or a hydrocarbon radical; Ar is a monocyclic aromatic radical and R^1 is hydrogen, lower alkyl or an acyl radical of a carboxylic acid; or an acid addition salt thereof.

2. A compound according to Claim 1 having the general formula



where X is hydrogen, chlorine, bromine, nitro or trifluoromethyl; R is hydrogen, alkyl or alkenyl; Ar is phenyl or phenyl substituted by chlorine or fluorine or trifluoromethyl and R^1 is hydrogen, alkyl or an acyl radical of a carboxylic acid.

3. A compound according to Claim 1, in which Y is hydrogen and X is hydrogen or a chlorine, bromine, nitro, trifluoromethyl or

EXAMPLE 24

1,3 - Dihydro - 3 - hydroxy - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10. The latter can be made by the process of Example 1 from the 4 - oxide described in British Specification No. 972,968.

EXAMPLE 25

1 - Allyl - 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and allyl bromide according to the procedure of Example 15.

EXAMPLE 26

1,3 - Dihydro - 3 - hydroxy - 7 - chloro - 5 - (*o* - tolyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - chloro - 5 - (*o* - tolyl) - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 27

1,3 - Dihydro - 3 - hydroxy - 7 - methylsulphonyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - methylsulphonyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 28

1,3 - Dihydro - 3 - hydroxy - 7 - chloro - 5 - (*p* - trifluoro - methylphenyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 1,3 - dihydro - 7 - chloro - 5 - (*p* - trifluoromethyl - phenyl) - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

EXAMPLE 29

3 - Acetoxy - 7,9 - dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7, 9- dichloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1.

EXAMPLE 30

6 - Chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 3 - acetoxy - 6 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one according to the procedure of Example 10.

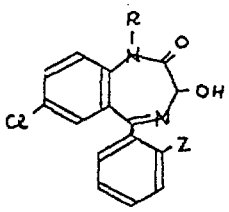
EXAMPLE 31

1 - Benzyl - 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and benzyl bromide according to the procedure of Example 15.

EXAMPLE 32

3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 5 - (*p* - methoxyphenyl) - 2H - 1,4 - benzodiazepin - 2 - one can be prepared from 7 - chloro - 1,3 - dihydro - 5 - (*p* - methoxyphenyl) - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide according to the procedure of Example 1.

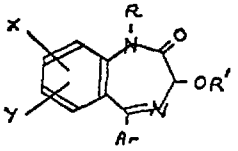
In this specification we make no *per se* claim to compounds of formula



where R is hydrogen and Z is hydrogen or a chlorine atom or to their acid addition salts or pharmaceutical compositions containing them as these are claimed in copending Application No. 37788/65 (Serial No. 1022644); also we make no *per se* claim to the compound where Z is hydrogen and R is a methyl group or to its acid addition salts or pharmaceutical compositions containing them as these are claimed in copending Application No. 37789/65 (Serial No. 1022645).

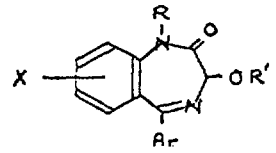
Subject to the above disclaimers WHAT WE CLAIM IS:—

1. A compound having the formula



where X and Y are hydrogen, chlorine, bromine, nitro, trifluoromethyl or methylsulphonyl; R is hydrogen or a hydrocarbon radical; Ar is a monocyclic aromatic radical and R^1 is hydrogen, lower alkyl or an acyl radical of a carboxylic acid; or an acid addition salt thereof.

2. A compound according to Claim 1 having the general formula



where X is hydrogen, chlorine, bromine, nitro or trifluoromethyl; R is hydrogen, alkyl or alkenyl; Ar is phenyl or phenyl substituted by chlorine or fluorine or trifluoromethyl and R^1 is hydrogen, alkyl or an acyl radical of a carboxylic acid.

3. A compound according to Claim 1, in which Y is hydrogen and X is hydrogen or a chlorine, bromine, nitro, trifluoromethyl or

methylsulphonyl substituent at the 7-position; R is hydrogen or lower alkyl, Ar is phenyl or chlorophenyl and R^1 is hydrogen, lower alkyl or an acyl radical of a lower carboxylic acid.

4. A compound according to Claim 1 in which Y is hydrogen and X is a chlorine atom at the 7-position; R is hydrogen or methyl; Ar is phenyl or a chlorophenyl group; and R^1 is hydrogen or an acyl radical of a lower carboxylic acid.

5. A compound according to any one of Claims 1 to 3, in which R is hydrogen or methyl.

6. A compound according to any one of Claims 1 to 3, in which R^1 is haloacyl or aminoacyl.

7. A 3 - aminoacyloxy - 5 - monocyclic - aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1.

8. A 3 - hydroxy - 7 - (chloro or bromo) - 1 - alkyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1.

9. A 3 - hydroxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1.

10. A 3 - alkanoyloxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1.

11. A 3 - alkanoyloxy - 7 - trifluoromethyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1.

12. 3 - Acetoxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

13. 3 - Acetoxy - 7 - chloro - 1 - methyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

14. 3 - Benzoyloxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

15. 3 - Ethoxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

16. 3 - Morpholinoacetoxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

17. 3 - Hydroxy - 7 - chloro - 1 - methyl - 5 - (*o* - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

18. A compound according to Claim 1 substantially as described herein and shown with reference to any one of Examples 1 to 8, 11, 13, 16 and 18 to 32.

