PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C 07 c, d

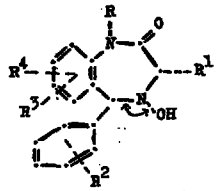
COMPLETE SPECIFICATION

Benzodiazepine Derivatives

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:—

The present invention is concerned with novel benzodiazepine derivatives.

The novel benzodiazepine derivatives provided by the invention are compounds of the general formulae



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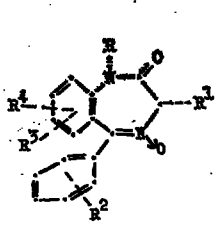


wherein R represents an alkyl, alkenyl, hydroxy - alkyl or aralkyl group, R^1 represents an alkyl, alkoxy - alkyl, aryl, hydroxy - aralkyl, alkylthio - alkyl or hydroxy - alkyl group, R^2 represents an alkyl, alkoxy or trifluoromethyl group or a halogen atom, R^3 represents a trifluoro - methyl, alkyl, alkoxy, alkyl - thio, hydroxyalkyl - thio, nitro, amino, alkylsulphinyl, alkylsulphonyl, hydroxy or acyl - amino group or a halogen atom and R^4, which can only be present if R^3 is other than the trifluoro - methyl group, represents any of the values of R^3 except the latter value and wherein the broken lines denote that the R-substituents and hydroxyl group attached thereby are optional and the double headed arrow signifies that, in the absence of the hydroxy substituent on the nitrogen atom in the 4 - position, the optional bond indicated thereby may exist as an additional bond in the 4,5 - position, and acid addition salts of those compounds which are basic. These substances are useful as sedatives, muscle relaxants and anticonvulsants. They may also be used for the relief of tension. They may be utilized by administering a therapeutic dosage (adjusted to route of administration and individual requirements) in a conventional liquid or solid vehicle to provide elixirs, suspensions, capsules, tablets or powders according to con-

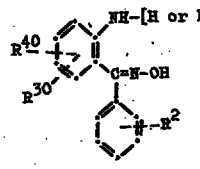
[*Price 4s. 6d.*]

ventional pharmaceutical practice.

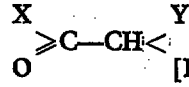
The preferred derivatives are those compounds of the foregoing formulae, and acid addition salts of the basic members, in which R is either absent or is a lower - alkyl group or a lower - alkenyl group, R^2 is either absent or is a lower - alkyl group or a halogen atom in the 2 - position, R^3 is either absent or is a trifluoromethyl group (in which case R^4 is absent) or a lower alkyl - thio, lower hydroxyalkyl - thio, lower alkylsulphinyl or lower alkylsulphonyl group or an amino, nitro or lower acyl - amino group; the term 'lower' being used in this description and in the claims appended hereto to indicate that the groups qualified by same contain up to seven carbon atoms. The lower-alkyl groups and lower-alkenyl groups maye be straight chain or branched chain groups such as methyl, ethyl, propyl, *iso*propyl, butyl, *iso*butyl, *tert*butyl, amyl and hexyl and allyl and butenyl. The preferred aralkyl group is the benzyl group. The aryl group can be the phenyl group. The hydroxy-aralkyl group can be the *p*-hydroxybenzyl group. The preferred alkylthio - alkyl groups are the methylthio - alkyl groups. The preferred halogeno substituents are chloro and bromo.

The compounds which are basic form acid addition salts with mineral acids; for example hydrohalic acids (such as hydrochloric acid and hydrobromic acid), nitric acid, sulphuric acid and phosphoric acid.

Those compounds of a limiting case of the second formula given herein, namely the case where R (when present) is an alkyl, alkenyl or aralkyl group and R^1 (when present) is an alkyl group, can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent No. 42399/60 (now serial No. 972,961). This process, described using R- and R^1-values consistent with the limitations aforesaid, comprises reacting a 2 - amino - benzophenone *beta*oxime of the general formula

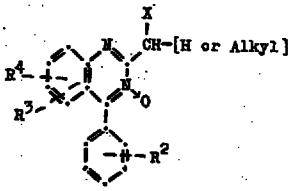


wherein R represents an alkyl, alkenyl or aralkyl group, R^{30} and R^{40} have any of the values except amino accorded to R^3 and R^4 hereinbefore and R^2 and the broken lines have the significance given earlier, with an α - halogeno - acyl halide of the general formula



wherein X and Y represent halogeno substituents and R^1 represents an alkyl group, in the presence of more than one mol of an acid-binding agent and, in the case where R^{30} and R^{40} were absent in the starting material, subjecting the benzodiazepine formed to one or more of the steps nitration, reduction of the nitro group and acylation of the resulting amino group where it is desired to introduce a nitro or amino or acylamino group, or, in the case where one or both of R^{30} and R^{40} were nitro groups in the starting material, subjecting the benzodiazepine formed to one or both of the steps of reduction of the nitro group or groups and acylation of the resulting amino group or groups where one or two amino or acylamino groups is or are required in the product to be derived from said starting material.

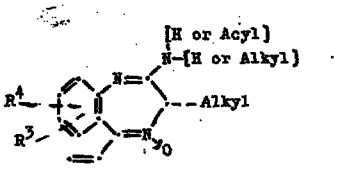
The compounds of a limiting case of the second general formula given herein, namely the case where R is absent and R^1 (when present) is an alkyl group, can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent no. 42400/60 (now serial No. 972,962). This process comprises reacting a quinazoline derivative of the general formula



wherein R^2, R^3, R^4 and the broken lines have the significance given earlier and X represents a halogen atom, or an acid addition salt thereof, with an alkali-metal or alkaline-earth metal hydroxide or ammonium hydroxide and, in the case where R^3 and R^4 were absent in the quinazoline derivative used, subjecting the benzodiazepine formed to one or more of the steps nitration, reduction of the nitro group and acylation of the amino group where a nitro or amino or acylamino group is required in the product, or, in the case where either or both R^3 and R^4 were nitro or amino in said derivative, subjecting if desired said benzodiazepine to reduction or reduction and acylation on the one hand or acylation on the other hand where one or two amino or acylamino groups are required in the product. The quinazoline derivatives used as starting materials in which R^3 and R^4 are absent or are respectively an alkyl group or halogen atom in the 6 - position and an alkyl group or halogen atom in the 7 - position and in which R^2 is absent or is a halogen atom, and their acid addition salts, are claimed *per*

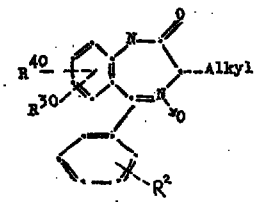
se in the specification of Letters Patent No. 864,825. Those quinazoline starting materials in which R^3 is a trifluoromethyl group in the 6- or 7-position and in which R^2 is absent are claimed *per se* in the specification of our copending application for Letters Patent No. 29834/62 (now serial No. 972,970).

The compounds of a limiting case of the first general formula given herein, namely the 4,5 - dehydro derivatives in which R is absent and R^1 (when present) is an alkyl group, and the compounds of a limiting case of the second general formula given herein, namely the case where R is absent and R^1 (when present) is an alkyl group, can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent No. 42401/60 (now serial No. 972,963). This process comprises hydrolysing a benzodiazepine derivative of the general formula



wherein R^2, R^3, R^4 and the broken lines have the significance given earlier, with a strong acid under conditions of temperature which avoid the hydrolysis of any acylamino value of R^3 and/or R^4 or the opening of the 7-membered ring in the product or both as the case may be and, in the case where R^3 and R^4 were absent in the derivative used as the starting ~~materials (and their acid addition~~ one or more of the steps nitration, reduction of the nitro group and acylation of the amino group where a nitro or amino or acylamino group is required in the product, or, in the case where R^3 or R^4 or both were nitro or amino in said derivative, subjecting the product if desired to reduction or reduction and acylation on the one hand or acylation on the other hand where one or two amino or acylamino groups are required in the product. Those benzodiazepine derivatives used as starting materials (and their acid addition salts) other than the N - oxides are claimed *per se* in the specification of our copending application for Letters Patent No. 42406/60 (now serial No. 932,495). The acylated N-oxides are claimed *per se* in the specification of our Letters Patent No. 932,496. Those optionally 3 - alkylated, but unacylated, N-oxides which have a trifluoro - methyl group as a substituent in the 7- or 8- position (and their acid addition salts) are claimed *per se* in the specification of our copending application for Letters Patent No. 1168/61 (now serial No. 972,969). Those optionally 3 - alkylated, but unacylated, N - oxides containing optional alkyl or halogeno substituents in the 7-and/or 8-positions and in which R^2 is an optional halogen atom or alkoxy group (and their acid addition salts) are claimed *per se* in the specification of our Letters Patent No. 864,824.

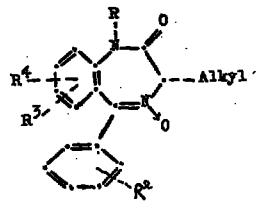
The compounds of a limiting case of the first general formula herein, namely the 4,5 - dehydro compounds in which R is present and R^1 (when present) is an alkyl group, and the compounds of a limiting case of the second general formula herein, namely the case where R is present and R^1 (when present) is an alkyl group, and the acid addition salts of those compounds which are basic can be manufactured by the process described and claimed in the specification of our copending application for Letters Patent No. 42402/60 (now serial no. 972,964). This process comprises reacting a compound of the general formula



wherein R^{30} and R^{40} have any of the values accorded to R^3 and R^4 hereinbefore except those of amino and acylamino and R^2 and the broken lines have the significance given earlier, or an alkali-metal derivative thereof, with an alkylating, alkenylating, hydroxyalkylating or aralkylating agent *and*, if desired in the case where R^{30} and R^{40} were absent in the compound used as the starting material, subjecting the product to one or more of the steps nitration, reduction of the nitro group and acylation of the amino group where a nitro or amino or acylamino group is required in the product, or, if desired in the case where one or both of R^{30} and R^{40} in the compound used as the starting material were nitro groups, subjecting the product to one or both of the steps of reduction of the nitro group or groups and acylation of the resulting amino group or groups where one or two amino or acylamino groups is or are required in the product to be derived from such starting material and/or converting the product (if a base) into a salt by treatment with an acid. The starting materials used in this process are claimed *per se* in this application.

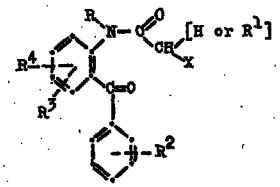
The compounds of a limiting case of the first formula herein, namely the case where R (when present) is an alkyl, hydroxy-alkyl or aralkyl group, and R^1 (when present) is an alkyl group and the alkylsulphinyl

or nitro value for R^3 and/or R^4 can only be present where a 4,5 - double bond is present, and acid addition salts of the basic compounds can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent No. 42403/60 (now serial no. 972,965). This process, described having regard to the R - limitation aforesaid, comprises *either* treating a compound of the formula



wherein R represents an alkyl, hydroxy - alkyl or aralkyl group and R^2, R^3 and R^4 and the broken lines have the significance given earlier, with a phosphorus trihalide (except in cases where a hydroxy - alkyl or hydroxyalkyl - thio substituent is present) or with hydrogen in the presence of RANEY - nickel (where R^3 and/or R^4 is absent or is other than nitro or alkylsulphinyl or where R^3 and/or R^4 is nitro or alkylsulphinyl and an amino or alkylsulphonyl group is required in the product) and, if desired where R^3 and R^4 are absent subjecting the product to one or more of the steps nitration, reduction of the nitro group and acylation of the amino group and, where R^3 and R^4 are either absent or have any of the values other than nitro or alkylsulphinyl accorded to them hereinbefore and a tetrahydro product is required, catalystically hydrogenating the double bond in the 4,5 - position of the resulting 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) with hydrogen in the presence of a platinum or other noble metal catalyst *or*, where a product is required in which R^3 and R^4 are either absent or have any of the values other than nitro or alkylsulphinyl accorded to them hereinbefore, catalytically hydrogenating the compound of said formula with hydrogen in the presence of a platinum catalyst so as to reduce the double bond in the 4,5 - position and convert the oxide component into a hydroxy substituent *and*, in either case if desired converting the product (if a base) into a salt by treatment with an acid. The starting materials for this process are claimed *per se* in this application.

The compounds of a limiting case of the first formula herein, namely the 4,5 - dehydro compounds where R^1 (when present) represents an alkyl or aryl group can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent No. 42404/60 (now serial No. 972,966). This process, described using the R^1 limitation aforesaid, comprises reacting a benzophenone derivative of the general formula

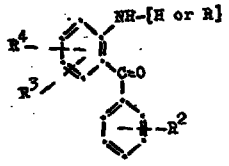


wherein R^1 represents an alkyl or aryl group, X represents a halogen atom and R, R^2, R^3, R^4 and the broken lines have the significance given earlier, with ammonia, heating any uncyclized product obtained to effect ring closure, and, in the case where R^3 and R^4 were absent in said benzophenone derivative, subjecting the benzodiazepine formed to one or more of the steps nitration, reduction of the nitro group and acylation of the amino group where it is desired to introduce a nitro or amino or acylamino group, or, where either or both of the groups R^3 and R^4 in said benzophenone derivatives were nitro or amino, converting if desired said groups into amino or acylamino as the case may be by reduction or reduction and acylation in the case of nitro or by acylation in the case of amino.

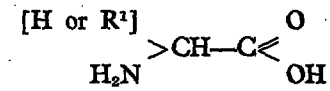
The benzophenone derivatives used as starting materials can be prepared from 2 - amino - benzophenone or a 2[(alkyl, alkenyl, hydroxyalkyl or aralkyl) - amino] - benzophenone or the appropriate nuclear - substituted derivative thereof by reaction with an α - halo - acyl halide (such as chloro - acetyl chloride). The compounds 2 - amino - 5 - trifluoromethyl - benzophenone and 2 - amino - 2', 5 - bis (trifluoromethyl) - benzophenone may be prepared by the method exemplified in the specification of our copending application for Letters Patent no: 40979/62 (now serial no: 972,973) where they are claimed *per se*. The 2 - amino - 5 - (alkylthio, hydroxyalkylthio or alkylsulphonyl) - benzophenones may be prepared according to the methods set forth in the specification of copending application for Letters Patent no: 40978/62 (now serial no. 972,972), where they are claimed *per se*. The 2 - alkenylamino - 5 - halo - benzophenones may be prepared as described in the specification of our copending application for Letters Patent No. 40977/62 (now serial No: 972,971), where they are claimed *per se*. The remaining 2 - alkenylamino compounds can be prepared similarly. The compounds 2 - methylamino - 5 - chloro - benzophenone and 2 - benzyl - amino - 5 - chloro - benzophenone may be prepared as described in the specification of our copending

application for Letters Patent No. 20070/63 (now serial no: 972,975), where they are claimed *per se*. The remaining 2 - (alkyl or aralkyl) - amino compounds can be prepared in a similar way.

The compounds of a limiting case of the first formula herein, namely the 4,5 - dehydro compounds where R (when present) is an alkyl, alkenyl or aralkyl group, and their acid addition salts can be manufactured in accordance with the process described and claimed in the specification of our copending application for Letters Patent No. 42405/60 (now serial no. 972,977). This process, having regard to the R limitation aforesaid, comprises reacting a benzophenone derivative of the general formula



wherein R represents an alkyl, alkenyl or aralkyl group and R^2, R^3, R^4 and the broken lines have the significance given earlier, or a salt thereof with a strong acid with an *alpha* amino acid of the general formula



wherein R^1 has the significance given earlier, or an ester thereof or a salt of such an amino acid or ester with a strong acid and, if desired in the case where a nitro or amino or acylamino group is required in the product but was absent in the starting material, subjecting the reaction product to one or more of the steps nitration, reduction of the nitro group and acylation of the amino group, or, where one or two amino or acylamino groups are required in the product but only the corresponding nitro or amino groups were present in the starting material, subjecting the reaction product to reduction or reduction and acylation on the one hand or acylation on the other hand, and/or, if desired, converting the product (if basic) into an acid addition salt; such process being carried out in the presence of a base when both starting materials are used in the form of salts.

These processes may be illustrated in detail thus:

Example 1

600 ml of acetic anhydride were added to a solution of 100 g of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide in 1.2 l of dry pyridine. The mixture was left at *ca* 20°C for 14 hours and concentrated *in vacuo*. The residue was crystallized from a mixture of ether/(petroleum ether) to obtain 7 - chloro - 2 - (N - methyl - acetamido) - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide, melting point = 186°—187°C.

