

PATENT SPECIFICATION

(11)

1351023

1351023

- (21) Application No. 32545/71 (22) Filed 12 July 1971
 (23) Complete Specification filed 11 July 1972
 (44) Complete Specification published 24 April 1974
 (51) International Classification C07D 41/00 A61K 27/00
 (52) Index at acceptance

C2C 1235 147X 1736 200 213 220 222 226 227 22X
 22Y 247 250 251 253 25Y 304 307 30Y 313 314
 31Y 323 326 32Y 337 338 342 34Y 351 352 353 360 361 364
 365 366 368 369 36Y 386 387 388 40X 40Y 47X
 48X 584 594 623 624 625 628 62X 62Y 645 650
 652 656 65X 662 672 678 73Y 760 761 762 790
 79Y KS LK NS TQ TT UB



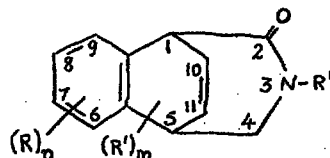
(72) Inventor RENE DENAYER

(54) BENZA-2-EPINONES

(71) We, UCB, of 4 Chaussée de Charleroi, Saint-Gilles-lez-Bruxelles, Belgium, a Body Corporate organised under the laws of Belgium, 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 benzazepinones and with the preparation thereof.

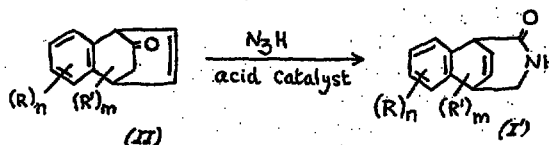
The new benzazepinones according to the present invention are 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-ones of the general formula:



(I)

wherein R and R', which may be the same or different, are hydrogen or halogen atoms or hydroxy groups or C₁—C₄-alkyl or C₁—C₄-alkoxy radicals, R occupying at least one of the positions 6, 7, 8 and 9 and R' occupying at least one of positions 1, 5, 10 and 11, R'' is a hydrogen atom or an alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, dialkylaminoalkyl or carbalkoxy radical, each alkyl group of which contains up to 5 carbon atoms, a C₂—C₄-alkenyl or aralkyl radical or a carbamoyl group having the general formula —CaONHR''', R''' being a hydrogen atom or a C₁—C₄-alkyl, C₂—C₄-alkenyl, aralkyl or aryl radical, and n and m, which may be the same or different, are 1 or 2; and the addition salts thereof with pharmaceutically acceptable acids.

a) In order to prepare compounds of general formula (I) in which R'' is a hydrogen atom, an (R)_n(R')_m-substituted 1,4-dihydro-1,4-ethano-naphthalen-9-one of the general formula (II) is reacted with hydrazoic acid in the presence of an acid catalyst according to the following equation:



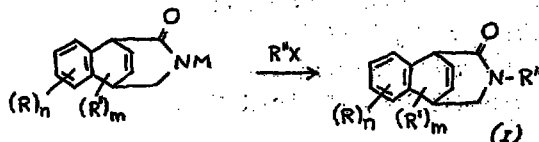
wherein R, R', n and m have the same meanings as above.

b) In order to prepare compounds of general formula (I) in which R'' is alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, dialkylaminoalkyl, carbalkoxy, alkenyl or aralkyl radical, a metallic derivative of a 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one of general formula (I) in which R'' is a hydrogen atom (e.g. prepared as in a) above)

[Price 25p]

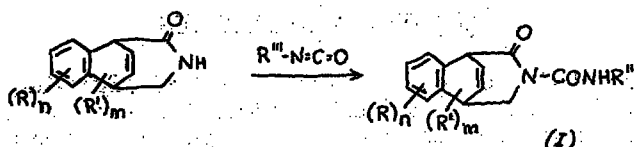
Price 33p

is reacted with a compound of general formula $R''X$ according to the following equation:



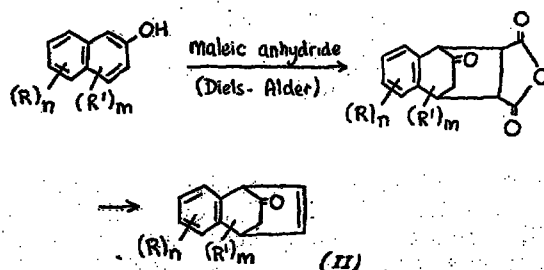
wherein M is an alkali metal or an alkaline earth metal, X is a halogen atom or a *p*-toluenesulphonyloxy radical, R'' is an alkyl, hydroxyalkyl, dialkylaminoalkyl, carbalkoxy, alkenyl or aralkyl radical in the reactant or additionally hydroxyalkoxyalkyl in the product and R , R' , n and m have the same meanings as above.

c) In order to prepare compounds of formula (I) in which R'' is a carbamoyl group having the general formula $-CONHR'''$, a 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one of general formula (I) in which R'' is a hydrogen atom (e.g. prepared as in a) above) is reacted with an isocyanate of general formula $R'''-NCO$ according to the following equation:



wherein R , R' , R''' , n and m have the same meanings as above.