19. A process for the production of a 3 - acyloxy- or 3 - hydroxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or acid addition salt thereof which comprises reacting an appropriate 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide with an organic carboxylic acylating agent as herein-before defined and, if desired, hydrolysing the 3 - acyloxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one obtained and, if desired, isolating the product as an acid addition salt.

20. A process for the production of a 3 - acyloxy- or 3 - hydroxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or acid addition salt thereof according to any one of Claims 1 to 14 and 16 to 18 which comprises reacting an appropriate 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide with an organic carboxylic acylating agent as hereinbefore defined and, if desired, hydrolysing the 3 - acyloxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one obtained and, if desired isolating the product as an acid addition salt.

21. A process for the production of a 3 - hydroxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or acid addition salt thereof according to any one of Claims 1 to 5, 8, 9, 17 and 18 which comprises hydrolysing a corresponding 3 - (acyloxy- or halo-) 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and, if desired, isolating the product as an acid addition salt.

22. A process according to Claim 19 or Claim 20, in which the acylating agent is a carboxylic acid halide or anhydride.

23. A process according to Claim 21, which comprises hydrolysing a 3 - alkanoyloxy - 1 - alkyl - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

24. A process according to Claim 21 which comprises hydrolysing a 3 - acyloxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

25. A process according to Claim 21 which comprises hydrolysing a 3 - alkanoyloxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

26. A process according to any one of Claims 19 to 22, 24 and 25 which includes the subsequent step of alkylation as hereinbefore defined in the presence of an alkali to introduce a 1 - hydrocarbon substituent.

27. A process according to Claim 22 which comprises treating a 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide with an anhydride or halide of an aliphatic carboxylic acid.

28. A process according to Claim 27 which comprises treating a 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide with acetic anhydride or acetyl chloride.

29. A process according to Claim 22 which comprises treating a 7 - trifluoromethyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one - 4 - oxide with an anhydride or halide of an aliphatic carboxylic acid.

30. A process according to any one of Claims

19 to 29 in which the hydrolysis of a 3 - acyloxy - 5 - monocyclic aryl - 1,3 - dihydro-2H - 1,4 - benzodiazepin - 2 - one is carried out in the presence of an alkali.

31. A process for the preparation of a 3 - amino - acyloxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or acid addition salt thereof according to any one of Claims 6, 7 and 16, in which a corresponding 3 - halo - acyloxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 6 is reacted with an amine and, if desired, the product is isolated as an acid addition salt.

32. A process for the preparation of a 3 - alkoxy - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to any one of Claims 1 to 3, 5 and 15, in which a corresponding 3 - halo - 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one is reacted with an alcohol and, if desired, the product is isolated as an acid addition salt.

33. A process for the production of a compound according to Claim 1 substantially as described herein and shown with reference to the Examples.

34. A compound according to any one of Claims 1 to 18 produced by a process according to any one of Claims 19 to 33 as appropriate or by an obvious chemical equivalent thereof.

35. A 3 - hydroxy - 7 - (chloro or bromo) - 1 - alkyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1 prepared by a process according to Claim 23 or by an obvious chemical equivalent thereof.

36. A 3 - hydroxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1 prepared by a process according to Claim 24 or Claim 25 or by an obvious chemical equivalent thereof.

37. A 3-alkanoyloxy - 7 - (chloro or bromo) - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1 prepared by a process according to Claim 27 or by an obvious chemical equivalent thereof.

38. 3 - Acetoxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one prepared by a process according to Claim 28 or by an obvious chemical equivalent thereof.

39. A 3 - alkanoyloxy - 7 - trifluoromethyl - 5 - phenyl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one according to Claim 1 prepared by a process according to Claim 29 or by an obvious chemical equivalent thereof.

40. 3 - Hydroxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - 1, 4- benzodiazepin - 2 - one produced by a process according to any one of Claims 19 to 22, 24, 25, 27, 28, 30 and 33.

41. A process for the manufacture of pharmaceutical preparations having sedative, anti-convulsant or muscle relaxant properties in which a compound according to any one of Claims 1 to 18 and 34 to 40 is put into a medicinally acceptable form.

42. A pharmaceutical preparation having sedative, anti-convulsant or muscle relaxant properties containing a compound according to any one of Claims 1 to 18 and 34 to 40 and a pharmaceutically acceptable carrier.

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PATENTS ACT, 1949

SPECIFICATION NO. 1,022,642

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the 21st day of June, 1966 this Specification has been amended under Section 29 in the following manner:-

Page 1, lines 36 and 37, *delete* "for instance alkyl or alkenyl, particularly" *insert* "such as"

Page 1, lines 52 and 53, page 5, lines 99 and 100, *for* "alkyl or alkenyl" *read* "lower alkyl or lower alkenyl"

Page 1, line 55, page 5, line 102, *before* "alkyl" *insert* "lower"

Page 4, line 58, *delete* "5-phenyl"

Page 6, lines 22 and 99, page 7, line 34, *before* "alkyl" *insert* "lower-"

THE PATENT OFFICE,
23rd September, 1966

D 75715/3