

L173.783



PATENT SPECIFICATION

DRAWINGS ATTACHED

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COMPLETE SPECIFICATION

New Biologically Active Derivatives of Piperazine and Process for the manufacture thereof

We, ORGANON LABORATORIES LIMITED, a British Company, of Crown House, Landon Road, Morden, Surrey, do hereby declare the invention for which we pray that a patent

5 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:—

10 This invention relates to new piperazine derivatives of the general formula I shown in the accompanying drawings, in which R₁ and R₂ each represent a hydrogen or halogen atom, a hydroxy, a lower acyloxy, alkyl or alkoxy group or a trifluoromethyl group, and

15 R₃ represents hydrogen, a lower alkyl or aralkyl group, an aminoethyl or aminopropyl group N-substituted by one or more lower alkyl groups, or a lower alkyl group forming a substituent of a nitrogen-containing hetero-

20 cyclic ring, the said ring being directly bonded to the nitrogen atom of the piperazine ring, and P represents a single bond, or a methylene, ethylene or —CH=CH— group, and acid addition salts thereof.

25 Several biologically-active derivatives of piperazine have already been described in the literature. Thus, U.S. Specification No. 2,794,804 describes piperazines substituted at both nitrogen atoms and elsewhere in the ring

30 by lower alkyl or hydroxylalkyl groups. These compounds possess an oral vasodilating activity and exert an inhibiting action on adrenergic effects. In addition, U.S. Specification No. 3,037,983 describes many other derivatives in

35 which the two nitrogen atoms are substituted, and in which there occurs in the nucleus, in the α-position in relation to the nitrogen atoms, a methyl group. This Specification states that these compounds have a dilating

activity on the bronchi and are usable in the treatment of asthma. 40

The compounds of the present invention can be prepared quite easily by one of the methods in actual use or described in the literature for the synthesis of piperazine derivatives. Further, it has been found that the present compounds can be prepared most advantageously by reducing a corresponding compound in which there are keto groups in at least one of the positions 3, 5 and 6 of the piperazine ring in formula I. 45 50

The compounds according to the invention exert an anti-inflammatory, anti-serotoninic and anti-histaminic, as well as strong anti-phlogistic activity. They also have a favourable effect in cardiovascular diseases. The free diamines according to formula III in the accompanying drawings, which are intermediates in the present preparation methods, exert a sedative, tranquilizing and anti-depressive activity. 55 60

The compounds in which the 2 aromatic six-membered rings are connected are called 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridines and bear the numbers of formula VIII. The starting compounds in the manufacture thereof bear the numbers of phenanthridine, see formula IX. If P represents a CH₂ group, the final products are 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - morphanthridines numbered in accordance with formula XI, and the starting compounds are morphanthridines according to formula X. If P represents a —CH=CH— group, the final products are called 2,3,4,4a - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - (1,2 - a) - azocines, see formula XII, and the starting compounds are called dibenzo - (c,g) - 65 70 75

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azocines. The nomenclature used is the one of "The Ring Index" of The American Chemical Society. Throughout the Specification, the expression "lower alkyl group" means an alkyl group with 1—6 carbon atoms, whether branched or not. Similarly, the expression "lower alkoxy group" as indicated, for example, by R_1 and R_2 means an alkoxy group with 1—6 carbon atoms, while a "lower acyloxy group" is an ester group derived from an aliphatic carboxylic acid with 1—6 carbon atoms.

The above reduction of the monoketo-, diketo- and triketo-piperazines is preferably performed with an alkali metal aluminium hydride, for example $LiAlH_4$, or with diborane, or with a mixture of the latter reducing agents, or with diisobutyl aluminium hydride. It is also possible to use catalytic hydrogenation with, for instance, Raney nickel or Adams platinum catalyst.

The said starting substances can be prepared by methods in actual use or described in the literature in respect of analogous compounds. Thus, the desired piperazine ring can be obtained by reacting a compound of formula II, in which R_1 , R_2 and P have the meanings indicated above and X represents a halogen, with an amine R_2NH_2 , in which R_2 has the meaning indicated above. The methods of preparation described below are, however, to be preferred.

Starting from a compound of formula III, a 5-keto-, 6-keto- and 5,6-diketo-piperazine can be obtained by reaction with a compound of formula IV, in which X represents a halogen or an alkoxy group with 1—6 carbon atoms and Z represents two hydrogen atoms or an oxygen atom.