250 ml of 1 - *N* hydrochloric acid was added at *ca*. 20°C to a solution of 84.4 g (0.25 mol) of 7 - chloro - 2 - (N - methyl - acetamido) - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide in 1250 ml of dioxan (prepared by heating). The mixture was left at *ca* 20°C for 14 hours, diluted with ice-water, made strongly alkaline with sodium hydroxide and extracted with ether to remove impurities. The product, 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, remained in the aqueous alkaline solution which was neutralized with acetic acid and extracted with methylene chloride. The methylene chloride solution was dried and concentrated to a small volume. The pure, crystalline product was precipitated by the addition of petroleum ether and crystallized from ethanol, melting point = 235°—236°C (with decomposition).

2.78 g (52.5 mmol) of sodium methoxide were added to a stirred, warm solution of 15 g (52.5 mmol) of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide in 700 ml of methanol. After 5 minutes, 5 ml (52.5 mmol) of dimethyl sulphate were added. The reaction mixture was heated under reflux for one hour, concentrated *in vacuo* to a small volume and diluted with ether and petroleum ether. The crystals which formed were filtered off and washed with water to obtain 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1,4 - benzodiazepinone - (2) 4 - oxide.

Example 2

14.3 g of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide were dissolved in 300 ml of dioxan and hydrogenated in the presence of 20 g of RANEY-nickel at atmospheric pressure and *ca* 20°C. The hydrogenation was stopped after the absorption of one mol of hydrogen. The reaction mixture was filtered, concentrated *in vacuo* to a small volume; and diluted with ether and petroleum ether. The precipitated crystals were recrystallized from acetone. The product, 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) formed colourless plates melting at 216°—217°C.

Example 3

7.6 g of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide were dissolved in 150 ml of glacial acetic acid and hydrogenated at *ca* 20°C and atmospheric pressure in the presence of 0.6 g of platinum oxide until the hydrogen uptake had slowed down considerably. This occurred after 6 hours with the absorption of about 1.5

mol of hydrogen. The reaction mixture was then heated, diluted with more glacial acetic acid to dissolve the precipitated hydrogenation product and filtered over diatomaceous earth. The filtrate was concentrated *in vacuo* to a small volume and the crystalline reaction product filtered off. After recrystallization from acetic acid, the product, 7 - chloro - 4 - hydroxy - 5 - phenyl - 2,3,4,5 - tetrahydro - 1H - benzodiazepinone - (2), formed colourless needles melting at 215°—216°C.

EXAMPLE 4

10.8 g of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 120 ml of glacial acetic acid and hydrogenated in the presence of 1.2 g of platinum oxide at *ca* 20°C and atmospheric pressure. Absorption of hydrogen stopped after the absorption of one mol (1 hour). The mixture was filtered, the filtrate concentrated *in vacuo* and the residue crystallized from dilute N,N - dimethyl - formamide. The pure product, 7 - chloro - 5 - phenyl - 2,3,4,5 - tetrahydro - 1H - 1,4 - benzodiazepinone - (2) melted at 184.5°—185.5°C.

EXAMPLE 5

10 ml of 1 - *N* sodium hydroxide were added at *ca* 20°C to a solution of 2.84 g (10 mmol) of 6 - methyl - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide in 75 ml of dioxan. After 15 hours, the mixture was diluted with ice-water and extracted with ether. The ether extract containing unchanged starting material was discarded. The aqueous layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo* and the residue crystallized from a mixture of methylene chloride/(petroleum ether). The 7-methyl-5-phenyl-2,3 - dihydro - 1H - 1,4 - benzodiazepinone-(2) 4 - oxide formed colourless rhombic plates melting at 226°—227°C.

EXAMPLE 6

20 ml of 1 - *N* sodium hydroxide were added to a suspension of 7 g (20 mmol) of 6 - bromo - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide in 75 ml of dioxan. The mixture was left at *ca* 20°C for 14 hours, concentrated *in vacuo* to a small volume, diluted with ice-cold 3 - *N* sodium hydroxide and extracted with methylene chloride. The methylene chloride solution was discarded. The alkaline solution containing the reaction product was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo* and the residue crystallized from a mixture of methylene chloride/(petroleum ether). The product, 7 - bromo - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, melted at 230°—231°C.

EXAMPLE 7

20 ml of acetic anhydride were added to a solution of 3.9 g of 7,8 - dimethyl - 2 - methylamino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide in 20 ml of pyridine. The solution was left at *ca* 20°C for 20 hours and then concentrated *in vacuo*. The residue was crystallized from a mixture of acetone/ether to obtain 7,8 - dimethyl - 2 - (N - methylacetamido) - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide in the form of colourless prisms melting at 193°—194°C (with decomposition).

6 ml of 1 - *N* hydrochloric acid were added at *ca* 20°C to a solution of 2 g (6 mmol) of 7,8 - dimethyl - 2 - (N - methylacetamido) - 5 - phenyl - 3H - 1,4 - benzodiazepine 4 - oxide in 30 ml of dioxan. After 15 hours, ice-water and 3 - *N* sodium hydroxide were added and the mixture extracted with methylene chloride. The organic layer containing impurities was discarded. The aqueous alkaline solution was acidified with dilute hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was dried and concentrated *in vacuo*. The residue, 7,8 - dimethyl - 5 - phenyl - 2,3 - dihydro - 1,4 - benzodiazepinone - (2) 4 - oxide, crystallized from a mixture of methyl chloride/(petroleum ether) in the form of colourless plates melting at 234°—235°C.

EXAMPLE 8

500 g of *p* - bromo - aniline were added with stirring at 120°C to 995 g of *p* - toluoyl chloride, causing a strong evolution of hydrogen chloride. The mixture solidified and was melted by heating to 200°C. 500 g of anhydrous zinc chloride were added with stirring, again causing the evolution of hydrogen chloride. The mixture was heated for 2 hours at 230°C and then poured with stirring into 2 l. of 0.5 - *N* hydrochloric acid. The precipitated solid was filtered off, pulverized, suspended in 4 l of 0.5 - *N* hydrochloric acid and heated under reflux for one hour. The mixture was cooled. The wet resinous material was filtered off and dissolved in a mixture of 1.5 l of acetic acid and 0.75 l of concentrated hydrochloric acid. The solution was heated under reflux for 18 hours and concentrated *in vacuo*. To the residue were added 3 l of benzene and an excess of sodium hydroxide. The precipitated sodium *para*toluate was filtered off and the aqueous layer discarded. The benzene layer was washed with 2 - *N* sodium hydroxide and then with an excess of 2 - *N* hydrochloric acid. The benzene layer was dried and concentrated, yielding crude 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone. After crystallization from a mixture of benzene/(petroleum ether), the pro-

duct formed yellow plates melting at 105°—106°C.

A mixture of 50 g of 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone, 28 g of hydroxylamine hydrochloride and 250 ml of ethanol was heated under reflux for 15 hours. The solution was neutralized with aqueous sodium carbonate and diluted with 100 ml of water and 100 ml of benzene. The precipitated crystals of 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone *alpha*oxime were filtered off. The benzene layer was separated from the filtrate, dried and partly concentrated *in vacuo* yielding an additional quantity of the product. The mother liquors were diluted with petroleum ether to obtain 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone *beta*-oxime. The *alpha*oxime was crystallized from ether and melted at 204°—205°C. The *beta*-oxime was crystallized from a mixture of benzene/(petroleum ether) and melted at 115°—116°C.

3 ml of chloro - acetyl chloride and an equivalent amount of 3 - *N* sodium hydroxide were introduced in small portions into a stirred, cooled solution (10°—15°C) of 9.15 g of 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone *alpha*oxime in 45 ml of dioxan. The chloro - acetyl chloride and sodium hydroxide were added alternately at a rate sufficient to keep the temperature below 15°C and the mixture neutral or slightly alkaline. After 30 minutes, the mixture was acidified to pH 5 with dilute hydrochloric acid, diluted with water and extracted with ether. The ether extract was dried, concentrated *in vacuo* and the oily residue crystallized by the addition of ether. The product, 2 - chloro - acetamido - 5 - bromo - 4¹ - methyl - benzophenone *alpha*oxime, crystallized from dioxan in the form of colourless prisms melting at 179°—180°C.

A solution of 3 g of 2 - chloro - acetamido - 5 - bromo - 4¹ - methyl - benzophenone *alpha*-oxime in 25 ml of boiling acetic anhydride was cooled to 75°C and saturated with hydrogen chloride. The mixture was left at *ca* 20°C for 30 minutes, again heated for 2 hours at 75°C, again saturated with hydrogen chloride and concentrated *in vacuo*. The residue was crystallized from a mixture of methylene chloride/(petroleum ether) forming yellow needles of 6 - bromo - 2 - chloromethyl - 4 - (*p* - tolyl) - quinazoline 3 - oxide, melting at 162°—164°C.

20 g of 6 - bromo - 2 - chloromethyl - 4 - (*p* - tolyl) - quinazoline 3 - oxide were added in portions at 0°C to 150 ml of a 50% (wt/vol) solution of methyl amine in methanol. The reaction mixture was stirred at *ca* 20°C for one hour, then cooled to 5°C and filtered. The reaction product remaining on the filter, 7 - bromo - 2 - methylamino - 5 - (*p* - tolyl) - 3H - 1,4 - benzodiazepine 4 - oxide, was recrystallized from ethanol forming yellow prisms melting at 255°—256°C.

3 g of 7 - bromo - 2 - methylamino - 5 - (*p* - tolyl) - 3H - 1,4 - benzodiazepine 4 - oxide were dissolved in a mixture of 16 ml. of pyridine and 16 ml of acetic anhydride and the solution was left to stand at *ca* 20°C for 16 hours. Some of the starting material precipitated out and was filtered off, and the mother liquor was then concentrated *in vacuo* and crystallized by the addition of ether, petroleum ether and acetone. After recrystallization from a mixture of acetone/(petroleum ether), the product, 7 - bromo - 2 - (N - methylacetamido) - 5 - (*p* - tolyl) - 3H - 1,4 - benzodiazepine 4 - oxide, formed colourless needles melting at 209°—210°C.

3 ml of 1 - *N* hydrochloric acid were added at *ca* 20°C to a solution of 1.2 g (3 mmol) of 7 - bromo - 2 - (N - methylacetamido) - 5 - (*p* - tolyl) - 3H - 1,4 - benzodiazepine 4-oxide in 30 ml of ethanol. The mixture was heated under reflux for one hour, partly concentrated *in vacuo* and diluted with ice-water. The crystalline reaction product precipitated out, was filtered off and recrystallized from a mixture of methylene chloride/(petroleum ether). The 7 - bromo - 5 - (*p* - tolyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide formed colourless plates melting at 237°—238°C.

EXAMPLE 9

To 500 g of molten *p* - chloro - aniline heated to 120°C were added with stirring 750 ml of *p*-chloro-benzoyl chloride, causing a violent evolution of hydrogen chloride. The mixture then solidified and was melted by heating to 200°C. At this temperature, 500 g of anhydrous zinc chloride were introduced. The stirring was continued and the mixture heated at 230°—242°C for 2 hours. It was then poured into one litre of 0.5 - *N* hydrochloric acid. The precipitated solid was filtered off, pulverized, suspended in one 1 of 0.5 - *N* hydrochloric acid and heated under reflux for one hour. The mixture was then cooled. The resinous material was filtered off and dissolved in a mixture of 14 1 of acetic acid and 3 1 of concentrated hydrochloric acid. The solution was heated under reflux for 18 hours and concentrated *in vacuo*. The residue was dissolved in 4 1 of benzene and stirred with an excess of sodium hydroxide. The precipitated sodium *p* - chloro - benzoate was filtered off and the aqueous layer discarded. The benzene layer was dried and concentrated to obtain the crude product. The 2 - amino - 4¹,5 - dichloro - benzophenone was crystallized from ethanol to obtain yellow needles melting at 118°—119°C.

A solution of 169 g of 2 - amino - 4¹,5 - dichloro - benzophenone and 73 g of hydroxylamine hydrochloride in 730 ml of ethanol was heated under reflux for 16 hours. The solu-

tion was concentrated *in vacuo*. The residue was diluted with water and ether and neutralized with 40% (wt/vol) sodium hydroxide aqueous solution. The ether layer was separated, dried over sodium sulphate and concentrated *in vacuo*. The residue was dissolved in 100 ml of benzene and crystallized by the gradual addition of about 2 l of petroleum ether. The crystalline slurry was cooled for 14 hours at 5°C. The so precipitated crude 2 - amino - 4¹,5 - dichloro - benzophenone oxime was dissolved in 900 ml of boiling benzene and treated with charcoal. The hot mixture was filtered and the oxime crystallized by the addition of 1000 ml of petroleum ether. After crystallization from a mixture of benzene/(petroleum ether), the pure *alpha*oxime was obtained in the form of colourless prisms, melting at 151°—154°C.

15 ml of chloro - acetyl chloride were added over a period of 0.5 hour to a solution of 28 g of 2 - amino - 4¹,5 - dichloro - benzophenone *alpha*oxime in 250 ml of glacial acetic acid at 50°C. The mixture was left at *ca* 20°C for 14 hours and then concentrated *in vacuo*. The residue was dissolved in hot methylene chloride and washed with ice-cold sodium hydroxide and water. The organic layer was separated, dried and concentrated *in vacuo* to about 300 ml. It was then diluted with 600 ml of petroleum ether and cooled. The reaction product, 6 - chloro - 2 - chloromethyl - 4 - (4 - chloro - phenyl) - quinazoline 3 - oxide, crystallized in fine yellow needles melting at 163°—164°C.

27 g of 6 - chloro - 2 - chloromethyl - 4 - (4 - chloro - phenyl) - quinazoline 3 - oxide were added in portions at 0°C to 150 ml of a 50% (wt/vol) solution of methyl amine in methanol. The reaction mixture was stirred at *ca* 20°C for 19 hours, then cooled to 5°C for 6 hours and filtered. The reaction product remaining on the filter was recrystallized from ethanol to obtain yellow prisms of 7 - chloro - 2 - methylamino - 5 - (4 - chloro - phenyl) - 3H - 1,4 - benzodiazepine 4 - oxide melting at 254°—255°C.

40 ml of acetic anhydride were added at *ca* 20°C to a solution of 6 g of 7 - chloro - 2 - methylamino - 5 - (4 - chloro - phenyl) - 3H - 1,4 - benzodiazepine 4 - oxide in 50 ml of pyridine. After 15 hours, a small amount of starting material which had precipitated out was filtered off. The solution was then concentrated *in vacuo* to a small volume, diluted with methylene chloride and washed with ice-cold dilute sodium hydroxide and acid. The methylene chloride solution was then dried, concentrated *in vacuo* and the residue crystallized from acetone. The product, 7 - chloro - 2 - (N - methylacetamido) - 5 - (4 - chloro - phenyl) - 3H - 1,4 - benzodiazepine 4 - oxide, formed colourless plates melting at 191°—192°C.

4 ml of 1 - *N* hydrochloric acid were added at *ca* 20°C to a solution of 1.4 g (4 mmol) of 7 - chloro - 2 - (N - methylacetamido) - 5 - (4 - chloro - phenyl) - 3H - 1,4 - benzodiazepine 4 - oxide in 30 ml of ethanol. The mixture was heated under reflux for one hour, partly concentrated *in vacuo* and diluted with ice-water. The crystalline reaction product, 7 - chloro - 5 - (4 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, was filtered off and recrystallized from methanol in the form of colourless plates melting at 250°—252°C.

Example 10

A mixture of 22 g (100 mmol) of 2 - amino - 5 - methyl - benzophenone, 21 g (150 mmol) of glycine ethyl ester hydrochloride and 120 ml of pyridine was heated under reflux. After one hour, 10 ml of pyridine were distilled off. The reaction mixture was then heated under reflux for 15 hours, concentrated *in vacuo* to a syrup and diluted with ether and water. Part of the product crystallized out and was filtered off. The ether layer was separated, concentrated *in vacuo* and the residual crude oil treated again with 21 g of glycine ethyl ester hydrochloride in boiling pyridine for 20 hours. The mixture was worked up to obtain additional reaction product. The combined product was treated with activated charcoal in boiling ethanol, concentrated and crystallized from acetone to obtain colourless prisms of 7 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 209°—210°C.

Example 11

A mixture of 50 g of 2 - benzamido - 3,5 - dimethyl - benzophenone, 170 ml of glacial acetic acid, 215 ml of concentrated sulphuric acid, and 115 ml of water was heated under reflux for 4 hours, cooled, made alkaline with sodium hydroxide solution, diluted with ice and extracted with ether. The ether solution was dried and concentrated *in vacuo*. The residue, a yellow oil, solidified after two weeks and was then recrystallized from petroleum ether. The 2 - amino 3,5 - dimethyl - benzophenone crystallized in heavy yellow plates melting at 68°—70°C.

