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PATENT SPECIFICATION

NO DRAWINGS

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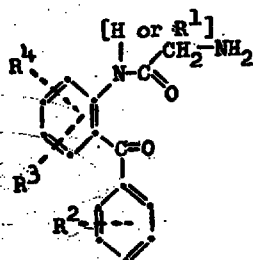
COMPLETE SPECIFICATION

Manufacture of 2-Glycylamido-Benzophenones and Cyclisation Derivatives thereof

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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 a process for the manufacture of 2-glycylamido-benzophenones and cyclisation derivatives thereof; more particularly, it is concerned with a process for the manufacture of said benzophenones and derivatives from novel benzyloxycarbonyl compounds, with the latter *per se* and with the preparation thereof.

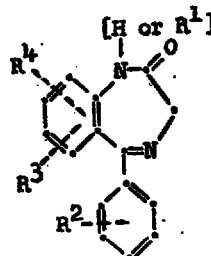
The 2-glycylamido-benzophenones aforesaid may be formulated thus



wherein R¹ stands for a lower-alkyl group, R², R³ and R⁴ are each a lower alkyl, alkoxy, alkanoyl-amino, alkyl-thio, alkyl-sulphinyl or alkyl-sulphonyl group or a halogen atom or the trifluoro-methyl, nitro, amino, mercapto, cyano or hydroxy group and the bonds shown as broken lines denote that the substituents R², R³ and R⁴ attached thereby are optional. They have been found to be valuable therapeutic agents having anticonvulsant, muscle relaxant, sedative and tranquilizer activity.

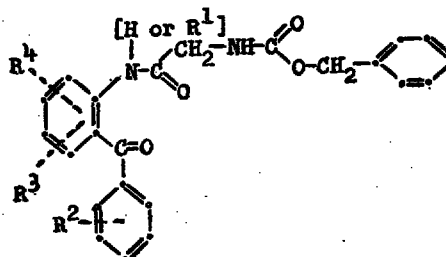
[Price 4s. 6d.]

They can be administered internally, orally and parenterally for example, and can be administered in any conventional pharmaceutical form; for example, as solutions, suspensions, capsules, tablets and suppositories. They are also valuable as intermediates in the manufacture of cyclization derivatives of the general formula



(wherein the symbols R¹, R², R³ and R⁴ and the broken lines have the significance already given) which, in turn, are medicinally useful as anticonvulsants, muscle relaxants, and sedatives and are also useful as intermediates.

The 2-glycylamido-benzophenones and cyclisation derivatives formulated earlier are manufactured in accordance with the invention by reacting a benzyloxycarbonyl compound of the general formula



(wherein the symbols R^1 , R^2 , R^3 and R^4 and the broken lines have the significance given earlier) with a hydrohalic acid in the presence of acetic acid and, where the cyclisation derivative is required, cyclising the resulting 2 - glycyllamido - benzophenone by alkalisng to a pH of 7 or more.

The reaction step, which results in the selective fission of the amido group furthest from the nucleus, yields a 2 - glycyllamido - benzophenone of the general formula first written. It is preferred to use hydrobromic acid as the hydrohalic acid but hydrochloric acid etc. can also be used. The hydrolysis can be carried out in aqueous or anhydrous media and at ordinary, elevated or lowered temperatures.

The cyclisation step, which results in the formation of an azepine ring, yields a 5-phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) of the general formula second written. The cyclisation proceeds readily at ordinary temperatures but is accelerated by heat. Either strong or weak bases can be used for the alkalisation to the necessary pH value. For example, ammonia, alkali-metal hydroxides, alkaline - earth - metal hydroxides (e.g. calcium hydroxide) and the like can be used. The 2 - glycyllamido - benzophenone need not be isolated prior to cyclisation since it is sufficient merely to alkalinize the crude product of the reaction step.

The benzyloxycarbonyl compounds used in the process are novel compounds which form part of the invention and can be prepared by acylating the corresponding 2 - amino-benzophenones using acylating agents such as benzyloxycarbonyl-glycine or the anhydride or a halide thereof. The acylation can be carried out at ordinary temperatures or at elevated or reduced temperatures. Preferably it is effected by condensing benzyloxycarbonyl-glycine with the appropriate 2-amino-benzophenone in the presence of an N,N^1 - disubstituted carbodiimide. The N,N^1 - disubstituted-carbodiimides used can be obtained in various ways. If suitable substituted carbodiimides (e.g. N,N^1 - dicyclohexyl - carbodiimide) are used there are obtained as by-products urea derivatives which can easily be separated from the acylation product. The acylation can, for example, be carried out at a temperature between 0°C . and 50°C .—preferably at room temperature or a temperature slightly below room temperature. A solvent is used with advantage. Suitable solvents include organic solvents (e.g. methylene chloride, chloroform, dioxan, tetrahydro-furan, N,N -dimethyl-formamide, acetonitrile and the like) as well as water.