When the starting compounds, i.e. the 1,4-dihydro-1,4-ethanonaphthalen-9-ones of general formula (II) , are not known from the literature, they can be prepared from the corresponding $(R)_n$, $(R')_m$ -substituted β -naphthols and maleic anhydride to form 9-oxo-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-dicarboxylic acid anhydrides, which are thereafter converted into compounds of general formula (II) according to the following equation:



wherein R , R' , n and m have the same meanings as above.

The acid-addition salts of the new compounds (I) can be prepared in the usual way by neutralising the free bases with pharmaceutically acceptable inorganic or organic acids.

The following Examples are given for the purpose of illustrating the present invention:

Preparation of Starting Naphthalenones.

A. Preparation of 7-chloro-9-oxo-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3-dicarboxylic acid anhydride

A mixture of 44.7 g. (0.25 M) 6-chloro-2-naphthol and 122.5 g. (1.25 M) maleic anhydride is heated for 30 minutes at 180°C ., with vigorous stirring. After cooling, excess maleic anhydride is distilled off under reduced pressure.

The residue is extracted with 500 ml. benzene in the presence of animal charcoal. After filtration and evaporation of the solvent, the product is recrystallised from a benzene-ether mixture. 48.4 g. of purified 7-chloro-9-oxo-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3-dicarboxylic acid anhydride is obtained with a yield of 70%; m.p. $165-190^\circ\text{C}$. (mixture of endo/exo forms).

Analysis for $C_{14}H_9ClO_4$ (M.W. 276.5):

calc.:	C 60.7%;	H 3.3%;	Cl 12.8%
found:	60.5%;	3.1%;	12.6%

The following compounds were also prepared by this method:

- 4 - methyl - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 180—183°C.; yield 65%.
5 7 - bromo - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 220—226°C.; yield 56% (known compound).
7 - ethyl - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
10 M.p. 155—185°C. (endo-exo mixture); yield 75%.
7 - methyl - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 190—194°C.; yield 22%.
15 7 - methoxy - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 242—245°C.; yield 41%.
6,7 - dimethyl - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 255—257°C.; yield 8%.
20 6 - methoxy - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 272—273°C.
6 - hydroxy - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
25 M.p. 295°C. (known compound).
7 - hydroxy - 9 - oxo - 1,2,3,4 - tetrahydro - 1,4 - ethano - naphthalene - 2,3 - dicarboxylic acid anhydride.
M.p. 277—278°C. (known compound).

B. Preparation of 1,4-dihydro-1,4-ethano-naphthalen-9-one.

- 150 ml. triethylamine is added to a solution of 150 g. (0.62 M) 9-oxo-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2,3-dicarboxylic acid anhydride in 2.2 litres of a 90:10 pyridine-water mixture. The mixture is electrolysed, while stirring (1.3 amperes, platinum electrodes), for 76 hours, the temperature of the electrolysis cell being maintained at about 5°C. by means of a cryostat. At the end of the reaction, the mixture is poured into 8 litres benzene. The benzene phase is decanted, washed with water, filtered, dried and evaporated under reduced pressure. The residue is purified by distillation (b.p. 120—130°C./1 mm.Hg.) and then, by recrystallisation, from a 1:3 ether-hexane mixture. 37.3 g. of the desired product is obtained with a 35% yield; m.p. 56—57°C. (according to K. Kitahonoki and Y. Takano, Tetrahedron Letters, 1963, 1597, the m.p. is 56.5—58°C.).
35
40

This compound can also be prepared by the following method:

- 25.5 g. (0.04 mole) di-(triphenyl-phosphine)-nickel dicarbonyl are added to a solution of 9.6 g. (0.04 mole) 9-oxo-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2,3-dicarboxylic acid anhydride in 150 ml. diglyme and the mixture heated under reflux for 3 hours. The solvent is then evaporated under reduced pressure and the residue treated with water and thereafter with a 1:1 chloroform-ether mixture. The organic phase is separated, dried over anhydrous sodium sulphate and then evaporated. The residue is purified by chromatography on a silica column (eluent: toluene). 1.1 g. of the desired product is thus obtained with a yield of 15%.
45
50

The following naphthalenones were also prepared by the electrolysis method.