A mixture of 39 g of 2 - amino - 3,5 - dimethyl - benzophenone, 40 g of glycine ethyl ester hydrochloride and 200 ml of pyridine was heated under reflux. After 5 hours, 10 ml of pyridine were distilled off and an additional 36 g of glycine ethyl ester hydrochloride added. The reaction mixture was then heated under reflux for 15 hours, concentrated *in vacuo* and diluted with ether and water. The ether layer was washed with water, separated, concentrated *in vacuo*, the residual crude oil dissolved in ether and left to crystallize. The material was purified by treatment with charcoal and ethanol and crystallized from acetone to obtain 7,9 - dimethyl - 5 - phenyl - 2,3 -

dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 210°—211°C.

EXAMPLE 12

A solution of 60.2 g of 2 - acetamido - 5 - chloro - benzophenone in a mixture of 137 ml of acetic acid and 82 ml of nitric acid was saturated with hydrogen chloride. The mixture was left at *ca* 20°C for one hour and then diluted with water and extracted with methylene chloride. The methylene chloride solution was washed with water, dried and concentrated *in vacuo*. The residue was dissolved in ether and crystallized by the addition of petroleum ether to obtain colourless prisms of 2 - acetamido - 3,5 - dichloro - benzophenone melting at 143°—144°C.

A mixture of 72 g of this ketone, 600 ml of ethanol and 600 ml of concentrated hydrochloric acid was heated under reflux for 3 hours, then diluted with ice, made alkaline with dilute sodium hydroxide and extracted with ether. The ether solution was dried and concentrated. The product, 2 - amino - 3,5 - dichloro - benzophenone, was crystallized from a mixture of ether/(petroleum ether) forming yellow prisms melting at 93°—94°C.

A mixture of 18.5 g of 2 - amino - 3,5 - dichloro - benzophenone, 14 g of glycine ethyl ester hydrochloride and 150 ml of pyridine was heated under reflux. After 3 hours, 20 ml of pyridine were distilled off and 14 g of glycine ethyl ester hydrochloride added. The reaction mixture was heated under reflux for an additional 15 hours, concentrated *in vacuo* and then diluted with ether and water. The reaction product, 7,9 - dichloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), crystallized out, was filtered off and recrystallized from acetone, melting point 207°—208°C.

EXAMPLE 13

A mixture of 11 g (41 mmol) of 2 - amino - 4¹,5 - dichloro - benzophenone, 8.3 g (60 mmol) of glycine ethyl ester hydrochloride and 200 ml of pyridine was heated under reflux. After 3 hours, 20 ml of pyridine were distilled off and 8.3 g of glycine ethyl ester hydrochloride added. The reaction mixture was then heated under reflux for an additional 15 hours, concentrated *in vacuo* and diluted with ether and water. The reaction product, 7 - chloro - 5 - (4 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), crystallized out, was filtered off, decolorized by treatment with activated charcoal and ethanol and recrystallized from ethanol, melting point 247°—248°C.

EXAMPLE 14

A mixture of 11.6 g (40 mmol) of 2 - amino - 5 - bromo - 4¹ - methyl - benzophenone, 8.3 g (60 mmol) of glycine ether ester hydrochloride and 200 ml of pyridine was heated under reflux. After 5 hours, 10 ml of pyridine were distilled off. The reaction mixture was heated under reflux for an additional 15 hours, concentrated *in vacuo* and then diluted with ether and water. Part of the product crystallized out and was filtered off. The ether layer was separated, concentrated *in vacuo* and the residual crude oil treated again with 6.3 g of glycine ethyl ester hydrochloride in 100 ml of boiling pyridine for 20 hours. The mixture was worked up to obtain additional reaction product. The product, 7 - bromo - 5 - (*p* - tolyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was decolorized by treatment with charcoal in boiling ethanol and crystallized from acetone, melting point 239°—240°C.

EXAMPLE 15

14 g (65 mmol) of α - bromo - propionyl bromide and an equivalent amount of 3 - *N* sodium hydroxide were introduced in small portions into a stirred, cooled (10°C) solution of 11.6 g (50 mmol) of 2 - amino - 5 - chloro - benzophenone in 200 ml of dioxan. The α - bromo - propionyl bromide and sodium hydroxide were introduced alternately at such a rate as to keep the temperature below 10°C and the mixture neutral or slightly alkaline. The reaction was completed after 30 minutes. The final pH of the solution was neutral. The mixture was diluted with ice and water, then extracted with methylene chloride. The extract was washed with water, dried and concentrated *in vacuo*. The gummy residue was crystallized from a mixture of ether/(petroleum ether). The 2 - (α - bromo - propionamido) - 5 - chloro - benzophenone was recrystallized from ether/(petroleum ether) in the form of colourless needles, melting point 114°—115°C.

3 g of 2 - (α - bromo - propionamido) - 5 - chloro - benzophenone were dissolved in 100 ml of methanolic ammonia at *ca* 20°C. After 4 days, the clear amber solution was concentrated to dryness *in vacuo* and the residue partitioned between 100 ml of ether and 100 ml of water. Some reaction product was filtered off and two further crops were obtained from the ether solution on concentration. The product, 7 - chloro - 3 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was crystallized from a mixture of benzene/(petroleum ether), melting point 220°—221°C.

EXAMPLE 16

1.08 g. (0.02 mol) of sodium methoxide were added to a solution of 5.4 g (0.02 mol) of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide and 300 ml of benzene. 100 ml of benzene were distilled off in order to remove the liberated methanol. Then 1.73 ml (0.02 mol) of allyl bromide were added. The solution was heated under reflux for 2.5 hours, then washed with

water, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue, 7 - chloro - 1 - allyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, crystallized from a mixture of acetone/(petroleum ether) in colourless plates, melting point = 150°—151°C.

EXAMPLE 17

A mixture of 3 g (0.01 mol) of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, 30 ml of chloroform and 1 ml of phosphorus trichloride was heated under reflux for 1 hour. The reaction mixture was then poured on ice and stirred with an excess of a 40% (wt/vol) sodium hydroxide aqueous solution. The chloroform was then separated, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was dissolved in methylene chloride and crystallized by the addition of petroleum ether. The product, 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was recrystallized from a mixture of acetone/(petroleum ether) forming colourless plates melting at 125°—126°C.

EXAMPLE 18

A mixture of 22.5 g of 2 - amino - 4,5 - dimethyl - benzophenone (0.1 mol), 21 g of glycine ethyl ester hydrochloride (0.15 mol) and 300 ml of pyridine was heated under reflux. After one hour 20 ml of pyridine were distilled off and an additional 21 g (0.15 mol) of glycine ethyl ester hydrochloride added. The reaction mixture was then heated under reflux for 15 hours, concentrated partly at atmospheric pressure and then *in vacuo*. Ether and water were added to the residue and the crude, crystalline 7,8 - dimethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) which precipitated was filtered off. After recrystallization from methanol, the product was obtained in the form of colourless prisms melting at 255°—256°C.

EXAMPLE 19

A mixture of 27.6 g of 2 - amino - 5 - bromo - benzophenone (0.1 mol), 21 g of glycine ethyl ester hydrochloride (0.15 mol) and 300 ml of pyridine was heated under reflux. After one hour, 21 ml of pyridine were distilled off and then an additional 21 g (0.15 mol) of glycine ethyl ester hydrochloride added. The reaction mixture was then heated under reflux for 15 hours, concentrated partly at atmospheric pressure and then *in vacuo*. Ether and water were added to the residue and the crude crystalline 7 - bromo - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) was filtered off. After recrystallisation from acetone, the product formed colourless prisms melting at 220°—221°C.

EXAMPLE 20

2 g of 2 - amino - 5 - trifluoromethyl - benzophenone [prepared as described in the specification of our copending application for Letters Patent no: 40979/62 (now serial no: 972,973)] in 5 ml of pyridine were heated under reflux for 1 - 1.5 hours with 2.0 g of glycine ethyl ester hydrochloride. Thereafter an additional 1.0 g of glycine ethyl ester hydrochloride in 2 ml of pyridine were added. Then 3 ml of the solvent were distilled off. Heating under reflux was continued for an additional 2 - 2.5 hours. The reaction mixture was extracted with benzene, the organic layer washed with water and dried over sodium sulphate. After evaporation of the solvent, a crude oil was obtained. This was dissolved in hexane. After standing for 2 days at 0°C, the precipitated pure crystalline 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) was filtered off. It melted at 198°—199°C.

By using *alpha*alanine methyl ester hydrochloride instead of the glycine ethyl ester hydrochloride, 7 - trifluoromethyl - 3 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) is obtained.

EXAMPLE 21

13.3 g of 2 - amino - 5 - trifluoromethyl - benzophenone [prepared as described in the specification of our copending application no. 40979/62 (now serial no. 972,973)] in 60 ml of ethanol were heated under reflux for 24 hours with 6 g of hydroxylamine hydrochloride. The reaction mixture was adjusted to about pH 6 by the addition of a solution of 12 g of sodium acetate in 100 ml of water. The mixture was then extracted with ether to yield an oil which, after repeated crystallization from a mixture of ether/hexane, gave 2 - amino - 5 - trifluoromethyl - benzophenone oxime melting at 175°—177°C.

2.8 g of 2 - amino - 5 - trifluoromethyl - benzophenone oxime obtained above were dissolved in 15 ml of acetic acid and, after addition of 1.5 ml of chloro - acetyl chloride, kept for 1 hour at 20°C, then for 2 hours at 70°C. The mixture was diluted with ether and washed with water. The ether solution was concentrated *in vacuo* and gave a solid residue which was crystallized from methylene chloride/ether to yield pure, yellow 2 - chloromethyl - 4 - phenyl - 6 - trifluoromethyl - quinazoline 3 - oxide, melting point = 149°—150°C.

538 mg of 2 - chloromethyl - 4 - phenyl - 6 - trifluoromethyl - quinazoline 3 - oxide were dissolved in 20 ml of ethanol and, after the addition of 5 ml of 3 - *N* sodium hydroxide, the solution was kept for 4 hours at 25°C. After acidification with 6 ml of 3 - *N* hydrochloric acid, the reaction product was extracted

with ether. The ether solution was concentrated *in vacuo* and the residue crystallized from benzene to yield pure 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, melting point = 211°—212°C.

1.60 g of 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide were dissolved in 60 ml of benzene, containing 0.30 g of sodium methoxide. After the addition of a solution of 0.50 ml of dimethyl sulphate in 20 ml of benzene, the reaction mixture was heated under reflux for 1 hour and then cooled. The organic layer was separated, washed with water and dried over sodium sulphate. Evaporation of the solvent *in vacuo* yielded an amorphous crude product which was crystallized from ether/hexane to give pure 1 - methyl - 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, in the form of small prisms, melting point = 177°—180°C.

1.0 g of 1 - methyl - 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide was dissolved in 20 ml of chloroform. After addition of 0.3 ml of phosphorus trichloride, the solution was heated under reflux for 0.5 hour. The reaction mixture was diluted with ether and washed with sodium bicarbonate solution and water. After drying over sodium sulphate the solvent was evaporated *in vacuo* to give 1 - methyl - 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) as the residue.

EXAMPLE 22

100 g of 2 - nitro - 4 - trifluoromethyl - benzonitrile were dissolved in 2.5 l of methanol and hydrogenated at atmospheric pressure in the presence of 20 g of wet RANEY - nickel catalyst. The reaction was continued until 3 molar proportions of hydrogen were absorbed. The catalyst was filtered off and the methanol solution evaporated to dryness. The residue was crystallized from a mixture of ether/(petroleum ether). The 4 - trifluoromethyl - anthranilamide formed colourless needles melting at 151°—152°C.

68.5 g of this amide were heated under reflux with 700 ml of a 50% (wt/vol) sulphuric acid solution in water for one hour and poured on to ice. The precipitated reaction product was filtered off and washed with water. The 4 - trifluoromethyl - anthranilic acid was crystallized from a mixture of ethanol/water and then melted at 175°C.

A solution of 23 g of the product in 150 ml of acetic anhydride was heated under reflux for one hour. Then the solvent was removed by distillation under reduced pressure and the residue crystallized from benzene/hexane to obtain 2 - methyl - 7 - trifluoromethyl - 4H - 3,1 - benzoxazinone - (4), melting point = 68°—70°C.

A solution of phenyl magnesium bromide (prepared from 2.4 g of magnesium, 15.2 g of bromo - benzene and 150 ml of ether) was added to a solution of 18 g of 2 - methyl - 7 - trifluoromethyl - 4H - 3,1 - benzoxazinone - (4) in 100 ml of benzene while stirring and cooling with ice. The GRIGNARD reagent was added slowly over a period of one hour. After stirring for one additional hour at 5°C, the reaction mixture was treated with ice and ammonium chloride. The crude reaction product was extracted with ether. The ether extract was concentrated *in vacuo* and the residue heated under reflux for 1 hour with a mixture of 100 ml of 3 - *N* sodium hydroxide and 100 ml of methanol. The reaction mixture was extracted with benzene. The benzene extract was concentrated *in vacuo* and the residual, crude 2-amino-4-trifluoromethyl-benzophenone dissolved in hexane and purified by chromatography using a 20 fold amount of neutral alumina (BROCKMANN activity grade III). Elution with a mixture of hexane/ether (1:1) and evaporation yielded yellow 2 - amino - 4 - trifluoromethyl - benzophenone which was recrystallized from hexane, melting point 55°—56°C.

2 g of the product obtained were reacted with 2.0 g of glycine ethyl ester hydrochloride in pyridine as described in Example 20. The crude reaction product was crystallized from ether/hexane to yield pure 8 - trifluoromethyl-5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 186°—186.5°C.

By following the procedure described in Example 21 but using a 2 - amino - 4 - trifluoromethyl - benzophenone as the starting material, 8 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide is obtained.

EXAMPLE 23

42 g (0.15 mol) of 2 - amino - 5 - methylmercapto - benzophenone [prepared as described in the specification of our copending application no: 40978/62 (now serial no: 972,972)] were heated with 40 g (0.29 mol) of glycine ethyl ester hydrochloride in 75 ml of pyridine at 118°—120°C for 6 hours. The pyridine was distilled off slowly and fresh pyridine added to maintain a constant volume. At the end of the heating period, the mixture was concentrated *in vacuo* and the residue partitioned between 500 ml of benzene and 200 ml of water. The desired product was precipitated from the benzene phase by the addition of skellysolve B and filtered off. The product, 7 - methylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), crystallized from acetone in yellow needles melting at 216°—218°C.

EXAMPLE 24

20 g (0.078 mol) of 2 - amino - 5 - ethylmercapto - benzophenone [prepared as

described in the specification of our copending application for Letters Patent no: 40978/62 (now serial no: 972,972)] were heated with 20 g of glycine ethyl ester hydrochloride in 75 ml of pyridine at 114°C for 5.5 hours. Part of the pyridine was distilled off and replaced with fresh pyridine. The reaction mixture was then concentrated *in vacuo* and the residual oil partitioned between 200 ml of benzene and 200 ml of water. The benzene phase was concentrated and the residue dissolved in 200 ml of acetone. The product thus obtained, 7 - ethylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was isolated as the hydrochloride by the addition of 15 ml of 20% (wt/vol) hydrogen chloride in *iso*propanol.. The pure material, 7 - ethylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) hydrochloride, crystallized in yellow needles from acetonitrile/ethanol; melting point 273°C.

EXAMPLE 25

23 g (0.081 mol) of 2 - amino - 5 - butylmercapto - benzophenone [prepared as described in specification of our copending application for Letters Patent no: 40978/62 (now serial no: 972,972)] were heated with 25 g (0.10 mol) of glycine ethyl ester hydrochloride in 75 ml of pyridine at 118°C for 3 hours. An additional 10 g of the glycine ester hydrochloride were added and the heating was continued for 6 hours. Part of the pyridine was distilled off and replaced by fresh pyridine to maintain a constant volume. At the end of the heating period, the reaction mixture was concentrated to dryness *in vacuo* and the residue partitioned between benzene and water. The benzene phase was evaporated to dryness to leave crude 7 - butylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2). This crude residue was dissolved in about 200 ml of hot acetone. Addition of 20% (wt/vol) hydrogen chloride in *iso*propanol yielded the product 7 - butylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) hydrochloride. The pure substance crystallized from a mixture of acetonitrile/ethanol in yellow needles melting at 247°—249°C.

EXAMPLE 26

33 g (0.12 mol) of 2 - amino - 5 - hydroxyethylmercapto - benzophenone [prepared as described in the specification of our copending application for Letters Patent No. 40978/62 (now serial no: 972,972)] were heated with 35 g (0.25 mol) of glycine ethyl ester hydrochloride in 75 ml of pyridine at 117°C for 6 hours. Part of the pyridine was distilled off and replaced by fresh pyridine in order to keep the volume constant. The mixture was concentrated *in vacuo* and the residue partitioned between benzene and water. The benzene phase was evaporated to dryness and the residue taken up in acetone. The acetone solution was passed through a 0.5 x 16 in. alumina column. Three 50 ml fractions were collected. The middle fraction was concentrated *in vacuo* to give crude 7 - hydroxyethylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2). After dissolving in benzene, the crude product was treated with *iso*propanolic hydrogen chloride. The 7 - hydroxyethylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) hydrochloride thus obtained was crystallized from *iso*propanol/ethanol to obtain the pure product in yellow prisms melting at 252°—253°C (with decomposition).