By reacting a compound of formula III with a 1,2-dihalo-ethane, the desired piperazine ring can be obtained directly.

Further 3-keto-piperazines can be prepared by reacting a compound of formula V, in which R_1 , R_2 and P have the meanings indicated above and R represents an alkyl group with 1—6 C-atoms, with a compound of the formula $halCH_2-CN$, in which hal represents a halogen atom, followed by catalytic hydrogenation of the resulting nitrile and finally of cyclisation of the resulting amine by intramolecular aminolysis.

By using a diamine of formula III, the 6-ketopiperazines can be obtained in a simple manner by building up the piperazine ring at the ring nitrogen atom while blocking the amino group of the side chain. For this purpose the diamine (formula III), in which R_1 , R_2 and P have the meanings indicated above and R_2 represents hydrogen, is, for instance, reacted with chloroformic acid benzyl ester in an organic base 1. The resulting product is reacted with a halogenated acetic acid halide, after which the benzyloxy-carbonyl group is split off by catalytic reduction and the piper-

azine ring in the resulting product is finally formed by cyclization at increased temperature whether under the influence of a base or not.

A very good method of preparation of the 3,6-diketo-piperazines according to the invention comprises reacting a compound of formula V with a compound of the formula $halCH_2-COhal$, in which hal represents a halogen atom, followed by cyclisation of the resulting condensation product with an amine R_2NH_2 wherein R_2 has the meaning given above.

It is also possible to react a compound of formula V with a compound of the formula $halCH_2-COOR$ and to cyclise the resulting diester with an amine R_2NH_2 to form a 3,5-diketo-piperazine, R_1 , R_2 and hal having the meanings previously given.

The 6-keto-piperazines can, for instance, also be prepared by converting a compound of formula VI, in which X represents a halogen, with a compound of the formula $halCH_2-COhal$ (the symbol "hal" representing a halogen atom), in a basic medium, followed by condensation of the dihalide formed with a compound R_2NH_2 where R_2 has the meaning given above.

The intermediate product of formula II, in which X represents halogen, which yields the desired final products by condensation with an amine R_2NH_2 (R_2 having the meaning previously given), can be prepared from a compound of formula VII by reduction of the ester group to the corresponding alcohol group and halogenation of the resulting diol with, for example, thionyl chloride.

R_2 , see formula I, when other than a hydrogen atom, can be introduced during or after the synthesis by substitution of R_2 for the hydrogen atom bonded to the nitrogen atom in position 4 of the piperazine ring. The heterocyclic N-containing ring with which a lower alkyl group may be substituted (the whole being represented by R_2), may be, for instance, the pyridine, imidazole, pyridazine, pyrimidine, pyrazine, morpholine, pyrrole or pyrrolidine ring.

The new compound can be used as drugs, for example in the form of pharmaceutical preparations. For that purpose they are mixed with one or more pharmaceutical vehicles suitable for oral administration, or with liquid or solid auxiliaries, such as water, benzyl alcohol, propylene glycol, polyalkylene glycols, vegetable oils, gelatin, starch, lactose and magnesium stearate. The preparations may be shaped into tablets, coated tablets, grains, pills or capsules, or they may be in liquid form, such as solutions, emulsions or suspensions, or in the form of suppositories. They can also contain the required auxiliaries, such as fillers, lubricants, preservatives and emulsifying agents, and are prepared by any suitable method. Per dosage unit the preparation can contain, for example, 2—200 m. grams

of the active substance, depending upon the way in which it is to be administered as well as the nature and the degree of the biological activity. Thus, for example, the daily dosage may vary from 4 to 800 m. grams.

The compounds may also be prepared for external use by introducing them into a spray together with a suitable propellant and, if desired, a solvent, by mixing them as a fine powder together with a suitable filler, or by combining them with suitable auxiliaries to produce a cream.

The compounds according to the invention may be isolated and used in the form of their acid addition salts with therapeutically acceptable acids, such as the inorganic acids, hydrochloric acid, sulphuric acid, hydrobromic acid and phosphoric acid, and organic acids, such as acetic acid, propionic acid and substitution products thereof (for example β - cyclohexyl - propionic acid and β - phenyl - propionic acid), tartaric acid, malic acid, citric acid, ascorbic acid, gluconic acid, mandelic acid, lactic acid, benzoic acid, fumaric acid, maleic acid, methanesulphonic acid, ethanesulphonic acid, succinic acid, aspartic acid, glutamic acid and sulfaminic acid.