- 7-bromo-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 125—130°C.; yield 32%.
7-chloro-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 124—126°C.; yield 26%.
55

Analysis for $C_{12}H_9ClO$ (M.W. 204.5):

calc.:	C 70.6%;	H 4.4%
found:	71.1%;	4.6%

7-methyl-1,4-dihydro-1,4-ethano-naphthalen-9-one.

M.p. 99—100°C.; yield 21%.

- 60 Analysis for $C_{13}H_{11}O$ (M.W. 184):

calc.:	C 84.8%;	H 6.5%
found:	83.7%;	6.3%

7-ethyl-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 48—49°C.; yield 28%.

Analysis for $C_{14}H_{14}O$ (M.W. 198):

5	calc.:	C 85.0%;	H 7.1%	5
	found:	84.3%;	7.3%	

4-methyl-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 89—90°C.; yield 28%.

Analysis for $C_{13}H_{12}O$ (M.W. 184):

10	calc.:	C 84.8%;	H 6.5%	10
	found:	83.1%;	6.7%	

6,7-dimethyl-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 70—71°C., yield 10%.

Analysis for $C_{14}H_{14}O$ (M.W. 198):

15	calc.:	84.9%;	H 7.1%	15
	found:	83.9%;	7.2%	

7-methoxy-1,4-dihydro-1,4-ethano-naphthalen-9-one.
6-methoxy-1,4-dihydro-1,4-ethano-naphthalen-9-one.
M.p. 63—64°C.; yield 70%.

Analysis for $C_{13}H_{12}O_2$ (M.W. 200):

20	calc.:	C 78.1%;	H 6.0%	20
	found:	78.8%;	6.2%	

Preparation of Benzazepinones according to the present Invention.

Example 1

Preparation of 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

25 47 g. (0.276 mole) 1,4-dihydro-1,4-ethano-naphthalen-9-one are added to a mixture of 200 ml. chloroform, 75 ml. concentrated sulphuric acid and 12 g. phosphorus pentoxide. This mixture is cooled to 0°C. and 270 ml. of a 1N solution of hydrazoic acid in chloroform (containing 11.6 g. HN_3) is added dropwise, while stirring.

30 The reaction medium is allowed to warm up to 15°C. and is then poured on to ice. The mixture is neutralised by adding aqueous sodium hydroxide and then filtered over "Hyflocel". The filtrate obtained is composed of a chloroform phase and of an aqueous phase. The chloroform phase is separated, the aqueous phase is extracted with 200 ml. chloroform and this extract is added to the chloroform phase, which is thereupon washed with water and then dried over anhydrous sodium sulphate.

35 The chloroform solution is evaporated to dryness and the residue taken up in diethyl ether. A white crystalline precipitate is formed, which is separated by filtration and recrystallised from ethanol, to give 12.6 g. 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one; m.p. 209°C.; yield 23%.

Analysis for $C_{12}H_{11}NO$ (M.W. 185):

40	calc.:	C 77.8%;	H 5.9%;	N 7.6%	40
	found:	77.9%;	6.1%;	7.4%	

By evaporation of the ethereal filtrate to dryness and distillation of the residue at 110—115°C./0.001 mm.Hg., there are obtained 22 g. 1-naphthalene-acetonitrile.

45 The 1,4-dihydro-1,4-ethano-naphthalen-9-one used as starting product is a known compound (cf. H. E. Zimmermann *et al.*, J. Am. Chem. Soc., 90, 6105/1968).

Example 2

Preparation of 7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

50 149 ml. hydrazoic acid in chloroform (0.97 M) is added dropwise, with vigorous stirring, to a mixture of 29 g. (0.14 mole) 7-chloro-1,4-dihydro-1,4-ethano-naphthalen-9-one, 150 ml. chloroform and 70 ml. concentrated sulphuric acid and cooled to -15°C. The reaction is continued for 90 minutes at -10°C. The reaction mixture is

then poured on to a mixture of 500 g. ice, 200 g. sodium carbonate and 500 ml. chloroform, while maintaining the temperature at or below 0°C. The mixture is filtered over "Hyflocel" and the organic phase is separated. The aqueous phase is extracted three times with 200 ml. portions of chloroform. The combined organic phases are washed with water and dried over anhydrous sodium sulphate. The solvent is evaporated and the solid residue obtained is recrystallised from a 1:2 chloroform-hexane mixture. 7.9 g. of purified 7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one are obtained with a 25% yield; m.p. 223—224°C.