EXAMPLE 27

16 g of (0.058 mol) of 2 - amino - 5 - methylsulphonyl - benzophenone [prepared as described in the specification of our copending application for Letters Patent no: 40978/62 (now serial no: 972,972)] were heated with 30 ml of pyridine and 12.5 g (0.089 mol) of glycine ethyl ester hydrochloride at 121°—128°C for 4.5 hours. The pyridine was slowly distilled off and replaced with fresh pyridine to keep the volume constant. A total of 110 ml of distillate was collected.

The reaction mixture was then concentrated *in vacuo* to a syrup and stirred with a mixture of 100 ml of benzene and 100 ml of water at 70°C for 0.5 hour. The mixture was then cooled and the precipitated product filtered off. The pure 7 - methylsulphonyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) formed yellow needles on crystallization from acetone/(Skellysolve B) melting at 256°—258°C.

EXAMPLE 28

46 g of (0.2 mol) of 2-amino-5-chlorobenzophenone were added to 120 ml of sulphur monochloride. The reaction mixture was heated at 60°—65°C for 2 hours. After the addition of 200 ml of toluene and stirring for 1.5 hours, the mixture was filtered on a fritted glass funnel. The precipitate was filtered off, washed with toluene and carbon tetrachloride and sucked dry. The 4 - benzoyl - 6 - chloro - 2,3,1 - benzothiazathiolium chloride thus obtained [see PATTERSON, "Ring Index," page 140, system 1051, for numbering system adopted] was added to 100 g of ice. 1 l of water was then added and the suspension stirred for 2 hours. The solid material was filtered off and introduced at 40°C into a mixture of 100 ml of ethanol, 100 ml of water, 100 ml of 40% (wt/vol) sodium hydroxide and 6 g of sodium dithionite. The reaction mixture at this point gave a blue colour with INDANTHRENE - yellow paper [the word 'Indanthrene' being a registered trade mark], indicating an excess of sodium dithionite. 20 ml of dimethyl sulphate were then added dropwise while the temperature rose to 47°C.

The methylation was then completed as shown by a negative reaction with lead acetate.

The reaction mixture was diluted with 100 ml of water, stirred for 2 hours and the oily hioether extracted with 3 portions of 200 ml f benzene. The benzene phase was dried and concentrated *in vacuo* to give the oily reaction product, 2 - amino - 5 - chloro - 3 - methylmercapto - benzophenone. The same product was also obtained by the following procedure:

2 - amino - benzophenone was dissolved in acetone with the addition of a saturated solution of hydrogen choride in *iso*propanol until acid to congo red. The precipitated 2 - amino - benzophenone hydrochloride was filtered, washed with cold acetone and sucked dry.

7 g (0.024 mol) of the foregoing hydrochloride were added to 80 ml of sulphur monochloride. After the addition of 1 g of aluminium chloride and 10 ml of glacial acetic acid, the reaction mixture was stirred for 3 hours at 60°—80°C. The mixture was then stirred with 200 ml of toluene for 4 hours and the thiazathiolium compound filtered off, washed with toluene, carbon tetrachloride and finally sucked dry. This product was added to 100 g of crushed ice, diluted with 1 l of water and the resulting suspension stirred for 2 hours. The material was then filtered off and added at 42°C to a mixture of 50 ml of water, 50 ml of ethanol, 50 ml of 40% (wt/vol) sodium hydroxide and 10 g of sodium dithionite. The mixture at this point gave a blue colour with INDANTHRENE - yellow paper (the word 'Indanthrene' being a registered trade mark], indicating an excess of sodium dithionite. 10 ml of dimethyl sulphate were then added dropwise while the temperature rose to 54°C. The lead acetate reaction was negative at this point, indicating the completion of the methylation. The reaction mixture was diluted with 200 ml of water, stirred for 0.5 hour and the oily thioether extracted with three 150 ml portions of benzene. The benzene phase was dried and after concentration *in vacuo* yielded the same oily reaction product.

38 g (0.14 mol) of 2 - amino - 5 - chloro - 3 - methylmercapto - benzophenone were heated with 40 g (0.28 mol) of glycine ethyl ester hydrochloride in 75 ml of pyridine at 121°C. The pyridine was distilled off slowly and replaced by fresh pyridine to keep the volume constant. After 5 hours the reaction mixture was allowed to cool to 80°C and 15 g of glycine ethyl ester hydrochloride were added. Heating was resumed for 3 hours. The reaction mixture was concentrated to dryness *in vacuo* and the residue partitioned between 100 ml of water and 100 ml of benzene. The greenish material which separated was filtered off and dried. The product, 7 - chloro - 9 - methylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), crystallized in yellow needles from acetonitrile/ethanol, melting point 189°—191°C.

EXAMPLE 29

78 g (0.32 mol) of 2 - amino - 5 - methylmercapto - benzophenone [prepared as described in the specification of our copending application no. 40978/62 (now serial no. 972,972)] were heated under reflux for 16 hours with 37 g (0.53 mol) of hydroxylamine hydrochloride in 400 ml of ethanol. After evaporating to dryness *in vacuo*, the residue was taken up in 125 ml of water. Careful addition of 40 ml of 40% (wt/vol) sodium hydroxide and 25 ml of 20% (wt/vol) sodium carbonate, followed by 20 ml of glacial acetic acid made the mixture slightly acid to litmus. 125 ml of ether and 125 ml of Skellysolve B were then added and the mixture was kept in a refrigerator for 16 hours. The supernatant liquid was decanted and the gummy precipitate was dissolved in 500 ml of ether. After washing with water, the ether solution was dried over sodium sulphate. It was then concentrated *in vacuo* to an oil which, on treatment with 200 ml of ether and 100 ml of Skellysolve B, yielded crystalline 2 - amino - 5 - methylmercapto - benzophenone oxime. The pure oxime crystallized in yellow needles from dilute ethanol and melted at 149°—150°C.

15.5 g (0.06 mol) of 2 - amino - 5 - methylmercapto - benzophenone oxime were dissolved in 150 ml of glacial acetic acid at 40°C. 9.5 ml (14 g = 0.125 mol) of chloroacetyl chloride were added at 55°—60°C. The reaction mixture was stirred at 50°—60°C for 0.5 hour and then at *ca* 20°C for 4 hours. The solution was concentrated *in vacuo* and the resulting oily residue was dissolved in 150 ml of boiling methylene chloride. The solution was cooled and diluted with about 150 g of crushed ice. 1 - *N* sodium hydroxide was added with stirring until the mixture was alkaline to phenolphthalein. The methylene chloride phase was separated and dried over sodium sulphate. Concentration of the methylene chloride solution to incipient crystallization gave the product, 6 - methylmercapto - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide. The pure substance crystallized from methylene chloride in yellow needles, melting point 155°—156°C.

12 ml (0.12 mol) of 1 - *N* sodium hydroxide were added dropwise to a suspension of 3.2 g (0.01 mol) of 6 - methylmercapto - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide in 20 ml of ethanol. The mixture was warmed to 45°C and then cooled to 25°C. 10 ml of acetone were added and the reaction mixture was stirred for 3 hours, then left at *ca* 20°C for 15 hours. The mixture was cooled in ice, the precipitate filtered off, washed with a small amount of cold ethanol and dried. The

pure product, 7 - methylmercapto - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide, crystallized in needles from water (containing a few drops of alcohol), melting point 191°—193°C.

EXAMPLE 30

A mixture of 16.8 g of 2 - amino - benzophenone, 11.9 g of glycine ethyl ester hydrochloride and 200 ml of pyridine was heated under reflux. After 1 hour, 20 ml of pyridine were distilled off. The solution was heated under reflux for 15 hours, 11.9 g of glycine ethyl ester hydrochloride were added and the heating under reflux continued for an additional 4 hours. The reaction mixture was concentrated *in vacuo*, then diluted with ether and water. The reaction product, 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), crystallized out, was filtered off and recrystallized from acetone in the form of colourless rhombic prisms, melting point = 182°—183°C.

Nitration can be performed as follows:

A. 48 g (0.2 mol) of 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) was dissolved in 250 ml of concentrated sulphuric acid by stirring at 15°C for 0.5 hour. The solution was then cooled to 0°C and a mixture of 9.1 ml of fuming nitric acid (90%; specific gravity = 1.50) and 11.8 ml of concentrated sulphuric acid was added dropwise with stirring, keeping the temperature of the reaction mixture between −5°C and 0°C. After completion of the addition of the nitric acid/sulphuric acid mixture, stirring was continued for 1 hour and the reaction mixture kept in a refrigerator for 16 hours.

The mixture was then added dropwise to 2 kg of crushed ice with stirring and cooling (keeping the temperature at 0°C). After stirring for 1 hour in the cold, 640 ml of concentrated ammonium hydroxide were added dropwise at 0°C to pH 8. Stirring was continued for 0.5 hour and the crude product filtered off, washed with a small amount of ice-water and sucked dry for 16 hours. The crude product was suspended in a mixture of 100 ml of methylene chloride and 1700 ml of ethanol. 50 g of decolorizing charcoal were added and the mixture heated under reflux with stirring for 2 hours. After standing at 20°C for 16 hours, 15 g of diatomaceous earth filter aid were added and the heating under reflux was resumed for 1.5 hours. The mixture was filtered while hot. The clear, light yellow filtrate was concentrated *in vacuo* to about 600 ml on a steam-bath with stirring. The concentrate was stirred and cooled in ice for about 2 hours, the precipitated crystalline product filtered off, washed with petroleum ether and sucked dry. The product, 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was recrystallized from a mixture of 1000 ml of ethanol and 50 ml of methylene chloride to obtain white prisms melting at 224°—225°C.

B. 12 g (0.05 mol) of 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 65 ml of concentrated sulphuric acid by stirring at 10°C. The mixture was cooled to 0°C and to it was added dropwise within 1 hour, a solution of 5.3 g of potassium nitrate in 30 ml of concentrated sulphuric acid, keeping the reaction temperature below 25°C. The mixture was warmed to 50°C for 2.5 hours and then added dropwise to 500 g of crushed ice with stirring and cooling to 0°C.

After standing for 16 hours in a refrigerator the reaction mixture was neutralized to pH 8 by the dropwise addition of 260 ml of concentrated ammonia at 0°C. The crude material was filtered off, washed with ice-water, sucked dry and crystallized from 125 ml of boiling chloro - benzene. The product, 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was obtained in the form of light yellow prisms.

A suspension of 5.6 g (0.02 mol) of this product was reduced catalytically in a shaking autoclave using RANEY - nickel as catalyst at a hydrogen gauge pressure of 265 lbs. The hydrogen uptake was 100% of theory at 58°C. The catalyst was filtered off and the clear, almost colourless filtrate concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of 75 ml of acetonitrile and 25 ml of ethanol to obtain colourless prisms of 7 - amino - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) melting at 236°—239°C.

14 g (0.056 mol) of this product and 100 ml of pyridine were stirred on a water-bath at 40°C for 1 hour to obtain a fine suspension. 15 ml of acetic anhydyride were added dropwise at 10°C to 15°C with slight cooling. A clear solution resulted which was stirred at *ca* 20°C for 3 hours. After standing for 16 hours at 20°C, the slightly brown reaction mixture was evaporated to dryness *in vacuo* on a steam-bath. Several portions of ethanol were added and distilled off to remove traces of acetic anhydride. The residue was heated under reflux in 500 ml of ethanol and filtered while hot. After concentrating the filtrate to 200 ml, the pure product, 7 - acetamido - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), separated in white needles melting at 278°—279°C.

EXAMPLE 31

To a stirred suspension of 58 g (0.25 mol) of 2 - (N,N - dimethyl - formamidino) - benzoic acid hydrochloride in 750 ml of chloro - benzene was added in portions 60 g of phosphorus pentachloride. The mixture was heated on a steam-bath for 2 hours and cooled in ice to 10°C. 135 g of aluminium chloride were added in 4 portions keeping the temperature

of the reaction mixture below 10°C. After completing the addition of the aluminium chloride, the mixture was heated on a steam-bath for 3 hours at 95°C.

The reaction mixture was cooled in ice and 500 g of crushed ice were added in portions, keeping the temperature below 40°C. 500 ml of 40% (wt/vol) sodium hydroxide were added dropwise again keeping the temperature of the reaction mixture below 40°C. The pH at this point was about 11. The mixture was heated on a steam-bath at 95°C for 4 hours and then cooled to 40°C. The mixture was transferred to a separating funnel and the chloro - benzene phase separated. The aqueous phase was extracted with three 100 ml portions of chloro - benzene and the combined chloro - benzene phases concentrated *in vacuo* on a steam-bath yielding an oily residue. The oil was heated under reflux with stirring in a mixture of 150 ml of ethanol, 75 ml of water and 75 ml of 10% (wt/vol) sodium hydroxide for 24 hours. The solvents were distilled off at atmospheric pressure, the mixture cooled and 500 ml of water added dropwise with stirring. After standing in a refrigerator for 16 hours, the solid yellow product, 2 - amino - 4[1] - chloro - benzophenone, was filtered off, sucked dry, dried *in vacuo* at *ca* 20°C over sodium hydroxide, then crystallized from 200 ml of hot ethanol in the form of yellow needles, melting point 98°—99°C.

A stirred mixture of 15.5 g (0.067 mol) of 2 - amino - 4[1] - chloro - benzophenone, 35 ml of pyridine and 15 g (0.1 mol) of glycine ethyl ester hydrochloride was slowly distilled at 115°—120°C. The pyridine was slowly distilled off and replaced dropwise by fresh pyridine to keep the volume constant. After 5 hours, the reaction mixture was concentrated to dryness *in vacuo*. The residue was heated on a steam-bath with 50 ml of benzene and 50 ml of water. The extract was decanted and the residue was re-extracted with 50 ml of benzene and 50 ml of water. The insoluble brown precipitate was filtered off and sucked dry. The crude product, 5 - (*p* - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), was recrystallized twice from ethanol to obtain white plates melting at 262°—263°C.

33 g (0.12 mol) of 5 - (*p* - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 158 ml of concentrated sulphuric acid by stirring for 0.5 hour. The solution was cooled to 0°C and a mixture of 6.1 ml of 90% (wt/vol) fuming nitric acid (specific gravity = 1.50) and 7.3 ml of concentrated sulphuric acid was added dropwise at −5°C to 0°C. After an additional stirring period of 2 hours in the cold, the reaction mixture was added dropwise to 750 g of crushed ice with stirring at 0°C. The suspension was neutralized by the dropwise addition of 390 ml of ammonium hydroxide at 0°C. The crude yellow product was filtered off, washed with 1 l of ice-water and sucked dry for 16 hours.

Purification was carried out by heating the crude material under reflux for 2 hours in a mixture of 500 ml of ethanol, 500 ml of methylene chloride, 35 g of charcoal and 15 g of filter aid. After filtration, the light yellow filtrate was concentrated *in vacuo* to about 500 ml with stirring. Cooling of the concentrate in ice yielded the pure compound, 7 - nitro - 5 - (*p* - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), in white plates, which melted at 253°—254°C.

Example 32

A solution of 2.2 g (9.1 mmol) of 2 - amino - 4 - nitro - benzophenone in 150 ml of benzene and 30 ml of ether was treated with 0.75 ml (9.1 mmol) of bromo - acetyl bromide. After standing for 5 minutes, the solution was washed with 150 ml of water and the procedure was repeated with further quantities of bromo-acetyl bromide and water until the yellow colour of the solution had disappeared. The organic layer was washed with water until the washings were neutral, dried over sodium sulphate and concentrated *in vacuo*. The residue was crystallized, first from hexane/ether and then hexane/chloroform to give 2 - bromo-acetamido - 4 - nitro - benzophenone in the form of straw - coloured plates melting at 120°—121°C.

A solution of 2.03 g (5.6 mmol) of 2 - bromoacetamido - 4 - nitro - benzophenone in a mixture of 100 ml of ether and 50 ml of a 10% solution of ammonia in methanol (wt/vol) was allowed to stand at *ca* 20°C for 18 hours. The solution was then concentrated to dryness *in vacuo* at a water-bath temperature of 30°C. The residue was partitioned between ether/water and some insoluble material was filtered off. The ether solution was dried over sodium sulphate and concentrated *in vacuo*. The residue was extracted with hot benzene to leave undissolved material melting at 243°C (with decomposition). The two portions of insoluble material were combined and recrystallized from ethanol after treatment with charcoal to obtain colourless prisms of 8 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) melting at 252°C (with decomposition).