The following compounds, in particular, show a high activity: 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - [1,2 - f] - phenanthridine, the corresponding compounds having a lower alkoxy group in the 10-position, 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - [1,2 - f] - morphanthridine, and their acid addition salts.

EXAMPLE I

Preparation of 3 - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine

(a) 120 gm of 6 - methylaminomethyl - phenanthridine of m.p. 130—134°C are suspended in 1700 ml of a 12% by weight solution of methylamine in benzene and stored in a refrigerator for 18 hours. This solution is stirred now and again. Next the benzene solution is washed twice with 100 ml of water, dried and freed from its solvent at reduced pressure to obtain 107 gm of an oil which, according to the sheet chromatogram, is homogeneous.

(b) 6 - methylaminomethyl - 5,6 - dihydro - phenanthridine.

107 gm of the oil prepared above are dissolved in 750 ml of anhydrous diethyl ether and added, while stirring, to a paste of 50 gm of LiAlH_4 in 250 ml of anhydrous diethyl ether, in a nitrogen atmosphere. After completion of the addition, the mixture is refluxed for 1.5 hours, after which it is cooled in ice and hydrolysed with 200 ml of water. The ethereal solution is then filtered over sodium sulphate and freed from ether by evaporation at reduced pressure. A light precipitate is formed which is

removed by filtration. The ether is distilled off to obtain 90 gm of an oil, which is used directly for the next conversion.

(c) 1,2 - diketo - 3 - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine.

65 gm of the oil prepared under b and 50 ml of ethyl oxalate are heated in half an hour from 100 to 160°C, and next in half an hour from 160 to 180°C, during which process 25 ml of ethanol are produced. After cooling down, a gummy mass is obtained, which crystallises by triturating it with 100 ml of benzene to obtain 33.1 gm of the above diketo compound of m.p. 220—225°C. After recrystallising from dimethylformamide-toluene the melting point is 227—229°C.

(d) 20.8 gm of the compound prepared under c are suspended in 500 ml of anhydrous tetrahydrofuran and stirred vigorously. Next a dry current of nitrogen is led through this solution with diborane. The temperature of the mixture rises a little, while the starting product disappears and a light precipitate is formed. After completion of the reaction the mixture is refluxed for 1 hour. Next ethyl alcohol is added to the cooled solution till no more gas develops and the precipitate has disappeared. The solvents are removed by evaporation and the residue is treated with 150 ml of 6N aqueous hydrochloric acid solution while heating it a little. After filtration the solution is cooled and made alkaline with a 6N NaOH solution. The resulting oil is extracted with diethyl ether, the organic layer washed with a saturated solution of sodium chloride in water, dried and freed from ether. The final product, 3 - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine, is converted into the monohydrochloride which, after crystallisation from methanol-ether, melts at 235—240°C with decomposition. Yield 16.6 gm.

In the same manner the 3 - methyl - 10 - methoxy - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine is prepared starting from 2 - methoxy - 6 - methyl - amino - methyl - phenanthridine; the maleate of the said product melts at 165—170°C (decomposition).

EXAMPLE II

By the method described in Example I, starting from 2 - bromo - 6 - methylaminomethyl - phenanthridine, the double bond in the 5-6 position is reduced, after which by heating with ethyl oxalate the 1,2 - diketo - 3 - methyl - 10 - bromo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine is formed of m.p. 251—253°C. This after reduction with NaBH_4 yields the corresponding 3 - methyl - 10 - bromo 2,3,4,4a - tetrahydro - 1H - pyrazino -

(1,2 - f) - phenanthridine hydrochloride of m.p. 244—245°C (decomposition). The maleate melts at 195—196°C.

- 5 In the same manner, the 3 - methyl - 10 - chloro - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine monohydrochloride of melting point 210°C (decomposition), is prepared starting from 2 - chloro - 6 - methylaminomethyl - phenanthridine.

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EXAMPLE III

In the same manner as described in Example I, 1,2 - diketo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine is prepared of m.p. 265—270°C. This product is converted into the 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) (1,2 - f) - phenanthridine by reduction with LiAlH_4 .