5

5

Analysis for $C_{12}H_{10}ClNO$ (M.W. 219.5):

10

calc.: C 64.6%; H 4.5%; N 6.0%
found: 65.4%; 4.4%; 6.1%

10

The following N-unsubstituted benzazepinones were also prepared by the method of Example 1 or 2:

7-bromo-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

15

15

M.p. 245—247°C.; yield 10%.

Analysis for $C_{12}H_{10}BrNO$ (M.W. 264):

calc.: C 54.6%; H 4.1%; N 5.3%
found: 54.9%; 3.9%; 5.4%

7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

20

20

M.p. 170—171°C.; yield 18%.

Analysis for $C_{14}H_{15}NO$ (M.W. 213):

calc.: C 78.9%; H 7.0%; N 6.6%
found: 78.7%; 7.1%; 6.6%

7-methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

25

25

M.p. 221—223°C.; yield 20%.

Analysis for $C_{13}H_{13}NO$ (M.W. 199):

calc.: C 78.4%; H 6.5%; N 7.0%
found: 78.4%; 6.6%; 7.1%

1-methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

30

30

7,8-dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 249—251°C.; yield 21%.

Analysis for $C_{14}H_{15}NO$ (M.W. 213):

calc.: C 78.8%; H 7.0%; N 6.5%
found: 78.6%; 7.0%; 6.5%

7-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

35

35

8-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 205—206°C.; yield 14%.

Analysis for $C_{13}H_{13}NO_2$ (M.W. 215):

calc.: C 72.5%; H 6.1%; N 6.5%
found: 72.4%; 6.1%; 6.5%

7-hydroxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

40

40

8-hydroxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

8-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

Example 3

Preparation of 3-methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

45

45

18 g. (0.097 mole) 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one (obtained as in Example 1) are dissolved in 180 ml. anhydrous dimethylformamide. 3.89 g. (0.162 mole) sodium hydride is added and the mixture is agitated for a quarter of an hour at ambient temperature. 50 g. (0.35 mole) methyl iodide are introduced and the resulting mixture is agitated for about 20 minutes. The reaction mixture is poured on to ice and

50

50

extracted with benzene. The benzene extract is washed with water, dried and evaporated to dryness. The residue is dissolved in acetone and hexane is added until crystallisation commences; 12 g. 3-methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one are obtained; m.p. 140—141°C.; yield 62%.

5 Analysis for $C_{16}H_{15}NO$ (M.W. 199):

calc.: C 78.4%; H 6.6%; N 7.0%
found: 78.2%; 6.6%; 7.1%

5

Example 4

10 Preparation of 3-(2-hydroxyethyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one and 3-[2-(2-hydroxyethoxy)-ethyl]-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

15 1.16 g. (0.004 mole) sodium hydride is added, with vigorous stirring, to a suspension of 4.5 g. (0.024 mole) 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one in 50 ml. xylene. This mixture is heated under reflux for 5 minutes and then cooled to 10°C. 1.96 g. (0.024 mole) ethylene chlorohydrin, dissolved in 10 ml. xylene, is added dropwise. The mixture is then heated under reflux for 3 hours and poured on to ice. The organic phase is decanted, dried and evaporated to dryness under reduced pressure.

The residue is chromatographed on a silica column. Two fractions are isolated:

- 20 1) 1.75 g. of starting material (eluent: chloroform)
2) 1.2 g. of a 1:2 mixture of:
a) 3-[2-(2-hydroxyethoxy)-ethyl]-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 135—136°C.

25 Analysis for $C_{16}H_{15}NO_2$ (M.W. 273):

calc.: C 70.2%; H 7.0%; N 5.1%
found: 69.6%; 6.9%; 4.7%

25

Mass spectrum m/e: 273, 255, 242; and

b) 3-(2-hydroxyethyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 100—101°C.

30 Analysis for $C_{14}H_{15}NO_2$ (M.W. 229):

calc.: C 73.2%; H 6.6%; N 6.1%
found: 73.3%; 6.6%; 6.0%

30

Mass spectrum m/e: 229, 211, 198, 185 eluent: 1:1 mixture of chloroform-ethyl acetate.

35 The following N-substituted benzazepinones were prepared by the method of Example 3 or 4:

3-methyl-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-1-one.
M.p. 145—146°C.; yield 74%.