Both the acylation of the various 2-amino-benzophenones and the reaction of the resulting benzyloxycarbonyl compounds with hydrohalic acid in the presence of acetic acid gives good yields.

Those 2 - amino - benzophenones in which R^1 , R^2 and R^4 are absent and in which R^3 is a 5-alkylthio or 5-alkylsulphonyl group are described and claimed in the specification of our copending application for Letters Patent no: 40978/62 (now serial no: 972,972). The 2 - amino - benzophenones in which R^1 and R^4 are absent and in which R^2 is either absent or is a 2^1 - trifluoromethyl group and R^3 is a 5-trifluoromethyl group are described and claimed in the specification of our copending application for Letters Patent no: 40979/62 (now serial no: 972,973). The 2-amino-benzophenone in which R^1 is methyl, R^2 and R^4 are absent and R^3 is a 5-chloro substituent is described and claimed in the specification of our copending application for Letters Patent no: 20070/63 (now serial no: 972,975). The 2 - amino - 5 - bromo - 4^1 -methyl-, 2 - amino - 5,4 ^{1} - dichloro-, 2-amino - 4 - trifluoromethyl-, 2 - amino - 5-chloro - 3 - methylthio-, 2 - amino - 4^1 -chloro-, 2 - amino - 6 - chloro-, 2 - amino - 5,2 ^{1} - dichloro-, 2 - amino - 5 - chloro - 2^1 -methyl-, 2 - amino - 5 - chloro - 2^1 - fluoro-, 2 - amino - 5 - chloro - 3^1 - fluoro-, 2 - amino - 5 - bromo - 2^1 - fluoro-, 2 - amino - 5 - bromo - 4 - methoxy-, 2 - amino - 5-methoxy-, 2 - amino - 5 - hydroxy-, 2 - amino - 5 - chloro - 2^1 - methoxy-, 2 - amino - 5-chloro - 2^1 - hydroxy-, 2 - amino - 4 - chloro-, 2 - amino - 4^1 - trifluoromethyl-, 2 - amino - 3^1 - trifluoromethyl and 2 - amino - 2^1 -trifluoromethyl - benzophenone compounds are described in the specification of our copending application for Letters Patent no: 42408/60 (now serial no: 972,968). The 2-amino - 5 - cyano-, 2 - amino - 5 - methyl- 2^1 - fluoro- and 2 - amino - 5 - cyano - 2^1 -chloro - benzophenone compounds are described in the specification of our copending application for Letters Patent no: 10120/62 (now serial no: 985,657). The other 2-amino - benzophenones which may be used for the preparation of the starting materials can be made in a similar fashion to the foregoing.

The following examples are illustrative of the manner in which the process of the invention can be carried into effect:

EXAMPLE 1.

1. The preparation of 2 - (N^1 - benzyloxycarbonyl - glycyllamido) - 5 - chloro-benzophenone:

A) 2.2 g of N,N^1 - dicyclohexyl - carbodiimide were added to a solution of 2.3 g of 2 - amino - 5 - chloro - benzophenone and 2.1 g of benzyloxycarbonyl - glycine in 25 ml of tetrahydro-furan. After stirring for several minutes, dicyclohexyl - urea began to crystallize. Stirring was continued for 2 hours and dicyclohexyl-urea was then filtered off. The filtrate was then treated with 2 ml of acetic acid to decompose any excess N,N^1 -dicyclohexyl - carbodiimide. After 0.25 hour,

additional solid was removed by filtration. The filtrate was taken to dryness *in vacuo* and the residue was dissolved in benzene and washed successively with 1 - *N* hydrochloric acid, water and with 5% sodium bicarbonate and then dried over sodium sulphate. The benzene layer was concentrated to ca. 30 ml and hexane added to turbidity. On seeding 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - chloro - benzophenone crystallized and, upon recrystallization from ethanol, melted at 116°—117°C.