Example 33

A solution of 2.25 g (9.3 mmol) of 2 - amino - 5 - nitro - benzophenone in 150 ml of benzene was treated with 2 ml (18.6 mmol) of α - bromo - propionyl bromide. Dry air was blown through the solution for 1 hour until the hydrogen bromide had been removed. The solution was then concentrated *in vacuo* and the residue crystallized from ether. The 2 - (α - bromo - propionamido) - 5 - nitro - benzophenone was recrystallized from a mixture of chloroform/hexane to obtain light

straw-coloured needles melting at 116°—117°C.

A solution of 2.37 g (6.3 mmol) of 2 - (α - bromo - propionamido) - 5 - nitro - benzophenone in 40 ml of dioxan and 10 ml of a 13% solution of ammonia in methanol (wt/vol) was allowed to stand for 24 hours at *ca* 20°C. The solution was concentrated to dryness *in vacuo* and the residue paritioned between water and an ether/(methylene chloride) mixture. The organic layer was dried over sodium sulphate, treated with charcoal and then concentrated *in vacuo*. The residue was chromatographed on a 10 g alumina column using first a benzene/hexane eluant which removed the starting material and then 2 - amino - 5 - nitro - benzophenone. The column was then eluted with ether to obtain 7 - nitro - 5 - phenyl - 3 - methyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) which was isolated and melted at 219°—221°C.

EXAMPLE 34

A solution of 17.5 g of 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) in 100 ml of glacial acetic acid was hydrogenated in the presence of 1.2 g of platinum oxide at *ca* 20°C and atmospheric pressure. The hydrogen uptake stopped after three hours after absorption of one mol of hydrogen. The mixture was filtered and the solution concentrated *in vacuo* to dryness. The residue was dissolved in methylene chloride and extracted with a large volume of dilute hydrochloric acid. The methylene chloride solution was discarded and the aqueous layer cooled, made alkaline and extracted again with methylene chloride. The organic layer was dried, filtered and concentrated *in vacuo* to dryness. The residue, 5 - phenyl - 2,3,4,5 - tetrahydro - 1,4 - benzodiazepinone - (2) was crystallized from acetone, then recrystallized from a mixture of acetone/(petroleum ether) to obtain colourless needles melting at 147°—148°C.

EXAMPLE 35

5.6 g (0.02 mol) of 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) was suspended in 75 ml of methanol. 1.1 g (0.022 mol) of sodium methoxide were added with stirring. The clear yellow-brown solution was concentrated to dryness *in vacuo* giving the yellow sodium derivative. This sodium derivative was dissolved in 70 ml of N,N - dimethyl - formamide. 3.8 ml (8.52 g = 0.06 mol) of methyl iodide were added dropwise, the temperature rising to 30°C. The reaction mixture was cooled and stirred for 1.5 hours. The clear brown solution was added to about 500 ml of ice and water with stirring. The fine yellow precipitate was filtered off, washed with ice-water, sucked dry and dried *in vacuo* at 50°C over sodium hydroxide. The pure 1 - methyl - 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) crystallized in needles from dilute ethanol and melted at 156°—157°C.

EXAMPLE 36

A solution of 75 g of 2 - acetamido - 6 - chloro - benzoic acid in 300 ml of acetic anhydride was heated under reflux for one hour. The reaction mixture was then concentrated to dryness *in vacuo* and the residue crystallized from a mixture of benzene/hexane to give 5 - chloro - 2 - methyl - 4H - 3,1 - benzoxazinone - (4), melting point 142°—147°C. Recrystallization from benzene/hexane raised the melting point to 143.5°—146°C.

A GRIGNARD reagent (prepared from 23.6 g of bromo - benzene and 3.9 g of magnesium in 400 ml of ether) was slowly added to an ice-cold suspension of 29.3 g of 5 - chloro - 2 - methyl - 4H - 3,1-benzoxazinone-(4) in 450 ml of benzene and 150 ml of ether. The brown suspension gradually turned tan-yellow. The reaction mixture was stirred for one hour on an ice-bath after the addition of the GRIGNARD reagent was completed and then stirred for one hour at *ca* 20°C. After chilling to 0°C in an ice/salt-bath, the magnesium complex was decomposed by the careful addition of 250 ml of 2 - *N* hydrochloric acid. A white solid was filtered off. The organic layer was separated and washed successively with water, dilute sodium hydroxide, and water then dried over sodium sulphate and the solvent removed by distillation *in vacuo*. The residual oil of crude 2 - acetamido - 6 - chloro - benzophenone was hydrolyzed by heating under reflux for 3 hours in 500 ml of ethanol and 250 ml of 6 - *N* hydrochloric acid. After concentration to dryness *in vacuo*, the white crystalline residue was slurried with water, made alkaline with ammonia and extracted with benzene. An orange solid was obtained on evaporation of the benzene. Crystallization from hexane gave 2 - amino - 6 - chloro - benzophenone, melting point 101°—102.5°C. Recrystallization did not alter the melting point.

A solution of 8.8 g of 2 - amino - 6 - chloro - benzophenone and 8.0 g of glycine ethyl ester hydrochloride in 90 ml of pyridine was heated under reflux for one hour. About 10 ml of pyridine were distilled off and then 8.0 g of glycine ethyl ester hydrochloride and 10 ml of pyridine added. Heating under reflux was continued for a total of 11 hours. The pyridine was distilled off *in vacuo* and the residue partitioned between water and benzene. Solid material suspended between the two phases was filtered off and dried. Recrystallization from a mixture of ethyl acetate/hexane gave 6 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 243.5°—245°C. An additional crop (melting point 241°—243°C) was obtained from the benzene layer.

EXAMPLE 37

A solution of 5.0 g of 2 - amino - 3 - chloro - benzophenone and 8.8 g of glycine ethyl ester hydrochloride in 60 ml of pyridine (containing 3 drops of piperidine) was heated under reflux for 24 hours. The solvent was distilled off *in vacuo* and the residue partitioned between benzene and water. The benzene layer was dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue crystallized from benzene/hexane to give 9 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 173°—175°C. The dark product was decolorized in acetone and then crystallized from benzene/hexane to give the pure product, melting point 174.5°—176.5°C.

EXAMPLE 38

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

The water - insoluble brown mass was finally treated with a mixture of 350 ml of water, 500 ml of acetic acid and 650 ml of concentrated sulphuric acid and heated under reflux for 17 hours. After cooling the homogeneous dark solution was poured into ice-water, the mixture extracted with ether and the ether extract neutralized with 2 - *N* sodium hydroxide. Concentration of the ether solution and addition of a small amount of petroleum ether yielded yellow crystals of 2 - amino - 2^1,5 - dichloro - benzophenone (melting point = 85°—88°C). Recrystallization from ether/(petroleum ether) yielded the pure compound, melting point = 88°—89°C.

112 g of the foregoing ketone were dissolved in a solution containing 180 g of glycine ethyl ester hydrochloride in 500 ml of pyridine and 5 ml of piperidine. After heating under reflux for 18 hours, the solvents were evaporated, the residue taken up in ether and the ether extract washed with water. The ether phase was repeatedly extracted with 2 - *N* hydrochloric acid thus separating the salt of 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) from the unreacted ketone which remained in the ether and was recovered. The aqueous acidic solution was neutralized and extracted with ether to yield 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 199°—201°C (after crystallization from methanol).

15.2 g of 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 250 ml of methanol and 50 ml of a 1 - *N* solution of sodium methoxide added. The solvent was removed *in vacuo* and the residue dissolved in 50 ml of N,N - dimethyl - formamide, then 10 ml of methyl iodide were added. In a spontaneous reaction the temperature of the solution rose to 50°C. After 0.5 hour the main amount of the solvent was evaporated *in vacuo*, the residue poured into water and extracted with ether. From the ether solution crystals of 1 - methyl - 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) (melting point = 131°—133°C) were isolated. Recrystallization from methanol yielded the pure product (melting point = 135°—138°C).

EXAMPLE 39

5 g of 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were suspended in 75 ml of acetic acid with 0.5 g of platinum oxide. After uptake of 600 ml of hydrogen, the reaction was interrupted and 75 ml of acetic acid add to the reaction mixture and the catalyst filtered off. On concentration of the solution, crystals of 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3,4,5 - tetrahydro - 1H - 1,4 - benzodiazepinone - (2) were formed which, after recrystallization from acetic acid/water, melted at 235°—237°C.

EXAMPLE 40

171 g of 2 - amino - 2^1,5 - dichloro - benzophenone were dissolved in a solution of 134 g of hydroxylamine hydrochloride, 500 ml of pyridine and 5 ml of piperidine and heated under reflux for 16 hours. The solvent was removed *in vacuo*, and the residue treated with water and ether. The ether solution was repeatedly extracted with 2 - *N* hydrochloric acid. The acidic aqueous phase was neutralized and extracted with ether. After drying and concentrating the ether solution, crystals of 2 - amino - 2^1,5 - dichloro - benzophenone oxime (melting point 132°—135°C) were obtained on addition of petroleum ether. Recrystallization from benzene/(petroleum ether) gave crystals which melted at 137°—139°C.

22 g of 2 - amino - 2^1,5 - dichloro - benzophenone oxime were dissolved in 100 ml of acetic acid and then 22.5 g of chloro - acetyl chloride were added. The mixture was kept on a steam - bath for 5 hours during which time a slow stream of hydrogen chloride was passed into the flask. After concentrating the solution, the crystals which separated on cooling were filtered off. The crystals were treated with an ice - cold sodium carbonate solution and a mixture of methylene chloride and ether.

The organic phase after washing with water and concentrating gave crystals of 6 - chloro - 2 - chloro - methyl - 4 - (2 - chloro - phenyl) - quinazoline 3 - oxide which after recrystallization from methylene chloride/(petroleum ether) had a melting point of 140°—143°C.

4 g of 6 - chloro - 2 - chloromethyl - 4 - (2 - chloro - phenyl) - quinazoline 3 - oxide were dissolved in 60 ml of a 6 - *N* solution of methyl amine in methanol and kept at *ca* 20°C for 16 hours. After evaporation of the solvent the residue was taken up in methylene chloride and the solvent washed with water. Crystals of 7 - chloro - 5 - (2 - chloro - phenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine 4 - oxide were obtained having a melting point of 247°—248°C (with decomposition).

A solution of 3 g of the base in 30 ml of methanolic hydrogen chloride (0.4 - *N*) was concentrated *in vacuo*. The obtained crystals of 7 - chloro - 5 - (2 - chloro - phenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine 4 - oxide hydrochloride melted at 243°—246°C (with decomposition).

5 g of 7 - chloro - 5 - (2 - chloro - phenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine 4 - oxide were dissolved in 50 ml of ethanol and then 37 ml of 1 - *N* sodium hydroxide were added. The clear solution was left for 16 hours. The main amount of ethanol was removed *in vacuo* and the solution extracted with ether and methylene chloride. The aqueous phase was acidified with hydrochloric acid and extracted with ether in methylene chloride. The organic phase yielded crystals of 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide on evaporation, which after recrystallization from benzene/ether melted at 248°—249°C (with decomposition).

Example 41

100 g of *o* - toluoyl chloride were heated to 100°C in a three-necked flask equipped with thermometer, condenser, and mechanical stirrer. 38 g of *p* - chloroaniline were added and the mixture heated to 180°C at which temperature 54 g of zinc chloride were added. The temperature was raised to 230°C in the course of 1 hour and kept there for 1 additional hour. After cooling to 120°C water was cautiously added and the mixture heated under reflux. The hot water layer was decanted and the procedure repeated five times. The water-insoluble material was heated under reflux for 17 hours with a mixture of 350 ml of hydrobromic acid (48% wt/vol) and 350 ml of acetic acid. The dark solution was cooled and poured into water. Extraction with ether, washing the ether with 2-*N* sodium hydroxide and evaporating the solvent yielded a dark brown solution which was distilled at 0.2 mm. Between 150°—160°C a yellow viscous oil was collected. A sample was purified by gas chromatography and on scratching gave crystals of 2 - amino - 5 - chloro - 2¹ - methyl - benzophenone which after recrystallization from heptane melted at 50°—55°C. With these seeding crystals the whole amount finall was brought to crystallization.

9 g of 2 - amino - 5 - chloro - 2¹ - methyl benzophenone were heated under reflux in a mixture of 50 ml of pyridine, 40 g of glycine ethyl ester hydrochloride and 1 ml of piperidine for 19 hours. The solvent was removed *in vacuo* and the residue treated with water and ether. The ether extract was washed with water and finally extracted with 3 - *N* hydrochloric acid. From the ether unreacted ketone could be recovered, whereas the acidic extract after neutralizing gave 7 - chloro - 5 - (*o* - tolyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) which was extracted with ether, melting point = 180°—181°C (recrystallized from ether).

4 g of 7 - chloro - 5 - (*o* - tolyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were dissolved in 50 ml of methanol and 16 ml of a 1 - *N* solution of sodium methoxide in methanol were added. The solvent was evaporated *in vacuo* and the residue dissolved in 25 ml of N,N - dimethyl - formamide. 4 ml of methyl iodide were added whereby an exothermic reaction took place (temperature about 50°C). After 30 minutes the solvent was removed *in vacuo* and the residue treated with water and ether/(methylene chloride). From the organic phase crystals of 1 - methyl - 7 - chloro - 5 - (*o* - tolyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were isolated which after recrystallization from methanol melted at 137°—139°C.

Example 42

A mixture of 176 g (1.125 mol) of *o* - fluoro - benzoyl chloride and 64 g (0.5 mol) of *p* - chloro - aniline was stirred and heated to 180°C, at which temperature 87 g (0.64 mol) of zinc chloride were introduced. Then the temperature was raised to 200°—205°C and maintained at this temperature for forty minutes. The golden coloured melt was quenched by the careful addition of 500 ml of 3 - *N* hydrochloric acid and the resulting mixture heated under reflux for 5 minutes. The acid solution was decanted and the process repeated three times to remove all of the *o* - fluoro - benzoic acid. The grey granular residue was dissolved in 300 ml of 75% (vol/vol) sulphuric acid and heated under reflux for forty minutes to complete the hydrolysis. The hot solution was poured over 1 kg of ice and diluted to 2 l with water. The organic material was extracted with four 300 ml portions of methylene chloride which were subsequently washed with two 500 ml portions of 3 - *N* hydrochloric acid to remove traces of *p* - chloro - aniline, three 500 ml portions of 5 - *N* sodium hydroxide solution to remove

o - fluoro - benzoic acid and finally with two 200 ml portions of saturated sodium chloride solution. The methylene chloride extract was dried over anhydrous sodium sulphate and the solvent removed to give the crude 2 - amino - 5 - chloro - 2^1 - fluoro - benzophenone. Recrystallization from methanol gave the pure product forming yellow needles, melting point = 94°—95°C.

A mixture of 20 g (0.08 mol) of 2 - amino - 5 - chloro - 2^1 - fluoro - benzophenone and 35 g (0.25 mol) of glycine ethyl ester hydrochloride was heated under reflux in 200 ml of pyridine, containing 0.5 ml of piperidine, for 18 hours. The mixture was distilled until 100 ml of pyridine had been collected, and the residue poured into water. The remaining pyridine was neutralized with dilute hydrochloric acid and the product extracted with two 100 ml portions of methylene chloride. The extracts were combined, washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulphate, and the solvent removed under reduced pressure. The oil remaining was dissolved in acetone, treated with charcoal, filtered and recrystallized from a mixture of acetone/hexane to give 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) in white needles, melting point 205°—206°C.

The sodium derivative of 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) was prepared by treating 16.5 g (0.0608 mol) of the compound with one equivalent of a methanolic solution of sodium methoxide, stirring for 0.5 hour under reflux and concentrating to an oil. The derivative was not purified but dissolved in 50 ml of N,N - dimethyl - formamide and reacted with 11.4 ml (26 g = 0.1824 mol) of methyl iodide. The mixture was warmed under reflux on a steam - bath for 0.5 hour and then poured into 1 l of water. The oil which came out of solution was extracted with three 100 ml portions of methylene chloride. The extracts were combined, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The oil obtained was distilled at 200°—210°C/0.1 mm by a bulb to bulb technique and the pale yellow viscous oil obtained was chromatographed on alumina (Activity grade III). The fractions obtained using benzene as an eluant were discarded and the product, a viscous colourless oil, was obtained from the ether fraction. This oil, 7 - chloro - 1 - methyl - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) could not be induced to crystallize.