40 Analysis for $C_{13}H_{12}ClNO$ (M.W. 233.7):

calc.: C 66.8%; H 5.2%; N 5.9%
found: 66.4%; 4.9%; 6.1%

40

3-methyl-7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
B.p. 149—155°C./0.001 mm.Hg.; yield 69%.

45 Analysis for $C_{15}H_{17}NO$ (M.W. 227):

calc.: H 7.5%; N 6.2%
found: 7.4%; 5.5%

45

3,7-dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 81—84°C.; yield 31%.

50 Analysis for $C_{14}H_{15}NO$ (M.W. 213):

calc.: C 78.8%; H 7.0%; N 6.6%
found: 78.3%; 6.9%; 6.9%

50

3-isopropyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
3-allyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
B.p. 130—132°C./0.001 mm.Hg., yield 71%.

5 Analysis for $C_{15}H_{15}NO$ (M.W. 225):
calc.: C 80.0%; H 6.7%; N 6.2%
found: 79.7%; 6.6%; 6.5% 5

3-benzyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
3-carbethoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 99—100°C.; yield 73%.

10 Analysis for $C_{15}H_{15}NO_2$ (M.W. 257):
calc.: C 70.0%; H 5.9%; N 5.5%
found: 70.7%; 5.1%; 5.2% 10

3-(2-diethylaminoethyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
1,3-dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
15 3-methyl-7-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
3-methyl-8-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 137—138°C.; yield 50%. 15

Analysis for $C_{14}H_{15}NO_2$ (M.W. 229):
calc.: C 73.5%; H 6.6%; N 6.1%
found: 72.9%; 6.6%; 6.2% 20

3,7,8-trimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 95—97°C.; yield 38%.

Analysis for $C_{15}H_{17}NO$ (M.W. 227):
calc.: C 79.3%; H 7.5%; N 6.2%
found: 78.7%; 7.3%; 6.2% 25

3-(*p*-methoxybenzyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
B.p. 200—205°C./0.001 mm.Hg., yield 76%.

Analysis for $C_{20}H_{19}NO_2$ (M.W. 305):
calc.: C 78.7%; H 6.3%; N 4.6%
found: 77.9%; 6.3%; 4.4% 30

Example 5

Preparation of 3-(*N*-methylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

35 A solution of 12 g. (0.21 mole) methyl isocyanate in 20 ml. xylene is added dropwise, with vigorous stirring, to a suspension of 12 g. (0.065 mole) 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one in 250 ml. xylene, heated to 100°C. When the addition of the isocyanate is completed, the mixture is heated under reflux for 2 hours and then evaporated to dryness under reduced pressure. The residue is dissolved in diethyl ether in the presence of animal charcoal and the solution is then filtered and evaporated to dryness. The solid obtained is recrystallised from diisopropyl ether. 13.2 g. 3-(*N*-methylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one are obtained in the form of a white solid; m.p. 119—121°C.; yield 83%. 40

Analysis for $C_{14}H_{14}N_2O_2$ (M.W. 242):
calc.: C 69.4%; H 5.8%; N 11.6%
found: 69.7%; 5.9%; 11.5% 45

The following *N*-carbamoyl-benzazepinones were also prepared by the method of Example 5:

3-(*N*-allylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 87—90°C.; yield 90%.

50 Analysis for $C_{16}H_{16}H_2O_2$ (M.W. 304):
calc.: C 71.6%; H 5.9%; N 10.5%
found: 70.9%; 5.6%; 10.4% 50

3-(N-phenylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-3-one.
M.p. 176—177°C.; yield 94%.

Analysis for $C_{19}H_{18}N_2O_2$ (M.W. 304):

calc.: C 75.0%; H 5.3%; N 9.2%
found: 74.2%; 5.3%; 8.8%

3-(N-ethylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
M.p. 83.5—86°C.; yield 35%.

Analysis for $C_{18}H_{20}N_2O_2$ (M.W. 256):

calc.: C 70.3%; H 6.3%; N 10.9%
found: 71.0%; 6.2%; 10.9%

3-(N-methylcarbamoyl)-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 156—158°C.; yield 69%.

Analysis for $C_{14}H_{13}ClN_2O_2$ (M.W. 276.5):

calc.: C 60.8%; H 4.7%; N 10.1%
found: 61.9%; 4.8%; 10.1%

3-(N-allylcarbamoyl)-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 116—118°C.; yield 67%.

Analysis for $C_{18}H_{17}ClN_2O_2$ (M.W. 302.5):

calc.: C 63.4%; H 4.9%; N 9.3%
found: 64.6%; 4.8%; 9.3%

3-(N-phenylcarbamoyl)-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 147—149°C.; yield 62%.