B) A solution of 1.1 g of 2 - amino - 5 - chloro - benzophenone and 2.0 g of benzyloxycarbonyl - glycine anhydride in 25 ml of dry pyridine was stirred for 2 hours at ca 20°C., kept for 16 hours at ca 20°C. and then heated for 1 hour on a steam-bath. The solvent was removed by distillation *in vacuo* and the residue then dissolved in 75 ml of benzene, washed with dilute hydrochloric acid, water and dilute sodium bicarbonate. After drying over sodium sulphate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - chloro - benzophenone.

C) 7.0 g of 2 - amino - 5 - chloro - benzophenone were added to a solution of 7.1 g of crude benzyloxycarbonyl - glycine chloride in 150 ml of dry pyridine. After warming for 1 hour on a steam-bath, the solvent was distilled off *in vacuo*. The residue was dissolved in methylene chloride and washed successively with dilute hydrochloric acid, water and dilute sodium carbonate. After drying over sodium sulphate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - chloro - benzophenone.

2. A) The reaction:

A solution of 3.1 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - chloro - benzophenone in 30 ml of 20% hydrogen bromide in acetic acid was stirred for 35 minutes at ca 20°C. Then, 175 ml of anhydrous ether were added rapidly while stirring. The gummy material which separated was stirred for 10 minutes, the supernatant liquid decanted off and the residue again stirred for 10 minutes with 125 ml of ether. The ether was decanted off and the residue then dissolved in 100 ml of water to produce a turbid solution. This solution was extracted twice with ether and the washings discarded. On addition of ammonia to the aqueous solution to pH 11, a white crystalline product separated. This was extracted with methylene chloride and, after drying over sodium sulphate, the methylene chloride was evaporated *in vacuo* at 20°C. leaving a residue which, upon crystallisation from benzene/hexane yielded 5 - chloro - 2 - glycylamido - benzophenone melting at 101°—103°C.

B) The reaction and cyclization:

A solution of 3.1 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - chloro - benzophenone in 30 ml of 20% hydrobromic acid in glacial acetic acid was stirred for 0.75 hours at ca. 20°C. On addition of 175 ml of anhydrous ether, a gummy solid precipitated. After several minutes the ether solution was decanted off. The resultant 5 - chloro - 2 - glycylamido - benzophenone was not isolated, but about 155 ml of ether were added to the residue and, after chilling in an ice-bath, 10% sodium hydroxide was added until the mixture was alkaline. The ether layer was then separated, washed twice with water and dried over sodium sulphate. After filtration, the ether solution was concentrated to dryness *in vacuo*. The residue was crystallized from benzene to yield 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

EXAMPLE 2.

1) The preparation of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 2',5' - dichloro - benzophenone:

600 g of *o*-chloro-benzoyl chloride were heated to 110°C. in a 5-litre three-necked flask equipped with thermometer, mechanical stirrer and reflux condenser. 175 g of *p*-chloro-aniline were added to this with stirring. The mixture was then heated to 180°C. and 230 g of zinc chloride were added. The temperature was now gradually raised to 220°—230°C. and kept there until the evolution of hydrogen chloride had ceased (1—2 hours). After cooling to 120°C., water was cautiously added and the mixture heated to reflux. The hot-water layer was decanted and this procedure was repeated 2 or 3 times.

The water-insoluble brown mass was finally suspended in a mixture of 350 ml of water, 500 ml of acetic acid and 650 ml of concentrated sulphuric acid and heated to reflux for 17 hours. After cooling, the homogeneous dark solution was poured into ice-water, the mixture extracted with ether and the ether extract was neutralized with 2-*N* sodium hydroxide. Concentration of the ether solution and addition of a small amount of petroleum ether yielded 2 - amino - 2',5' - dichloro - benzophenone in yellow crystals which, after recrystallization from ether/(petroleum ether), yielded the pure compound of melting point 88°—89°C.

A solution of 5.0 g of 2 - amino - 2',5' - dichloro - benzophenone and 3.9 g of benzyloxycarbonyl - glycine in 125 ml of methylene chloride was cooled to 0°C. and 3.9 g of N,N¹ - dicyclohexyl - carbodiimide were added in four portions at intervals of 0.5 hour. The reaction was kept cool for 6 hours and then kept at ca 20°C. for 16 hours. About 4 ml of acetic acid were added to decompose excess N,N¹ - dicyclohexyl - carbodiimide. After stirring for 0.5 hours, dicyclohexyl-

urea was removed by filtration and the filtrate was then washed with dilute sodium bicarbonate, dried over sodium sulphate and concentrated to dryness *in vacuo*. Recrystallization from a mixture of benzene and hexane gave crude crystalline 2 - (N¹ - benzyloxycarbonyl-glycylamido) - 2',5 - dichloro - benzophenone which, upon recrystallization from benzene/hexane formed colourless needles melting at 148°—148.5°C.