Example 43

A mixture of 88 g (0.556 mol) of *m* - fluorobenzoyl chloride and 32 g (0.25 mol) of *p* - chloro - aniline was stirred and heated to 180°C, at which temperature 44 g (0.324 mol) of zinc chloride were introduced. Then the temperature was raised to 200°—205°C and maintained there for forty minutes. The golden coloured melt was quenched by the careful addition of 500 ml of 3 - *N* hydrochloric acid and the resulting mixture heated under reflux for five minutes. The acid solution was decanted and the process repeated three times to remove all of the *m* - fluoro - benzoic acid. The grey granular residue was dissolved in 300 ml of 75% (vol/vol) sulphuric acid and heated under reflux for forty minutes to complete the hydrolysis. The hot solution was poured over 1 kg of ice and diluted to two l with water. The organic material was extracted with four 300 ml portions of methylene chloride which were subsequently washed with two 500 ml portions of 3 - *N* hydrochloric acid to remove traces of *p* - chloro - aniline, three 500 ml portions of 5 - N sodium hydroxide solution to remove *m* - fluoro - benzoic acid, and finally two 200 ml portions of saturated sodium chloride solution. The methylene chloride extract was dried over anhydrous sodium sulphate and the solvent removed to give the crude 2 - amino - 5 - chloro - 3^1 - fluoro - benzophenone. Recrystallization from methanol gave the pure product forming yellow needles, melting point 90°—91°C.

A mixture of 15.9 g (0.0638 mol) of 2 - amino - 5 - chloro - 3^1 - fluoro - benzophenone and 26.6 g (0.192 mol) of glycine ethyl ester hydrochloride was heated under reflux in 100 ml of pyridine containing 0.3 ml of piperidine for 16 hours. The reaction mixture was poured into 1 l of water and extracted with methylene chloride (3 x 200 ml). The methylene chloride extracts were combined, washed three times with 100 ml portions of 1.5 - *N* hydrochloric acid (or until all pyridine had been removed as the hydrochloride) and finally with two 100 ml portions of saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulphate and the solvent removed. The residue was recrystallized from acetone to give white prisms of 7 - chloro - 5 - (3 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 200°—201°C.

Example 44

To a mixture of 580 g (3.35 mol) of *o* - fluoro - benzoyl chloride and 265 g (1.54 mol) of *p* - bromo - aniline at 180°C, 262 g (1.93 mol) of zinc chloride were added with stirring. The temperature was raised to 195°—205°C and maintained there for two hours. The reaction mixture was quenched by the careful addition of 500 ml of 3 - *N* hydrochloric acid and the resulting mixture heated under reflux for five minutes. The acid solution was decanted and the process repeated three times to remove all of the *o* - fluoro - benzoic acid. The residue was hydrolysed for 20 hours with

1 l. of 60% (vol/vol) sulphuric acid. The organic material was extracted with four 300 ml portions of methylene chloride which were subsequently washed with two 500 ml portions of 3 - *N* hydrochloric acid to remove traces of *p* - bromo - aniline, three 500 ml portions of 5 - *N* sodium hydroxide solution to remove *o* - fluoro - benzoic acid and finally with two 200 ml portions of saturated sodium chloride solution. The methylene chloride extract was dried over anhydrous sodium sulphate and the solvent removed to give the crude 2 - amino - 5 - bromo - 2^1 - fluoro - benzophenone. Recrystallization from methanol yielded yellow needles, melting point 101°—102°C.

A mixture of 8.5 g (0.029 mol) of the ketone obtained and 8.3 g (0.06 mol) of glycine ethyl ester hydrochloride was heated under reflux in 75 ml of pyridine containing 0.1 ml of piperidine for 17 hours. The reaction mixture was poured into 1 l. of water and extracted with methylene chloride (3 x 200 ml). The methylene chloride extracts were combined, washed three times with 100 ml portions of 1.5 - *N* hydrochloric acid (or until all pyridine had been removed as the hydrochloride) and with two 100 ml portions of saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulphate and the solvent removed. The crude product was separated from unreacted amino - benzophenone by chromatography on alumina (Activity grade III) using benzene as an eluant. Recrystallization of the fraction melting at 186°—187°C from acetone/(petroleum ether) gave white needles of 7 - bromo - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 187°—188°C.

A solution of 16.6 g (0.05 mol) of 7 - bromo - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) in 50 ml of methanol was treated with one equivalent of sodium methoxide in methanol. The mixture was heated under reflux for 0.5 hour. The solvent was removed under reduced pressure and the residue dissolved in 150 ml of N,N - dimethyl - formamide. The solution was cooled to 10°C and 37 ml (0.6 mol) of methyl iodide were added. The solution was stirred and heated under reflux on a steam-bath for 1 hour. The condenser was removed and excess methyl iodide distilled from the reaction mixture. The product was obtained by pouring the N,N - dimethyl - formamide solution into 2 l of water and extracting the organic material into methylene chloride (3 x 200 ml), washing the combined extracts with water (2 x 200 ml) and saturated sodium chloride solution (2 x 200 ml), drying over anhydrous sodium sulphate, and removal of the solvent *in vacuo*. The crude material was recrystallized from ether, yielding colourless needles of 7 - bromo - 1 - methyl - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 132°—132.5°C.

Example 45

Exhaustive hydrogenation of a solution of 5.9 g (0.0197 mol) of 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) in 60 ml of glacial acetic acid and in the presence of 0.600 g of platinum oxide gave a crystalline product on filtration and removal of solvent under reduced pressure. Recrystallization from acetone gave the pure 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3,4,5 - tetrahydro - 1H - 1,4 - benzodiazepinone - (2) (white needles, melting point 214°—215°C).

Example 46

5 g (0.0155 mol) of 7 - bromo - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) in 25 ml of glacial acetic acid were hydrogenated using 0.6 g of platinum oxide as catalyst. The theoretical uptake of one equivalent of hydrogen was completed in 0.5 hour. The reaction mixture was filtered and the solvent removed under reduced pressure yielding a crystalline product which was recrystallized from methanol. There were obtained white needles of 7 - bromo - 5 - (2 - fluoro - phenyl) - 2,3,4,5 - tetrahydro - 1H - 1,4 - benzodiazepinone - (2), melting point 224°—225°C.

Example 47

A solution of 22.6 g of 2 - amino - 4,5 - dimethyl - 2^1 - chloro - benzophenone and 24 g of glycine ethyl ester hydrochloride in 200 ml of pyridine was heated under reflux for 48 hours. The reaction mixture was concentrated to dryness, first at atmospheric pressure and then *in vacuo*. Water was added and the mixture extracted with ether. The ether extract was dried over sodium sulphate, concentrated *in vacuo* to dryness and the oily residue crystallized from ether yielding a crude reaction product. The crude material was purified by extracting impurities with acetone and recrystallization of the undissolved reaction product from dilute ethanol. The pure 7,8 - dimethyl - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) formed colourless prisms melting at 259°—260°C.

Example 48

To a warm, stirred suspension of 28.6 g (0.1 mol) of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide in 450 ml of dry benzene were added 5.4 g of sodium methoxide. The mixture was heated under reflux and part of the solvent was distilled off to remove the liberated methanol. To this clear solution were added 11.5 ml of benzyl chloride, 1 g of sodium

iodide and 200 ml of acetonitrile. The mixture was heated under reflux for 15 hours, then concentrated *in vacuo* to a smaller volume and diluted with water. The benzene layer was separated, dried over sodium sulphate and filtered. The filtrate was concentrated *in vacuo* and the oily residue dissolved in a small amount of a mixture of equal parts (by volume) of methylene chloride and petroleum ether. This was adsorbed on a column (3.5 cm diameter) prepared from 450 g of aluminium oxide and the above mixture of solvents. Elution with 2 l of the same solvent mixture removed impurities. The reaction product was eluted first with 2 l of methylene chloride and then with 500 ml of methanol and the methylene chloride/methanol eluates were combined and concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of methylene chloride/ether/(petroleum ether), yielding crude 1 - benzyl - 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide. The pure product forms colourless prisms melting at 151°—152°C.

A solution of 7.5 g (0.02 mol) of 1 - benzyl - 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide in 110 ml of methanol was hydrogenated in the presence of about 10 g of RANEY - nickel at atmospheric pressure at about 50°C. The hydrogenation was stopped after the absorption of 1 mol of hydrogen. The reaction mixture was filtered, and the filtrate concentrated *in vacuo* to a small volume. The precipitated reaction product was filtered off. Recrystallization from a mixture of methylene chloride/ether/(petroleum ether) yielded colourless prisms of 1 - benzyl - 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) melting at 174°—175°C.

Example 49

To a suspension of 5.75 g of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide in 150 ml of dry benzene were added 1.08 g of sodium methoxide. About 10 ml of the solvent containing methanol was distilled off. 2.34 ml of ethyl bromide were then added and the mixture was heated under reflux for 20 hours. The reaction mixture was then diluted with ice-water, the organic layer separated, dried and concentrated *in vacuo*. The oily residue was crystallized from a mixture of methylene chloride/(petroleum ether) and yielded a crude reaction product melting at 203°—204°C. Upon recrystallization from a mixture of acetone/(petroleum ether) the pure 7 - chloro - 1 - ethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide formed colourless plates melting at 207°—208°C.

A solution of 4 g of 7 - chloro - 1 - ethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide in 180 ml of methanol was hydrogenated in the presence of 5 g of wet RANEY - nickel at *ca* 20°C and atmospheric pressure. The uptake stopped after the absorption of 1 mol of hydrogen. The mixture was then filtered and the solution concentrated *in vacuo* to dryness. The oily residue was crystallized from acetone and yielded the crude reaction product. The pure 7 - chloro - 1 - ethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) after crystallisation from acetone forms colourless prisms melting at 127°—128°C.

Example 50

A solution of 23.15 g (0.1 mol) of 2 - amino - 5 - chloro - benzophenone and 32.4 g (0.15 mol) of ethyl α - amino - α - phenyl - acetate hydrochloride in 150 ml of pyridine was heated under reflux for 22 hours, with occasional distillation of pyridine, the volume being kept constant by the addition of fresh pyridine. The pyridine was finally removed *in vacuo* and the residual oil partitioned between ether and water. The insoluble product was then filtered off and washed with water and ether to give a yellow solid melting at 255°—257°C. This was then first extracted with acetone and the insoluble residue crystallized from acetonitrile to give flat colourless prisms of 7 - chloro - 3,5 - diphenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 269°—270°C.

Example 51

A solution of 12.5 g (0.06 mol) of *L* tyrosine ethyl ester hydrochloride and 9.3 g (0.04 mol) of 2 - amino - 5 - chloro - benzophenone in 85 ml of pyridine was heated under reflux for a total time of about 40 hours. At intervals some pyridine was distilled off, the volume being kept constant by additions of fresh pyridine. The final reaction mixture was concentrated *in vacuo* and the residue partitioned between 150 ml of ether and 50 ml of water. The ether layer was further extracted with 50 ml of water and then treated with 100 ml of 1.5 - *N* hydrochloric acid which resulted in the formation of an insoluble hydrochloride. This was filtered off, washed with ether and then treated with 5 - *N* ammonium hydroxide solution. The liberated base was extracted with ether, the ether solution washed with water and dried over sodium sulphate. On evaporation a solid was obtained. As this could not be crystallized the purification via the insoluble hydrochloride was repeated. The base finally obtained slowly crystallized from a mixture of ether/(petroleum ether). Three recrystallizations from benzene gave colourless needles of 7 - chloro - 5 - phenyl - 3 - (4 - hydroxy - benzyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) melting at 151° —153°C.

EXAMPLE 52

A suspension of 30 g of *DL* methionine in 200 ml of anhydrous methanol was saturated with hydrogen chloride, then heated under reflux for one hour and concentrated *in vacuo*. The residual oil was twice concentrated with the addition of benzene to remove any methanol and then dissolved in 150 ml of pyridine. 23.15 g (0.1 mol) of 2 - amino - 5 - chloro - benzophenone were added to the solution which was then heated under reflux for 16 hours. The pyridine was removed *in vacuo* and the residual oil crystallized from methanol to give methionine. The mother liquor was concentrated *in vacuo* and crystallized from a mixture of ether/(petroleum ether) to give a product melting at 176°C. Recrystallization from ethanol gave oblong plates of 7 - chloro - 3 - (2 - methylthio - ethyl) - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 179° —180°C.

EXAMPLE 53

A solution of 1.95 g (7.75 mmol) of 2 - amino - 3 - nitro - benzophenone in 60 ml of nitro - methane was treated with 2.15 ml (23.25 mmol) of bromo - acetyl bromide. After standing for 0.25 hour the colour lightened noticeably and dry air was then blown through the solution for 1.5 hours to remove hydrogen bromide. The solution was partly concentrated, diluted with ether and washed with water until the washings were neutral. The organic layer was dried over sodium sulphate, concentrated *in vacuo* and the residue crystallized from ether to give light - straw coloured prisms of 2 - bromoacetamido - 3 - nitro - benzophenone, melting at 120.5°—121.5°C.

A solution of 1 g (2.75 mmol) of 2 - bromoacetamido - 3 - nitro - benzophenone in 40 ml of nitro - methane was cooled in an ice-bath and saturated with ammonia during 20 minutes. After standing for 3 hours the solution was concentrated *in vacuo*. The residue was extracted from the inorganic salts with a mixture of ether/methylene chloride. The solution was treated with charcoal, filtered and concentrated *in vacuo*. The residue was crystallized from a mixture of benzene/hexane to give a product melting at 135°—137°C. Recrystallization from ethanol gave pale yellow needles of 9 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 144°—145°C.

EXAMPLE 54

4.4 g (0.02 mol) of 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) were suspended in 75 ml of methanol and 1.1 g (0.022 mol) of sodium methoxide added. The resulting clear solution was stirred at *ca* 20°C for 10 minutes. The reaction mixture was concentrated to dryness *in vacuo*. 95 ml of N,N - dimethyl - formamide were added to the brown residue. A clear solution resulted at first with the formation of a grey precipitate after a short time. 3.8 ml (8.52 g = 0.06 mol) of methyl iodide were added dropwise, the temperature of the reaction mixture rising to 30°C. After stirring for 1 hour at *ca* 20°C, the mixture was poured into 1000 ml of ice-water. After stirring for one hour in the cold, 2 g of sodium thiosulphate were added and the cold reaction mixture was extracted in a separating funnel with four 300 ml portions of methylene chloride. The combined methylene chloride extracts were washed with ice-water, dried over sodium sulphate and concentrated to a thick oil. On cooling in a refrigerator for 16 hours, the 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) crystallized in white prisms, melting point 153.5°—155.5°C.

EXAMPLE 55

72 g (0.30 mol) of 2 - amino - 5 - nitro - benzophenone were suspended in a mixture of 500 ml of ethanol, 25 ml of water, 34 g of hydroxylamine hydrochloride and 90 g of powdered potassium hydroxide. The reaction mixture was heated under reflux on a steam-bath with stirring for 15 minutes. It was then cooled to *ca* 20°C and poured into a solution of 160 ml of concentrated hydrochloric acid in 1000 ml of water. The suspension of the precipitated crude product was cooled in ice and then filtered off, washed free from acid with ice-water, and sucked dry, melting point 195°—200°C. The pure 2 - amino - 5 - nitro - benzophenone oxime crystallized from ethanol in needles, melting point 203°—205°C.

To a suspension of 10 g (0.039 mol) of 2 - amino - 5 - nitro - benzophenone oxime in 100 ml of acetic acid warmed to 50°—60°C was added with stirring in small portions 6 ml (0.08 mol) of chloro - acetyl chloride. The resulting brown solution was stirred at 50°—60°C for 3 hours and then allowed to stand at *ca* 20°C for 16 hours. The reaction mixture was then saturated with hydrogen chloride and concentrated *in vacuo*. The residue was dissolved in 200 ml of warm methylene chloride and then cooled to 0°C. 50 g of crushed ice were added to the reaction mixture, then 30 ml of 1 - *N* sodium hydroxide dropwise until a pH of 8—9 was reached. The mixture was transferred to a separating funnel and 150 ml of water were added. The organic phase was separated and dried over sodium sulphate. The methylene chloride solution was treated with activated charcoal, filtered and evaporated to dryness *in vacuo* to give a yellow crystalline residue. The crude product was purified by heating under reflux in a mixture of 200 ml of acetone and 100 ml of methylene chloride with 15 g of activated charcoal. The pure 2 - chloromethyl - 4 - phenyl - 6 - nitro - quinazoline 3 - oxide

crystallized in yellow prisms on cooling the filtered mixture, melting point 205°—207°C.