EXAMPLE IV

- 20 (a) Ten grams of 6 - aminomethyl - 5,6 - dihydro - phenanthridine are dissolved in 200 ml of absolute benzene, to which are added 4.2 ml of absolute pyridine, after which the mixture is cooled to 5—10°C. Next, 8.3 ml of a solution of chloroformic acid benzylester in 10 ml of benzene are added to the solution dropwise in 20 minutes. The mixture is then stirred for 15 minutes at 10°C and after that for 45 minutes at room temperature. After that, 30 200 ml of water and 100 ml of benzene are added and the mixture is shaken vigorously. It divides into 2 layers. The water layer is removed, after which benzene layer is washed with 1N aqueous hydrochloric acid solution and then with water until neutral reaction of the wash water. Next the benzene solution is dried and evaporated. The product obtained (14.5 gm) is oily and suitable for further conversion.
- 35 (b) To a solution of 14.5 gm of the 6 - (N - benzyloxycarbonyl) - aminomethyl - 5,6 - dihydrophenanthridine from (a) in 100 ml of benzene is added an equimolar quantity of pyridine. To this solution is added dropwise, while stirring, at 10—15°C, chloroacetyl chloride in a molar excess of 25%. Next, the mixture is stirred for half an hour at room temperature and after that for half an hour at 50°C. Water is then added, whereupon the mixture is shaken and the separated benzene layer washed with water. After drying and evaporation, a product is finally obtained which is recrystallised from methanol. Yield 85% by weight of the theoretical yield obtainable from the starting material.
- 50 (c) The 5 - chloroacetyl - 6 - (N - benzyloxycarbonyl) - aminomethyl - 5,6 - dihydro - phenanthridine obtained under (b) is dissolved in ethanol and stirred with palladium-carbon, during which process hydrogen is led through the mixture for 1 hour. After filtration and evaporation, the product

obtained with the free NH_2 group is converted directly, after the addition of pyridine at 40—60°C, into the corresponding 6 - keto - piperazine which is reduced in a suitable manner to 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine. The maleate thereof has a melting point of 185—190°C.

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EXAMPLE V

- (a) Twenty-five gm of 2 - benzylaniline dissolved in 150 ml of benzene are cooled in an ice bath to 8°C. To this solution are added 15 ml of pyridine and, after that, a solution of 15 ml of chloroacetyl chloride in 25 ml of benzene, maintaining the temperature of the reaction mixture at 10—15°C. After stirring for 1 hour at room temperature, 25 ml of water are added and the mixture is shaken for 30 minutes. Next, the benzene layer is separated and is washed successively with 2N HCl, a sodium carbonate solution and water. The extract dried on sodium sulphate is evaporated and the residue crystallised together with the crystals obtained already from benzene. Yield 18 gm; m.p. 130—133°C.
- 75 (b) Forty gm of N - chloroacetyl - 2 - benzylaniline from (a) are heated for 2 hours at 120°C together with 50 ml of phosphoroxychloride and 320 gm of polyphosphoric acid. Next, the reaction mixture is poured onto ice and extracted with benzene. The extract is washed and dried on sodium sulphate and the benzene distilled off. The product obtained (31 gm) yields after recrystallisation 24 gm of 6 - chloromethyl - morphanthridine of m.p. 136—137°C.
- 80 (c) Ten grams of 6 - chloromethyl - morphanthridine are passed into 150 ml of a solution of methylamine in benzene (10% by weight). After storage of the solution for 20 hours at 0—5°C, the methylamine hydrochloric formed is removed and the filtrate evaporated to dryness. There remains as residue 11 gm of crude 6 - methylaminomethyl - morphanthridine.
- 85 (d) Eleven grams of crude 6 - methylaminomethyl - morphanthridine are dissolved in 50 ml of absolute diethyl ether. While cooling in ice, 2.7 gm of lithium aluminium hydride, dissolved in 100 ml of absolute diethyl ether, are added. After boiling for 1 hour and cooling in ice, 11 ml of water are added slowly dropwise while stirring. After stirring for another 30 minutes at room temperature, the solids are removed and the filtrate evaporated to obtain 11 gm of crude 5,6 - dihydro - 6 - methylaminomethyl - morphanthridine in the form of a light yellow oil.
- 90 (e) Ten grams of 5,6 - dihydro - 6 - methylaminomethyl - morphanthridine are heated slowly, for 30 minutes from 100 to 160°C with 7 gm of pure diethyl oxalate and after

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that from 160—180°C for 45 minutes. After cooling down, the reaction mixture is stirred with benzene. The crystals are removed and yield, after crystallisation from dimethylformamide, 9 gm of 1,2 - diketo - 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - [1,2 - f] - morphanthridine of m.p. 245—247°C.