2) *The reaction:*

A solution of 2.5 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 2',5 - dichloro-benzophenone in 30 ml of 20% hydrobromic acid in acetic acid was stirred for 0.5 hour at ca. 20°C. On slow addition of 175 ml of anhydrous ether, a gummy precipitate formed. The supernatant liquid was poured off and the residue was stirred with water and ether. Dilute ammonia was added until the mixture was slightly alkaline. The ether layer was then separated, dried over sodium sulphate and, after the addition of some benzene, concentrated *in vacuo* to a small volume. On addition of hexane to the residue, 2',5 - dichloro - 2 - glycylamido - benzophenone crystallized; melting point=121°—122°C.

EXAMPLE 3.

1) *The preparation of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - benzophenone:*

A solution of 3.8 g of 2 - amino - benzophenone and 4.0 g of benzyloxycarbonyl-glycine in 150 ml of methylene chloride was cooled to 0°C, and 4.0 g of N,N¹ - dicyclohexyl - carbodiimide were added in four portions at intervals of 0.5 hour. After stirring for 6 hours in an ice-bath, the reaction mixture was kept for 16 hours at ca 20°C. then stirred for 20 minutes after the addition of 4 ml of acetic acid. Dicyclohexyl-urea was filtered off and the filtrate washed with dilute sodium bicarbonate. After drying over sodium sulphate, solvent was distilled off *in vacuo*. The residue was crystallized from a mixture of benzene and hexane to give 2 - (N¹ - benzyloxycarbonyl - glycylamido) - benzophenone which, upon being twice crystallized from benzene/hexane, melted at 116°—117°C.

2) *The reaction:*

A solution of 4.5 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - benzophenone in 45 ml of 20% hydrobromic acid in acetic acid was stirred for 0.5 hour at ca 20°C. 175 ml of anhydrous ether were then added. After pouring off the supernatant liquid, the residue was stirred with water and ether, cooled in an ice-bath and made slightly alkaline with ammonia. The ether layer was dried over sodium sulphate, filtered, some benzene added and the resulting solution concentrated *in vacuo* to a small volume. On addition of hexane to the residue, 2 - glycylamido - benzophenone crystallized and, upon recrystallization from benzene and hexane, melted at 76°—77°C.

EXAMPLE 4.

1) *The preparation of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 2¹ - nitro-benzophenone:*

4.3 g of N,N¹ - dicyclohexyl - carbodiimide were added in four portions at intervals of 0.5 hour to a solution of 5.0 g of 2 - amino - 2¹ - nitro - benzophenone and 4.3 g of benzyloxycarbonyl-glycine in 250 ml of methylene chloride cooled to 0°C. After stirring for 6 hours in an ice-bath, the reaction was kept at ca 20°C. for 2 days. After the addition of 4 ml of acetic acid, the reaction mixture was stirred for 20 minutes and dicyclohexyl-urea was filtered off. The filtrate was washed with dilute hydrochloric acid, water and dilute sodium bicarbonate. After drying over sodium sulphate, solvent was distilled off *in vacuo*. The residue was dissolved in ether and passed through a column of 150 g of WOELM alumina (neutral, grade I). Elution with ether gave recovered 2-amino - 2¹ - nitro - benzophenone. Further elution with a mixture of ether and ethyl acetate (3:1) gave crude 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 2¹ - nitro - benzophenone which, upon two crystallizations from a mixture of benzene and hexane, melted at 131°—132°C.

2) *The reaction:*

A solution of 3.1 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 2¹ - nitro - benzophenone in 30 ml of 20% hydrobromic acid in acetic acid was stirred for 0.5 hour at ca 20°C. On addition of 150 ml of anhydrous ether, crude 2 - glycylamido - 2¹ - nitro-benzophenone hydrobromide crystallized and upon recrystallization from a mixture of methanol and ether formed filament-like colourless needles melting at 201°—203°C.