6.3 g (0.02 mol) of 2 - chloromethyl - 4 - phenyl - 6 - nitro - quinazoline 3 - oxide were suspended in a mixture of 50 ml of ethanol and 20 ml of acetone. 24 ml of 1 - *N* sodium hydroxide were added dropwise, the reaction mixture turning a dark brown colour (pH = 9—10). The mixture was warmed to 40°C then stirred at *ca* 20°C for 16 hours. The reaction mixture was adjusted to pH 5 with dilute hydrochloric acid and concentrated to dryness *in vacuo*. The residue was heated under reflux with a mixture of 125 ml of ethanol and 30 ml of acetone. After filtration and concentration to 50 ml a small amount of starting material was filtered off and the reaction product obtained by precipitation with petroleum ether, melting point 205°—208°C (decomposition). The pure 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide crystallized in yellow prisms from ethanol/(petroleum ether), melting point 218°—220°C (decomposition).

EXAMPLE 56

A solution of 3.5 g (15.4 mmol) of 2 - amino - 4 - methoxy - benzophenone and 3.2 g (22 mmol) of glycine ethyl ester hydrochloride in 75 ml of dry pyridine was heated under reflux for one hour. After distilling off 25 ml of pyridine, an additional 3.2 g of glycine ethyl ester hydrochloride was added and the reaction mixture heated under reflux for a total of 15 hours. The solvent was removed by distillation *in vacuo* and the residue partitioned between ether and water. The ether layer was dried and evaporated to dryness *in vacuo*. The residue was crystallized from dilute acetonitrile to give recovered starting material. Concentration *in vacuo* to dryness of the acetonitrile gave a residue which was crystallized from benzene/hexane yielding 8 - methoxy - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 180°—184°C. Recrystallization from acetone/hexane raised the melting point to 186°—188°C.

EXAMPLE 57

A solution of 16.5 g (0.1 mol) of acetamido-*m*-anisidine and 17.5 g (0.125 mol) of benzoyl chloride in 95 ml of carbon disulphide was cooled to 7°C in an ice-bath and 19 g (1.4 mol of anhydrous aluminium chloride added slowly in portions. When about half of the aluminium chloride had been added, a viscous green aluminium chloride complex began to separate. The reaction mixture was warmed to 35°C and the remainder of the aluminium chloride added. At this point the dark green precipitate prevented stirring. The carbon disulphide was decanted from the viscous material and discarded. The residue was then decomposed with ice and dilute hydrochloric acid. The oily layer that separated was extracted with benzene, the benzene layer washed with dilute hydrochloric acid, water and then twice with dilute sodium hydroxide and water. Following drying over sodium sulphate the solvent was evaporated *in vacuo* leaving a viscous residue. Recrystallization from benzene/hexane gave 4 - acetamido - 2 - methoxy - benzophenone which was discarded. The benzene/hexane mother liquor was concentrated to dryness and the residue crystallized from aqueous ethanol to give 2 - acetamido - 4 - methoxy - benzophenone, melting point 116°—117°C. Further crystallization from dilute ethanol raised the melting point to 118°—119.5°C.

A solution of 5.2 g of 2 - acetamido - 4 - methoxy - benzophenone in 100 ml of acetic acid was warmed to 50°—55°C and 3.1 g of bromine in 25 ml of acetic acid added slowly. The bromine decolorized rapidly. After all the bromine had been added the reaction mixture was kept at 50°—55°C for 1 hour. The solvent was then removed by distillation *in vacuo* and the crystalline residue recrystallized from dilute ethanol, yielding 2 - acetamido - 5 - bromo - 4 - methoxy - benzophenone, melting point 144°—146°C. Recrystallization did not change the melting point.

5.5 g of 2 - acetamido - 5 - bromo - 4 - methoxy - benzophenone were hydrolyzed by heating under reflux for 3 hours in 250 ml of ethanol and 250 ml of 6 - *N* hydrochloric acid. The reaction mixture was concentrated to dryness *in vacuo*, the residue slurried with water, made alkaline with ammonia and then extracted with benzene. After drying over sodium sulphate, the solvent was removed by distillation *in vacuo*. Crystallization from benzene/hexane gave 2 - amino - 5 - bromo - 4 - methoxy - benzophenone, melting point 150°—151.5°C. Recrystallization did not alter the melting point.

To a solution of 3.8 g of this ketone in 150 ml of ether, 40 ml of 1 - *N* sodium hydroxide and 3.5 g of bromo - acetyl bromide were added while stirring. The yellow colour of the ether layer disappeared almost immediately on mixing. After 0.75 hour the organic layer was separated, washed with water and dried over sodium sulphate. The residue obtained after evaporation of the solvent was crystallized from benzene/hexane giving 2 - bromoacetamido - 5 - bromo - 4 - methoxy - benzophenone, melting point 143°—144.5°C. Recrystallization raised the melting point to 144°—145°C.

A suspension of 3.7 g of 5 - bromo - 2 - bromoacetamido - 4 - methoxy - benzophenone in 200 ml of 20% (wt/vol) ammonia in methanol was stirred for 24 hours at *ca* 20°C. The insoluble material was filtered off. Several recrystallizations from benzene or methylene chloride/hexane gave 5 - bromo - 2 - amino-

acetamido - 4 - methoxy - benzophenone which melted at 161°—163°C. On heating further, this material resolidified at 165°—168°C and remelted at 248°—251°C to give the cyclised compound 7 - bromo - 8 - methoxy - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

The methanolic ammonia filtrate obtained was concentrated to dryness *in vacuo*. The residue was recrystallized from dilute ethanol to give 1.25 g of 7 - bromo - 8 - methoxy - 5 - phenyl - 2,3 - dihydro - 1H -1,4 - benzodiazepinone - (2), melting point 248°—252°C. Recrystallization from benzene/hexane gave the pure product, melting point 260.5°—261.5°C.

75 mg of 5 - bromo - 2 - aminoacetamido - 4 - methoxy - benzophenone were heated on an oil - bath at 200°C for several minutes. The material melted at about 160°C and resolidified at 180°C. Crystallization from a mixture of benzene/hexane gave crude 7 - bromo - 8 - methoxy - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 249.5°—251.5°C.

EXAMPLE 58

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 1.5 hours to a solution of 27.1 g of 2 - methyl - 5 - methoxy - 4H - 3,1 - benzoxazinone - (4) dissolved in 375 ml of dry benzene and 125 ml of ether at 0°—5°C. The reaction mixture was stirred for 30 minutes at this temperature. After all the GRIGNARD reagent had been added the mixture was 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 the 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 concentrated to dryness *in vacuo* leaving 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 alumina (activity grade I, neutral). Elution with benzene/hexane (1:2) and (2:1) followed by benzene gave crude 2 - amino - 5 - methoxy - benzophenone. Crystallization from hexane gave the pure product melting at 50°—52°C.

A solution of 3.2 g. of 2 - amino - 5 - methoxy - benzophenone and 3.0 g of glycine ethyl ester hydrochloride in 50 ml of pyridine was heated under reflux for one hour. After distilling off 10 ml of pyridine, an additional 3.0 g of glycine ethyl ester hydrochloride and 10 ml of pyridine were added and heated under reflux for 16 hours. After concentrating to dryness *in vacuo*, the residue was partitioned between benzene and water. The benzene layer was dried and evaporated to dryness *in vacuo* leaving a dark residue. Crystallization from benzene/hexane gave crude 7 - methoxy - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 210.5°—213°C. Recrystallization from benzene/hexane gave a pure product melting at 217°—218°C.

EXAMPLE 59

5.4 g of 2 - amino - 5 - methoxy - benzophenone in 100 ml of 48% (wt/vol) hydrobromic acid was heated under reflux for 8 hours. During concentration to dryness *in vacuo*, a crystalline material separated. The residue was dissolved in about 100 ml of water and carefully neutralized with sodium bicarbonate. The yellow crystalline product was filtered off and recrystallized from benzene/hexane yielding 2 - amino - 5 - hydroxy - benzophenone, melting point 127°—128°C.

A solution of 4.0 g of 2 - amino - 5 - hydroxy - benzophenone and 4.0 g of glycine ethyl ester hydrochloride in 50 ml of pyridine was heated under reflux for one hour. About 10 ml of pyridine were then distilled off and an additional 4.0 g of glycine ethyl ester hydrochloride and 10 ml of pyridine added. Heating under reflux was continued for a total of 10 hours. The solvent was distilled off *in vacuo* and the residue partitioned between benzene and water. A tan solid, insoluble in both liquid phases was filtered off to give crude 7 - hydroxy - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 270°—272°C (with decomposition). Recrystallization from acetonitrile gave a product melting at 289°—291°C. An additional crop melting at 271°—274°C was obtained on neutralizing the aqueous layer with sodium bicarbonate. Recrystallization from acetonitrile raised the melting point to 282°—284°C.

EXAMPLE 60

A GRIGNARD reagent (prepared from 10.3 g of *o* - bromo - anisole and 1.3 g of magnesium in 100 ml of ether) was added slowly to an ice-cold solution of 9.8 g of 6 - chloro - 2 - methyl - 4H - 3,1 - benzoxazinone - (4) in 150 ml of benzene and 50 ml of ether. A yellow precipitate formed. The reaction mixture was stirred for 1 hour in an ice-bath and for 1 hour at *ca* 20°C. It was then chilled in an ice-salt-bath and decomposed by the careful addition of 100 ml of cold 2 - *N* hydrochloric acid. The organic layer was washed with water, dilute sodium carbonate and water, then dried over sodium sulphate. The residue after evaporation of the solvent *in vacuo* was recrystallized from benzene/hexane. The mother liquor was taken to dryness *in vacuo* and the residue crystallized from

hexane to give 2 - acetamido - 5 - chloro - 2¹-methoxy - benzophenone, melting point 120°—125°C. Recrystallization from hexane gave the pure product melting at 124°—126°C.

A solution of 3.9 g of 2 - acetamido - 5 - chloro - 2¹ - methoxy - benzophenone in 100 ml of ethanol and 50 ml of 6 - *N* hydrochloric acid was heated under reflux for 2.5 hours. The solvent was distilled off *in vacuo* and the residue stirred with dilute sodium hydroxide and benzene. The benzene layer was separated, dried over sodium sulphate and concentrated to dryness leaving a residual yellow oil of crude 2 - amino - 5 - chloro - 2¹ - methoxy - benzophenone. The amine was then dissolved in 150 ml of ether, chilled in an ice-bath, and 20 ml of water added. Then 3.1 g of bromo - acetyl bromide was slowly added with the simultaneous addition of 1 - *N* sodium hydroxide to keep the reaction mixture slightly alkaline. The organic layer was separated, washed with water and dried over sodium sulphate. After distillation of the solvent a yellow oil remained which crystallized on standing. Recrystallization from acetonitrile afforded 2 - bromoacetamido - 5 - chloro - 2¹ - methoxy - benzophenone, melting point = 129°—130°C. Further recrystallization did not change the melting point.

A solution of 2.4 g of the foregoing ketone in 100 ml of 20% (wt./vol.) ammonia in methanol was kept at *ca* 20°C for 17 hours. Methanol and ammonia were distilled off *in vacuo* and the residue dissolved in benzene and water. The organic layer was dried over sodium sulphate and the solvent evaporated *in vacuo*. The residue was crystallized from a mixture of benzene/hexane to give 7 - chloro - 5 - (2 - methoxy - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) which melted partially at 188°—190°C, resolidified, and remelted at 204°C. Drying at 100°C *in vacuo* removed traces of solvent yielding the product which melted at 205.5°—206.5°C.

1.1 g of sodium methoxide were added to a suspension of 6.0 g of 7 - chloro - 5 - (2 - methoxy - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone-(2) in 100 ml of dry toluene at 40°C. The lemon coloured solution formed was heated to 100°C, allowed to cool and then about 20 ml slowly distilled off to remove methanol. The solution was then cooled to 50°C and 1.9 ml of dimethyl sulphate added. After heating under reflux for 1 hour, the cool toluene solution was washed with water and dilute sodium hydroxide and dried over sodium sulphate. Toluene was distilled off *in vacuo* and the residue crystallized from a mixture of ethyl acetate/hexane. Unreacted starting material was recovered. The filtrate was concentrated to dryness *in vacuo*, dissolved in a mixture of 25 ml of benzene and 50 ml of hexane, adsorbed on a column containing 50 g of alumina (neutral, activity grade I), then eluted with a mixture of benzene and hexane and then with benzene. From the eluates 7 - chloro - 5 - (2 - methoxy - phenyl) - 1 - methyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) (melting point = 158°—160°C) was obtained. Recrystallization from benzene/hexane gave a pure product melting at 161°—162°C.

EXAMPLE 61

A GRIGNARD reagent (prepared by the reaction of 30.8 g of *m* - bromo - anisole and 3.9 g of magnesium in 400 ml of anhydrous ether) was slowly added to an ice-cold suspension of 29.3 g of 6 - chloro - 2 - methyl - 4H - 3,1 - benzoxazinone - (4) in 450 ml of benzene and 150 ml of ether. After all of the GRIGNARD reagent was added the reaction mixture was stirred for 1 hour in an ice-bath then for 1 hour at *ca* 20°C. It was then chilled in a salt/ice-bath and decomposed by the addition of 250 ml of 2 - *N* hydrochloric acid. The organic layer was separated, washed with water, dilute sodium hydroxide and water, then dried over sodium sulphate. After evaporation of the solvent *in vacuo* a residual dark yellow oil of crude 2 - acetamido - 5 - chloro - 3¹ - methoxy - benzophenone was obtained.

A solution of 15 g of the crude product in 300 ml of ethanol and 150 ml of 6 - *N* hydrochloric acid was heated under reflux for 3 hours and then concentrated to dryness *in vacuo*. The solid residue was suspended in 75 ml of water and 400 ml of ether then made slightly alkaline by the addition of 40% (wt/vol) sodium hydroxide. The mixture was then cooled in an ice-bath and 10 g of bromoacetyl bromide added slowly with the simultaneous addition of 1 - *N* sodium hydroxide to keep the reaction mixture slightly alkaline. The organic layer was then separated, diluted with benzene, washed with water and dried over sodium sulphate. The residue obtained after evaporation of the solvent *in vacuo* was crystallized from hexane to give 2 - bromoacetamido - 5 - chloro - 3¹ - methoxy - benzophenone, melting point 93°—96°C. Recrystallization from hexane raised the melting point to 97°—98.5°C.

9.5 g of 2 - bromoacetamido - 5 - chloro - 3¹ - methoxy - benzophenone were dissolved in 250 ml of 20% (wt/vol) ammonia in methanol and kept at *ca* 20°C for 17 hours. The solvent was evaporated *in vacuo* and the residue then shaken with benzene and water. The organic layer was dried over sodium sulphate and the solvent distilled off. The residue was crystallized from acetone/hexane to yield 7 - chloro - 5 - (3 - methoxy - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 219°—221°C. Recrystallization did not alter the melting point.

EXAMPLE 62

A solution of 4.7 g of 2 - acetamido - 5 - chloro - 4¹ - methoxy - benzophenone in 100 ml of ethanol and 50 ml of 6 - *N* hydrochloric acid was heated under reflux for 3 hours. The solvent was then distilled off *in vacuo*. The 2 - amino - 5 - chloro - 4¹ - methoxy - benzophenone thus formed was not isolated but the crude material was stirred with 200 ml of ether and 50 ml of water and made slightly alkaline with 40% (wt/vol) sodium hydroxide. The mixture was then cooled in an ice-bath and 3.14 g of bromo - acetyl bromide were slowly added with the simultaneous addition of 1 - *N* sodium hydroxide to keep the reaction mixture slightly alkaline. The organic layer was diluted with benzene, separated, washed with water and dried over sodium sulphate. The residue after evaporation of solvent *in vacuo* was crystallized from benzene/hexane to give 2 - bromoacetamido - 5 - chloro - 4¹ - methoxy - benzophenone, melting point 116°—118°C. Recrystallization did not alter the melting point.

A suspension of 3.9 g of 2 - bromoacetamido - 5 - chloro - 4¹ - methoxy - benzophenone in 125 ml of 20% (wt/vol) ammonia in methanol was stirred for 19 hours at *ca* 20°C. A small amount of insoluble material was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was shaken with water and benzene, the organic layer obtained dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was crystallized from acetone/hexane to give 7 - chloro - 5 - (4 - methoxy - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting point 212°—214°C. An additional crop was obtained from the mother liquors. Further crystallization did not alter the melting point.

EXAMPLE 63

A solution of 100 g of 4 - chloro - anthranilic acid in 500 ml of acetic anhydride was heated under reflux for 30 minutes and then about 300 ml of a mixture of acetic acid and acetic anhydride were distilled off at normal pressure and the solid residue was dissolved in 500 ml of warm benzene. The solution was concentrated to about 200 ml and treated while still warm with 250 ml of petroleum ether (boiling range 60°—70°C). After standing for a few hours at 0°C, the precipitated product 2 - methyl - 7 - chloro - 4H - 3,1 - benzoxazinone - (4) was collected on a funnel, washed 3 times with 200 ml hexane and dried for 2 hours *in vacuo* at 65°C.