Analysis for $C_{19}H_{15}ClN_2O_2$ (M.W. 338.5):

calc.: C 67.3%; H 4.4%; N 8.3%
found: 66.8%; 4.5%; 8.5%

3-(N-methylcarbamoyl)-7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

B.p. 195—200°C./0.001 mm.Hg.; yield 79%.

Analysis for $C_{18}H_{18}N_2O_2$ (M.W. 270):

calc.: C 71.1%; H 6.7%; N 10.4%
found: 70.5%; 6.7%; 9.7%

3-(N-methylcarbamoyl)-7,8-dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

M.p. 151—153°C.; yield 75%.

Analysis for $C_{20}H_{20}N_2O_2$ (M.W. 270):

calc.: C 71.1%; H 6.7%; N 10.4%
found: 71.2%; 6.5%; 10.3%

Due to their activity on the central nervous system, the new benzazepinones of the present invention are useful as pharmaceuticals. They are, in particular, useful as anxiolytics and as stimulants of mental activity, as shown by the following pharmacological tests.

For these tests, the following compounds were used:

Compound

(A) 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one

(B) 3-methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one

(C) 3-(N-methylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one

- (D) 3-methyl-7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one
 (E) 3-methyl-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one
 (F) 3,7-dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one 23
 (G) 3 - (N - methylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one 5
 (H) 3 - (N - phenylcarbamoyl) - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H - 3 - benzazepin-2-one
 (I) 3 - (N - allylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one
 (J) 3 - (N - phenylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one. 10

Initial performance test in rats.

(unpublished original method of the Applicants):

- When preparing the rats for a conditioned reflex, the animal is taught an avoidance reaction by running away in response to an electric shock lasting 3 seconds, repeated several times per minute over a period of a few minutes. The innate running away reaction takes place before the end of the shock 15 to 20 times out of 20 tests. 15

- A few hours later, the training is repeated and a reduction in the avoidance performances is observed. This is interpreted as an expression of a conflicting situation which diminishes the performance during the second time round. Anxiolytic substances oppose this effect. 20

- A peritoneally administered dose of 1.2 mg./kg. body weight of product A already improves the performance.

- For the other compounds, the minimum dose, expressed in mg./kg., which improves the performance is: 25

Compound	(B)	11	
	(C)	3.1	
	(D)	7.1	
	(E)	2.3	
	(F)	2.1	30
	(G)	2.8	

Spinal fixation.

(T. J. Chamberlain *et al.*, J. Neuro-Physiol. 26, (4) 662—673/1963).

- Wister rats were anaesthetised with nembutal and a part of the interior lobe of the cerebellum was removed. Upon awakening, the animals had a postural asymmetry of the hind paws (hypertonic ipsilateral flexion and hypotonic contralateral extension). 35

- When the spinal medulla is sectioned within the 35 minutes which follow the appearance of the asymmetry, then all the animals lose this asymmetry, i.e. there is not a sufficient lapse of time for fixation.

- On the other hand, if there is a delay of 45 minutes or more, then 95% of the animals show a persistence of the asymmetry. The control animals, therefore, never show a persistence of the asymmetry with a delay of 35 minutes. 40

- The compounds which induce a persistence of this same delay diminish, therefore, the spinal fixation time.

- The intraperitoneal administration of the compounds according to the present invention before the cerebellar lesion brings about a diminution of the time necessary for the fixation, since the treated animals show a persistence of the asymmetry, in contradistinction to the control animals. 45

- For the following compounds of the present invention, the minimum active dose, expressed in mg./kg., is: 50

Compound	(A)	18.5	
	(B)	19.9	
	(C)	24.2	
	(H)	30.4	
	(I)	30.2	55
	(J)	33.8	

The benzazepinones of the present invention have a low toxicity. In the case of

intraperitoneal administration in rats, the LD 50, in mg./kg. animal body weight, is as follows:

	Compound (A)	550	
	(B)	>1000	
5	(C)	>1000	5
	(H)	>1000	

The compounds of the present invention consequently have potentials in the field of activity on the central nervous system and, more particularly, in the neuropsychiatric sphere.

The compositions according to the present invention which can be used for oral administration may be solid or liquid and may be, for example, in the form of tablets, pills, dragees, gelatine capsules, solutions or syrups. Likewise, the compositions for use by parenteral administration are the known pharmaceutical forms for this type of administration, for example solutions, suspensions or aqueous or oily emulsions. For administration by the rectal route, the compositions of the present invention generally take the form of suppositories.