A solution of the hydrobromide in water was made slightly alkaline with ammonia. The free base, 2 - glycylamido - 2¹ - nitro-benzophenone, crystallized. Recrystallization from a mixture of benzene and hexane gave colourless prisms melting at 160°—162°C.

EXAMPLE 5.

1) *The preparation of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - trifluoromethyl - benzophenone:*

80 g of sodium nitrite were added slowly with stirring to 460 ml of concentrated sulphuric acid. After heating to 70°C. a clear solution was obtained. This solution was cooled and 200 g of 2 - chloro - 5 - trifluoromethyl - aniline were slowly added at a temperature between 10° and 20°C. The reaction mixture was stirred for 1 hour at 20°C. and then poured into a mixture of 200 g of sodium chloride and 1.5 kg of ice. Excess sodium chloride was filtered off. A solution of 280 g of zinc chloride in 300 ml of water was added to the filtrate, whereupon a zinc chloride double salt of the corresponding diazonium compound precipitated.

pitated. After standing for 16 hours at 0°C., the double salt was filtered off and washed with a cold saturated salt solution.

291 g of the wet zinc chloride double salt were added with stirring and cooling with ice to a solution of 120 g of sodium cyanide and 72 g of cuprous cyanide in 300 ml of water. After the addition of 24 g of sodium carbonate, the mixture was first stirred for 1 hour at 20°C. and then at 70°C. for an addition 0.5 hour. The reaction mixture was cooled and extracted with ether to obtain crude 2 - chloro - 5 - trifluoromethyl - benzonitrile. The product was purified by steam distillation and crystallization of the organic part of the distillate from hexane to give the pure compound of melting point 39°—40°C.

A solution of 39 g of 2 - chloro - 5 - trifluoromethyl - benzonitrile in 200 ml of benzene was added with stirring to a solution of phenyl-magnesium bromide prepared from 9.5 g of magnesium, 58.5 g of bromobenzene and 500 ml of anhydrous ether. 400 ml of solvent were distilled off and the reaction mixture was then heated under reflux for 16 hours. The GRIGNARD complex was decomposed with 40 g of ammonium chloride and 200 g of ice. The mixture was then extracted with benzene. 2 - chloro - 5 - trifluoromethyl - benzophenone imine hydrochloride was precipitated from the benzene solution by the addition of 40 ml of concentrated hydrochloric acid. The product was filtered off, washed with benzene and dried *in vacuo* (melting point=248°—251°C.) and upon further purification melted at 250°—262°C.

60 g of 2 - chloro - 5 - trifluoromethyl - benzophenone imine hydrochloride were heated under reflux for 16 hours with a mixture of 300 ml of toluene and 300 ml of 25% sulphuric acid while stirring. The toluene layer was separated, washed with water, dried, concentrated *in vacuo* and the residue crystallized from hexane to yield pure 2 - chloro - 5 - trifluoromethyl - benzophenone of melting point 39°—40°C. (Corrected).

50 g of 2 - chloro - 5 - trifluoromethyl - benzophenone and 500 ml of concentrated aqueous ammonia were reacted in a closed vessel for 10 hours at 140°C. in the presence of 10 g of cuprous chloride catalyst. The reaction product was extracted with ether. The ether extract was concentrated *in vacuo*, the residue dissolved in hexane and purified by chromatography using a 10 fold amount of neutral alumina (BROCKMANN, activity state II). Elution with a hexane/ether mixture (1:1) and evaporation of the solvent gave 2 - amino - 5 - trifluoromethyl - benzophenone which was recrystallized from hexane to give yellow crystals of melting point 81°—82°C. (Corrected).

A solution of 10.0 g of 2 - amino - 5 - trifluoromethyl - benzophenone and 7.8 g of

benzyloxycarbonyl - glycine in 300 ml of methylene chloride was stirred and cooled to 0°C. in an ice-bath. 7.8 g. of N,N¹ - dicyclohexyl - carbodiimide were then added in four portions at intervals of 0.5 hours. Stirring was continued for 6 hours in an ice-bath and the reaction mixture was then kept for 16 hours at ca 20°C. 8 ml of acetic acid were then added and, after stirring for 0.5 hour, dicyclohexyl-urea was filtered off. The filtrate was washed with dilute bicarbonate solution, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue which crystallized on standing, was recrystallized from a mixture of benzene and hexane to give 2 - (N¹ - benzyloxycarbonyl - glycydamido) - 5 - trifluoromethyl - benzophenone which, upon two further crystallizations from benzene/hexane, melted at 128.5°—130°C.