A solution of phenyl magnesium bromide was prepared in the usual manner, using 12.35 g of magnesium, 76.0 g of freshly distilled bromo - benzene and 250 ml of anhydrous ether. This was added while stirring and cooling in an ice-bath over a period of one hour to a solution of 94.15 g of 2 - methyl - 7 - chloro - 4H - 3,1 - benzoxazinone - (4). The resulting reaction mixture was stirred for one hour at *ca* 20°C and then poured on to a mixture of 112 g of ammonium chloride and 900 g of crushed ice. The mixture was left for about 0.5 hour with occasional stir. Then the reaction product was extracted with 3 portions of 500 ml of benzene. After washing the benzene layers thoroughly with water and after drying over sodium sulphate, the solvent was distilled off *in vacuo* at 65°C to give a solid residue. This was directly hydrolyzed by heating under reflux for one hour in 500 ml of methanol and 500 ml of 3 - *N* sodium hydroxide solution. After cooling, the reaction mixture was extracted in 3 separating funnels with a total of 2 1 of benzene. After washing the benzene extract with water and after drying over sodium sulphate, the solvent was distilled off *in vacuo* at 65°C to give a brown oil. This was dissolved in petroleum ether (boiling range 60°—70°C) and purified by chromatography on 580 g of alumina (WOELM neutral; grade II). Petroleum ether was used as an eluant. The first 4 fractions (600 ml) contained the 2 - amino - 4 - chloro - benzophenone, which was crystallized from hexane at 0°C in light yellow needles; melting point 84°—85°C.

A solution of 11.6 g of 2 - amino - 4 - chloro - benzophenone and 10.5 g of glycine ethyl ester hydrochloride in 25 ml of pyridine was stirred and heated under reflux for 2 hours. An additional 4.0 g of glycine ethyl ester hydrochloride in 25 ml of pyridine were added and 25 ml of solvent was allowed to distil off. The resulting dark reaction mixture was heated under reflux for an additional 2 hours and then diluted with water. Extraction with benzene gave, after washing 3 times with water, a solid product, (melting at 211°—213°C) which separated from the benzene solution and was filtered off. Evaporation of the filtrate and crystallization of the residue from about 45 ml of ethanol at 0°C gave a second crop with the same melting point. Recrystallization from acetone gave the pure 8 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 214°—215°C and forming grey, hexagonal prisms.

EXAMPLE 64

A solution of (*p* - trifluoromethyl - phenyl) - magnesium bromide (prepared from 5.55 g of magnesium, 50.0 g of *p* - trifluoromethyl - phenyl bromide and 110 ml of anhydrous ether) was added with stirring over a period of 3 hours at 20°C to a solution of 33.0 g of 2 - methyl - 4H - 3,1 - benzoxazinone - (4) in 300 ml of methylene chloride. After stirring at *ca* 20°C for an additional 0.5 hour the reaction mixture was poured on to a mixture of 50 g of ammonium chloride and 500 g of ice. The mixture was

left for 16 hours at *ca* 20°C and then extracted with ether. The ether extract was concentrated to give a crude material, which was hydrolyzed by heating under reflux for one hour with a mixture of 300 ml of ethanol and 300 ml of 3 - *N* sodium hydroxide. Extraction with petroleum ether (boiling range 60°—70°C) yielded a yellow solid. Chromatography of the material which was soluble in petroleum ether on 200 g of neutral alumina (activity grade II, containing 3% water) gave, on elution with petroleum ether (boiling range 60°—70°C) and a petroleum ether (boiling range 60°—70°C)/ether (9:1) mixture, 11.61 g of yellow solid 2 - amino - 4^1 - trifluoromethyl - benzophenone. Crystallization from 150 ml of hexane yielded a pure product melting at 97°—99°C (yellow needles). An analytical sample melted at 99°—100°C.

2.00 g of 2 - amino - 4^1 - trifluoromethyl - benzophenone was treated with glycine ethyl ester hydrochloride as described in Example 13. Crystallization of the crude reaction product from a mixture of ether/hexane yielded the crystalline 5 - (4 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2). Recrystallization from acetone/benzene gave the pure compound, melting at 219°—220°C (colourless needles).

EXAMPLE 65

A solution of *m* - trifluoromethyl - phenyl magnesium bromide (prepared from 5.55 g of magnesium, 50.0 g of *m* - trifluoromethyl - phenyl bromide and 110 ml of anhydrous ether) was added with stirring over a period of 3 hours at 20°C to a solution of 33.0 g of 2 - methyl - 4H - 3,1 - benzoxazinone - (4) in 300 ml of methylene chloride. After stirring at *ca* 20°C for an additional 0.5 hour, the reaction mixture was poured over a mixture of 50 g of ammonium chloride and 500 g of ice and allowed to stand for 16 hours. The crude product obtained by extraction with ether and the evaporation of the solvent was hydrolyzed by heating under reflux for one hour with a mixture of 250 ml of ethanol and 250 ml of 3 - *N* sodium hydroxide. On addition of 200 ml of water, a yellow precipitate was formed. This was filtered off and washed with 50% (wt/vol) ethanol and then ether. Extraction of the filtrate with ether yielded a crude, solid material. This was chromatographed on 580 g of neutral alumina (activity grade III, containing 6% of water). After elution of unidentified material with petroleum ether (boiling range 60°—70°C), yellow 2 - amino - 3^1 - trifluoromethyl - benzophenone, melting at 89°—92°C, could be eluted with a mixture of petroleum ether (boiling range 60°—70°C) and ether (9:1). Crystallization from a mixture of 5 ml of ether and 50 ml of petroleum ether (boiling range 60°—70°C) yielded the pure amine, melting at 97°—99°C (yellow needles).

2.00 g of 2 - amino - 3^1 - trifluoromethyl - benzophenone was treated with glycine ethyl ester hydrochloride as described in Example 13. Crystallization of the crude reaction product, using ether and benzene, gave a crude product melting between 200°C and 205°C. This material was dissolved in 20 ml of acetone, filtered through a column of 5 g of neutral alumina (activity grade II, containing 3% of water) and then recrystallized from acetone/benzene to yield pure 5 - (3 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 204°—205°C (colourless, flat needles).

EXAMPLE 66

A solution of *o* - trifluoromethyl - phenyl magnesium bromide was prepared from 50.0 g of *o* - trifluoromethyl - phenyl bromide, 5.55 g of magnesium and 110 ml of anhydrous ether. This solution was added with stirring at 20°C over a period of 3 hours to a solution of 33.0 g of 2 - methyl - 4H - 3,1 - benzoxazinone - (4) in 300 ml of methylene chloride. The resulting dark but clear solution was left at *ca* 20°C for 16 hours and then poured over a mixture of 50 g of ammonium chloride and 600 g of crushed ice. Extraction with ether gave a crude reaction product which was directly hydrolyzed by heating under reflux for one hour in a mixture of 240 ml of ethanol and 240 ml of 3 - *N* sodium hydroxide. After standing for 16 hours the reaction mixture was extracted with ether. The ether layer was washed with water and concentrated *in vacuo* yielding an oil. This was purified in two portions by chromatography on a 20 - fold amount of neutral alumina (activity grade III, containing 6% of water). Elution with petroleum ether (boiling range 60°—70°C) and a mixture of petroleum ether (boiling range 60°—70°C) and ether (9:1) followed by crystallization from a mixture of ether/hexane yielded 2 - amino - 2^1 - trifluoromethyl - benzophenone, melting at 94°—96°C (yellow prisms).

To a solution of 5.0 g of 2 - amino - 2^1 - trifluoromethyl - benzophenone in 25 ml of anhydrous ether, cooled to 0°C, 1.7 ml of bromo - acetyl bromide were added with stirring. A precipitation occurred and the yellow colour of the solution gradually faded. The suspension containing 2 - bromoacetamido - 2^1 - trifluoromethyl - benzophenone (not isolated) was stirred for 0.5 hour at 0°C and for 2 hours at *ca* 20°C. Thereafter, 25 ml of liquid ammonia were condensed into the flask by introducing ammonia gas and using an efficient dry-ice/acetone condenser. The resulting mixture was stirred under reflux at the boiling point of liquid ammonia for 3 hours. After removing the condenser, the ammonia was allowed to evaporate for 16 hours. The reaction mixture was extracted with ether (the ether layers being washed 3

times with water) to yield the crude 2 - amino - 2¹ - (2 - trifluoromethyl - benzoyl) - acetanilide, melting at 139°—141° C. Recrystallization from a mixture of 15 ml of benzene and 15 ml of hexane gave the pure product, melting at 141°—142°C (colourless, rhombic plates).

3.0 g of the product thus obtained were heated in an open tube for 0.25 hour to 200° —205°C using an oil-bath. Water was given off. On cooling, a brown glass-like product was obtained which, on crystallization from a mixture of methanol/ether, gave crude 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 182°—185°C. The mother liquor was evaporated to dryness, dissolved in benzene and chromatographed on 60 g of neutral alumina (activity grade III, containing 6% of water). Elution with 300 ml of benzene gave a product which could be crystallized to give some starting material. Then, with 400 ml of benzene/ether - (1:1) mixture, a crude product could be eluted. This, on crystallization from ether/hexane, gave the pure 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 187°—188°C (almost colourless prisms).

EXAMPLE 67

A solution of 3.07 g (11.3 mmol) of 2 - allylamino - 5 - chloro - benzophenone [prepared as described in the specification of our copending application for Letters Patent No. 40977/62 (now serial no: 972,971)] in 100 ml of ether was treated with 1.1 ml (6 mmol) of bromo - acetyl bromide. The ether solution was then washed with 100 ml of water. This process was repeated once with 0.5 ml and then 3 times with 0.3 ml of bromo - acetyl bromide. The ether solution was finally washed with water until neutral, dried over sodium sulphate and concentrated to give colourless 2 - (2 - bromo - N - allylacetamido) - 5 - chloro - benzophenone, melting at 81°—82°C. On recrystallization from hexane colourless flat prisms melting at 85° —86°C were obtained.

A solution of 3.2 g of 2 - (2 - bromo - N - allylacetamido) - 5 - chloro - benzophenone in 25 ml of methanol and 30 ml of a 21% (wt/vol) solution of ammonia in methanol was allowed to stand for 16 hours at 25°C. The solution was concentrated *in vacuo* (water-bath temperature 20°—25°C). To the residue 100 ml of ether were added and the theoretical amount of ammonium bromide filtered off. The ether solution was treated with charcoal for 1 hour, filtered, concentrated *in vacuo*, and the residue crystallized from a mixture of ether/(petroleum ether) (1:9). This yielded 1 - allyl - 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 97°—100°C. Recrystallization from hexane gave colourless clusters of prisms melting at 105°—106°C.

EXAMPLE 68

11.64 g of 2 - amino - 2¹,5 - bis (trifluoromethyl) - benzophenone [prepared as described in the specification of our copending application for Letters Patent no: 40979/62 (now serial no: 972,973)] dissolved in 56 ml of anhydrous ether and 2.84 ml of pyridine, were treated at 0°C with 3.0 ml of bromo - acetyl bromide. An immediate precipitation occurred, the precipitate containing the 2 - bromoacetamido derivative which was not isolated. After stirring the reaction mixture first for 1 hour at 0°C, then for 3 hours at 25°C, 50 ml of liquid ammonia were introduced into the reaction flask, using a dry-ice/acetone condenser. After stirring for 3 hours at the reflux temperature of liquid ammonia, the dry-ice condenser was replaced with a conventional condenser and the ammonia allowed to evaporate for 16 hours. A crude, oily reaction product was obtained in the usual way. This was dissolved in a mixture of 50 ml of benzene and 50 ml of hexane and chromatographed on 280 g of aluminium oxide (activity grade III). Starting material was regenerated using 3 portions of 300 ml of a benzene/hexane mixture (1:1) as an eluant. Then using pure benzene, followed by ether, 2 - aminoacetamido - 2¹,5 - bis(trifluoromethyl) - benzophenone was eluted. Crystallization from benzene/hexane gave a product melting at 102° —106°C. An analytical sample was prepared by recrystallization from benzene/hexane (slightly yellow, cubic prisms) melting at 108° —109°C.

3.33 g of the material thus obtained were heated in an open tube to 210°C for 0.5 hour, using an oil-bath. The temperature of the reacting material was about 203°—205°C. At the beginning, the molten material bubbled strongly due to the water split off during dehydration. The gas evolution had almost completely stopped after 0.5 hour. Upon cooling, a glass-like product was obtained. This was dissolved in warm benzene and chromatographed on 100 g of aluminium oxide (activity grade III). Elution with three 100 ml portions of benzene gave an oil which was discarded. Elution with a benzene/ether mixture (1:1) yielded an oily material which crystallized readily upon addition of a few drops of benzene. It was further purified by dissolving in ether and extraction with 1 - *N* hydrochloric acid. The ether extract was then crystallized from a small amount of ether to give 7 - trifluoromethyl - 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), in two fractions, melting at 224°—226°C and 223°—225°C. An analytical sample, prepared by recrystallization from benzene/hexane, melted at 226°—227°C (colourless plates).

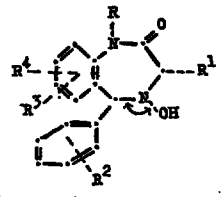
EXAMPLE 69

7.3 g of 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone -

(2) were dissolved at 0°C in 58.4 ml of concentrated sulphuric acid. To this, over a period of about 15 minutes, 3.22 g of potassium nitrate were added with stirring. After stirring the reaction mixture for 30 minutes at 0°C, it was allowed to stand for one hour at 25°C. Finally, it was heated to 50°C for 3 hours. After standing for 16 hours at 25°C, the yellow solution was poured over 250 g of ice and the precipitate obtained filtered and thoroughly washed with dilute ammonium hydroxide solution, dilute acetic acid and water. Crystallization from acetone/benzene of the obtained crude product afforded the 7 - nitro - 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2), melting at 233°—235°C (microcrystalline, slightly orange coloured). From the mother liquor and the filtrate, a second crop could be obtained of melting point 231°—233°C. An analytical sample was prepared by recrystallization from acetone/methanol. Slightly yellow, hexagonal prisms, melting at 233°—234°C, were obtained.

WHAT WE CLAIM IS:—

1. Benzodiazepine derivatives of the general formulae



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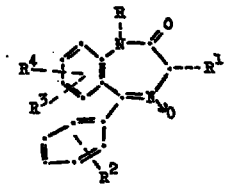

wherein R represents an alkyl, alkenyl hydroxy - alkyl or aralkyl group, R^1 represents an alkyl, alkoxy - alkyl, aryl, hydroxy - aralkyl, alkylthio - alkyl or hydroxy - alkyl group, R^2 represents an alkyl, alkoxy or trifluoro - methyl group or a halogen atom, R_3 represents a trifluoro - methyl, alkyl, alkoxy, alkyl - thio, hydroxyalkyl - thio, nitro, amino, alkylsulphinyl, alkylsulphonyl, hydroxy or acyly - amino group or a halogen atom and R_4, which can only be present if R_3 is other than the trifluoro - methyl group, represents any of the values of R_3 except the latter value and wherein the broken lines denote that the R - substituents and hydroxyl group attached thereby are optional and the double headed arrow signifies that, in the absence of the hydroxy substituent on the nitrogen atom in the 4 - position, the optional bond indicated thereby may exist as an additional bond in the 4,5-position, and acid addition salts of those derivatives which are basic.

2. Benzodiazepine derivatives as formulated in claim 1, wherein R is either absent or is a lower - alkyl group or a lower - alkenyl group, R^2 is either absent or is a lower - alkyl group or a halogen atom in the 2 - position, R_3 is either absent or is a trifluoro - methyl group (in which case R_4 is absent) or a lower alkylthio, lower hydroxyalkyl-thio, lower alkylsulphinyl or lower alkylsulphonyl group or an amino, nitro or lower acyl - amino group.

3. 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide.

4. 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydyro - 1H - 1,4 - benzodiazepinone - (2) 4 - oxide.

5. 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

6. 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

7. 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

8. 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

9. 7 - nitro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

10. 7 - chloro - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

11. 7 - chloro - 1 - methyl - 5 - (2 - chloro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

12. 7 - nitro - 5 - (2 - trifluoromethyl - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

13. 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

14. 7 - bromo - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepinone - (2).

15. 7 - chloro - 5 - phenyl - 2,3,4,5 - tetrahydro - 1H - 1,4 - benzodiazepinone - (2).

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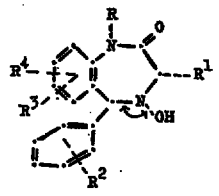
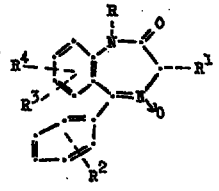


and



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