The pharmaceutical forms, such as solutions for injection, suspensions for injection, tablets, drops and suppositories, are prepared by the usual methods. The new compounds according to the present invention are mixed with a solid or liquid diluent or carrier, which is non-toxic and pharmaceutically acceptable, and optionally with a dispersing agent, a disintegrating agent, a lubricant or a stabiliser. It is to be understood that solutions, emulsions and dispersions intended for injection must be sterile. If necessary and/or desired, preservatives, sweeteners and colouring materials may be added.

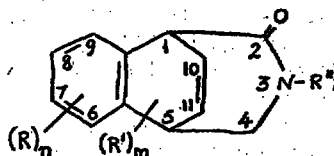
Likewise, the solid or liquid pharmaceutical vehicles used in these compositions are well known in the art. Solid pharmaceutical excipients for the preparation of tablets or capsules include, for example, starch, talc, calcium carbonate, lactose, sucrose and magnesium stearate.

The percentage of active product in the pharmaceutical compositions may vary within very wide limits, according to the conditions of use, particularly according to the frequency of administration.

Human dosage is of the order of 3×50 mg./day but may possibly vary from 20 mg. to 1 g. per day.

WHAT WE CLAIM IS:—

1. 1,3,4,5-Tetrahydro-1,5-etheno-2H-3-benzazepin-2-one derivatives of the general formula:



wherein R and R', which may be the same or different, are hydrogen or halogen atoms, hydroxyl groups or C_1-C_4 -alkyl or C_1-C_4 -alkoxy radicals, R occupying at least one of positions 6, 7, 8 and 9 and R' occupying at least one of positions 1, 5, 10 and 11, R'' is a hydrogen atom or an alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, dialkylamino-alkyl or carbalkoxy radical, each alkyl group of which contains up to 5 carbon atoms, a C_2-C_4 alkenyl or aralkyl radical or a carbamoyl group of the general formula $-CONHR'''$, R''' being a hydrogen atom or a C_1-C_4 -alkyl, C_2-C_4 -alkenyl, aralkyl or aryl radical, and n and m, which may be the same or different, are 1 or 2; and the addition salts thereof with pharmaceutically acceptable acids.

2. 1,3,4,5-Tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

3. 3-Methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

4. 3-(N-methylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

5. 3-Methyl-7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

6. 3-Methyl-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

7. 3,7-Dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

8. 7-Chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

9. 7-Bromo-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.

10. 7-Ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.



intraperitoneal administration in rats, the LD 50, in mg./kg. animal body weight, is as follows:

	Compound (A)	550	
5	(B)	>1000	5
	(C)	>1000	
	(H)	>1000	

The compounds of the present invention consequently have potentials in the field of activity on the central nervous system and, more particularly, in the neuropsychiatric sphere.

The compositions according to the present invention which can be used for oral administration may be solid or liquid and may be, for example, in the form of tablets, pills, dragees, gelatine capsules, solutions or syrups. Likewise, the compositions for use by parenteral administration are the known pharmaceutical forms for this type of administration, for example solutions, suspensions or aqueous or oily emulsions. For administration by the rectal route, the compositions of the present invention generally take the form of suppositories.

The pharmaceutical forms, such as solutions for injection, suspensions for injection, tablets, drops and suppositories, are prepared by the usual methods. The new compounds according to the present invention are mixed with a solid or liquid diluent or carrier, which is non-toxic and pharmaceutically acceptable, and optionally with a dispersing agent, a disintegrating agent, a lubricant or a stabiliser. It is to be understood that solutions, emulsions and dispersions intended for injection must be sterile. If necessary and/or desired, preservatives, sweeteners and colouring materials may be added.

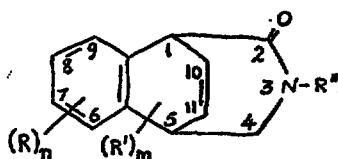
Likewise, the solid or liquid pharmaceutical vehicles used in these compositions are well known in the art. Solid pharmaceutical excipients for the preparation of tablets or capsules include, for example, starch, talc, calcium carbonate, lactose, sucrose and magnesium stearate.

The percentage of active product in the pharmaceutical compositions may vary within very wide limits, according to the conditions of use, particularly according to the frequency of administration.

Human dosage is of the order of 3×50 mg./day but may possibly vary from 20 mg. to 1 g. per day.