2) The reaction and cyclization:

A solution of 2.25 g of 2 - (N¹ - benzyloxycarbonyl - glycydamido) - 5 - trifluoromethyl - benzophenone in 15 ml of 20% hydrobromic acid in acetic acid was stirred for 25 minutes at ca 20°C. The resultant 2 - glycydamido - 5 - trifluoromethyl - benzophenone was not isolated, but 200 ml of anhydrous ether were added to the reaction mixture. Water was then added, the mixture cooled in an ice-bath and made slightly alkaline with ammonia. The organic layer was separated, washed with water, dried over sodium sulphate and the solution concentrated to dryness *in vacuo*. The residue was heated to reflux for 3 hours in 30 ml of pyridine. Following removal of the solvent *in vacuo*, the residue was crystallized from hexane yielding 7 - trifluoromethyl - 5 - phenyl - 2,3-dihydro - 1H - 1,4 - benzodiazepinone - (2).

EXAMPLE 6.

1) The preparation of 2 - (N¹ - benzyloxycarbonyl - glycydamido) - 5 - methoxybenzophenone:

A GRIGNARD reagent (prepared from 24 g of bromo-benzene and 3.6 g of magnesium in 200 ml of ether) was added slowly during 1.25 hours to a solution of 27.1 g of 2-methyl - 6 - methoxy - 3.1 - benzoxazinone-(4) dissolved in 375 ml of dry benzene and 125 ml of ether at 0°—5°C. After all the GRIGNARD reagent had been added, the reaction was stirred for 0.5 hour and 0°—5°C. and then allowed to come to ca 20°C. It was then cooled in an ice-bath and decomposed with 400 ml of 2-N hydrochloric acid. The organic layer was then separated and concentrated to dryness *in vacuo*. The residue was dissolved in 375 ml of ethanol and 125 ml of concentrated hydrochloric acid and heated under reflux for 2 hours. After removal of solvent by distillation *in vacuo*, the residue was stirred with dilute sodium hydroxide and extracted with benzene. The organic layer was then washed with water, dried over sodium sulphate and then concen-

- trated to dryness *in vacuo* leaving 20.6 g of a yellow-brown oil. The residue was dissolved in 160 ml of benzene and 370 ml of hexane and passed through a column of 250 g of WOELM alumina (grade 1, neutral). Elution with benzene/hexane (1:2 and 2:1) followed by benzene and crystallization from hexane gave 2 - amino - 5 - methoxy-benzophenone of melting point 50°—52°C.
- 5.2 g of N,N¹ - dicyclohexyl - carbodi-imide were added in four portions at intervals of 0.5 hour to a solution of 5.7 g of crude 2 - amino - 5 - methoxy - benzophenone and 5.2 g of benzyloxycarbonyl-glycine in 250 ml of methylene chloride cooled to 0°C. After 5 hours in an ice-bath, the reaction mixture was kept at ca 20°C for 2 days. Following the addition of 4 ml acetic acid, the reaction mixture was stirred for 0.5 hour and dicyclohexyl-urea was filtered off. The filtrate was washed with dilute sodium carbonate and dried over sodium sulphate. After filtration and concentration to dryness *in vacuo*, the residue was crystallized from benzene/hexane to give 2-(N¹ - benzyloxycarbonyl - glycylamido) - 5-methoxy - benzophenone. Recrystallization from a mixture of ethyl acetate and hexane gave colourless needles melting at 130°—132°C.

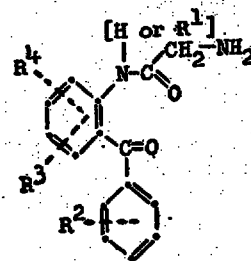
2) The reaction and cyclization:

- A solution of 3.0 g of 2 - (N¹ - benzyloxycarbonyl - glycylamido) - 5 - methoxy - benzophenone in 30 ml of 20% hydrobromic acid in acetic acid was stirred for 0.5 hour at ca 20°C. On slow addition of 175 ml of anhydrous ether, a gummy precipitate formed. The supernatant liquid was poured off and the residue was partitioned between water and ether. The resultant 2 - glycylamido - 5-methoxy - benzophenone was not isolated but, after cooling in ice, the mixture was neutralized with ammonia. The ether layer was then separated, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue crystallized on standing. Recrystallization from benzene/hexane gave 7-methoxy - 5 - phenyl - 2,3 - dihydro - 1H-1,4 - benzodiazepinone - (2).

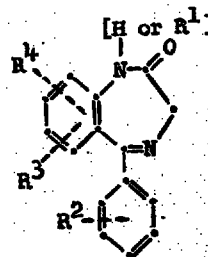
- It will be understood that the prefix "lower" is used in the foregoing description and in the following claims to indicate that the groups qualified therewith contain from one to seven carbon atoms.

WHAT WE CLAIM IS:—

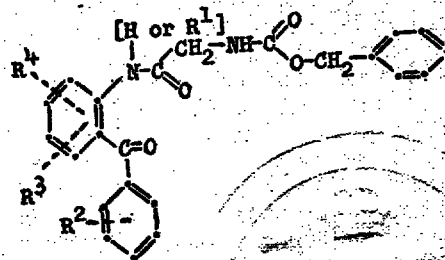
- 1) A process for the manufacture of 2-glycylamido - benzophenones of the general formula



(wherein R¹ stands for a lower-alkyl group, R², R³ and R⁴ are each a lower alkyl, alkoxy, alkanoyl-amino, alkyl-thio, alkyl-sulphanyl or alkyl-sulphonyl group or a halogen atom of the trifluoro-methyl, nitro, amino, mercapto, cyano or hydroxy group and the bonds shown as broken lines denote that the substituents R², R³ and R⁴ attached thereby are optional) and cyclisation derivatives thereof of the general formula



(wherein the symbols R¹, R², R³ and R⁴ and the broken lines have the significance already given), which process comprises reacting a benzyloxycarbonyl compound of the general formula



(wherein the symbols R¹, R², R³ and R⁴ and the broken lines have the significance given hereinbefore) with a hydrohalic acid in the presence of acetic acid and, where the cyclisa-

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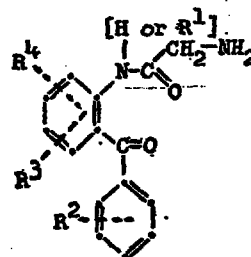
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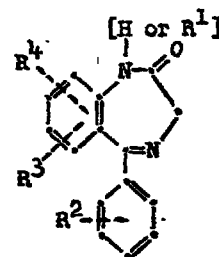
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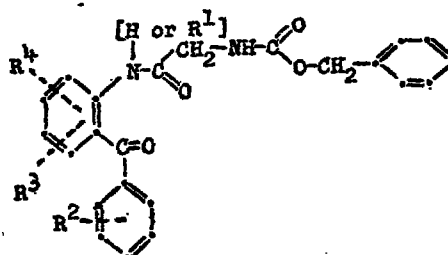
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tion derivative is required, cyclising the resulting 2 - glycydamido - benzophenone by alkalising to a pH of 7 or more.

2) A process in accordance with claim 1, wherein hydrobromic acid is the hydrohalic acid used.

3) A process in accordance with claim 1 or claim 2, wherein a 5-(chloro or trifluoromethyl) - 2 - (benzyloxycarbonyl - glycydamido) - benzophenone is used as the starting material.

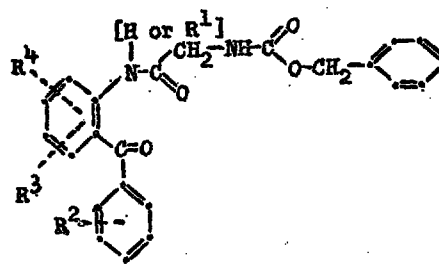
4) A process in accordance with claim 1, claim 2 or claim 3, which includes the additional and initial step of preparing said benzyloxycarbonyl compound by acylating an appropriately substituted 2 - amino - benzophenone with an agent which introduces a benzyloxycarbonyl-glycyl moiety on to the 2-amino group.

5) A process for the manufacture of the 2-glycydamido-benzophenones of the formula first written in claim 1 and cyclisation derivatives thereof of the formula second written in claim 1, substantially as described with reference to the examples.

6) 2-Glycydamido-benzophenones of the formula first written in claim 1 and cyclisation

derivatives thereof of the formula second written in claim 1, when manufactured by the process claimed in any one of the preceding process claims.

7) Benzyloxycarbonyl compounds of the general formula



, wherein R¹, R², R³ and R⁴ and the broken lines have the significance given in claim 1.

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