WHAT WE CLAIM IS:—

1. 1,3,4,5-Tetrahydro-1,5-etheno-2H-3-benzazepin-2-one derivatives of the general formula:

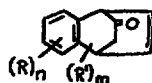


wherein R and R', which may be the same or different, are hydrogen or halogen atoms, hydroxyl groups or C_1-C_4 -alkyl or C_1-C_4 -alkoxy radicals, R occupying at least one of positions 6, 7, 8 and 9 and R' occupying at least one of positions 1, 5, 10 and 11, R'' is a hydrogen atom or an alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, dialkylaminoalkyl or carbalkoxy radical, each alkyl group of which contains up to 5 carbon atoms, a C_2-C_4 alkenyl or aralkyl radical or a carbamoyl group of the general formula $-CONHR'''$, R''' being a hydrogen atom or a C_1-C_4 -alkyl, C_2-C_4 -alkenyl, aralkyl or aryl radical, and n and m, which may be the same or different, are 1 or 2; and the addition salts thereof with pharmaceutically acceptable acids.

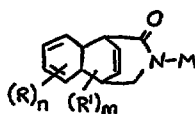
2. 1,3,4,5-Tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
3. 3-Methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
4. 3-(N-methylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
- 50 5. 3-Methyl-7-ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
6. 3-Methyl-7-chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
7. 3,7-Dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
8. 7-Chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
9. 7-Bromo-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
- 55 10. 7-Ethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.



11. 7-Methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 12. 1-Methyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 13. 7,8-Dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 14. 7-Methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 15. 8-Methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 16. 7-Hydroxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 17. 8-Hydroxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 18. 8-Chloro-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 19. 3-(2-Hydroxyethyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 20. 3-Isopropyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 21. 3-Allyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 22. 3-Benzyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 23. 3-Carbethoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 24. 3 - (2 - Diethylaminoethyl) - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H - 3 - benzazepin-2-one.
 25. 1,3-Dimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 26. 3-Methyl-7-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 27. 3-Methyl-8-methoxy-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 28. 3,7,8-Trimethyl-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 29. 3-(*p*-Methoxybenzyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 30. 3-(*N*-Allylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 31. 3-(*N*-Ethylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 32. 3 - (N - Methylcarbamoyl) - 7 - ethyl - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one.
 33. 3 - (N - Methylcarbamoyl) - 7,8 - dimethyl - 1,3,4,5 - tetrahydro - 1,5 - etheno-2H-3-benzazepin-2-one.
 34. 3 - (N - Methylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one.
 35. 3-(*N*-Phenylcarbamoyl)-1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one.
 36. 3 - (N - Allylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one.
 37. 3 - (N - Phenylcarbamoyl) - 7 - chloro - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one.
 38. 3 - [2 - (2 - Hydroxyethoxy) - ethyl] - 1,3,4,5 - tetrahydro - 1,5 - etheno - 2H-3-benzazepin-2-one.
 39. A process for the preparation of compounds of the general formula given in claim 1, in which R'' is a hydrogen atom, wherein a 1,4-dihydro-1,4-ethano-naphthalen-9-one of the general formula:



- in which R, R', *n* and *m* have the same meanings as in claim 1, is reacted with hydrazoic acid, in the presence of an acid catalyst.
 40. A process for the preparation of compounds of the general formula given in claim 1, in which R'' is an alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, dialkylaminoalkyl, carbalkoxy, alkenyl or aralkyl radical, wherein a metallic derivative of a 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one having the formula



- in which M is an alkali or alkaline earth metal and R, R', *n* and *m* have the same meanings as in claim 1, is reacted with a compound of the general formula R''X, in which X is a halogen atom or a *p*-toluene-sulphonyloxy radical and R'' is an alkyl, hydroxyalkyl, dialkylaminoalkyl, carbalkoxy, alkenyl or aralkyl radical.
 41. A process for the preparation of compounds of the general formula given in claim 1, in which R'' is a carbamoyl group of the general formula —CONHR''', R'''



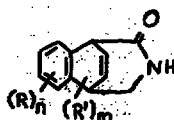
12

26

1,351,023

12

having the same meaning as in claim 1, wherein a 1,3,4,5-tetrahydro-1,5-etheno-2H-3-benzazepin-2-one of the general formula:



in which R, R' n and m have the same meanings as in claim 1, is reacted with an isocyanate of the general formula $R'''-NCO$, in which R''' has the same meaning as in claim 1.

42. A process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

43. Compounds according to claim 1, whenever prepared by the process according to any of claims 39—42.

44. Pharmaceutical compositions comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutically acceptable diluent or carrier.

VENNER, SHIPLEY & CO.,
Chartered Patent Agents,
Rugby Chambers,
2, Rugby Street,
London, WC1N 3QU.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.