(f) Nine grams of the diketo - pyrazino - morphanthridine compound obtained above are reduced with diborane by the method described in Example I(d) to obtain a thick oily compound which, with hydrochloric acid, yields the mono - hydrochloride of the final product in (e) above of m.p. 256—266°C with decomposition. The maleate thereof melts at 192—195°C.

By reacting 6 - chloromethyl - morphanthridine with n-propyl amine in accordance with (c) of this Example, followed by reduction of the double bond between the carbon atoms 5 and 6, and reaction of the product formed with diethyl-oxalate, 1,2 - diketo - 3(N) - propyl - 2,3,4,4a - tetrahydro - 1H - pyrazino - [1,2 - f] - morphanthridine is formed of melting point 196—199°C. By reducing the latter product with diborane, an oily compound is obtained which yields the monohydrochloride of the said diketo - pyrazino - morphanthridine of melting point 250—252°C.

EXAMPLE VI

(a) Ten grams of 5H - dibenzo[a,d] - cycloheptenone - 5 oxime (F. Sowinski and H. L. Yale, *Arzneimittel-Forschung* 14, 117, (1964)) are passed into 30 ml of benzene together with 5 ml of thionyl chloride. The mixture is refluxed for 16 hours. The clear liquid obtained is evaporated to dryness in vacuo incorporated in benzene (dry) and again evaporated to dryness. The latter process is repeated until all traces of thionyl chloride and hydrochloric acid have disappeared to obtain 10.5 gm of 6 - chloro - dibenzo - (b,f) - azocine. The product is converted into the corresponding 6 - nitrile without further purification.

(b) Ten grams of 6 - chloro - dibenzo - (b,f) - azocine are dissolved in 100 ml of dry dimethylformamide, after which 5 gm of sodium cyanide are added. The mixture is refluxed for 30 minutes. After cooling, it is poured onto ice and the crude nitrile removed. After crystallisation from methanol, the substance melts at 135—136°C. The yield is 6.2 gm of 6 - cyano - dibenzo - (b,f) - azocine.

(c) Six grams of 6 - cyano - dibenzo - (b,f) - azocine are dissolved in 80 ml of dry tetrahydrofuran. While stirring, this solution is added dropwise to a suspension of 13 gm of lithium aluminium hydride in 300 ml of dry tetrahydrofuran in a nitrogen atmosphere. Next the mixture is refluxed for 16

hours, whereupon, after cooling in ice, 50 ml of water are added dropwise, while stirring. After stirring for 1 hour at room temperature, the solids are removed and the filtrate evaporated to dryness in vacuo. The yield is 6 gm of 6 - aminomethyl - 5,6 - dihydro - benzo - (b,f) - azocine in the form of a thick yellow oil.

(d) Six grams of 6 - aminomethyl - 5,6 - dihydro - dibenzo - (b,f) - azocine are boiled for 2 hours in 50 ml of dry formic acid methyl ester, free from formic acid. The excess of said ester is distilled off to obtain 6.3 gm of 6 - formylaminomethyl - 5,6 - dihydro - dibenzo - (b,f) - azocine.

(e) Five grams of 6 - formylaminomethyl - 5,6 - dihydro - dibenzo - (b,f) - azocine are reduced with lithium aluminium hydride in tetrahydrofuran as described in example VI(c) to give 4.8 gm of 6 - methylaminomethyl - 5,6 - dihydro - dibenzo - (b,f) - azocine of melting point 122—123°C. This product obtained is heated with 3.6 ml of diethyl oxalate from 100 to 160°C for 1 hour and from 160 to 180°C for 30 minutes. After cooling, there remains a brown, tough mass, which crystallises after adding benzene. After removal of the solids, washing with benzene and drying, 2.9 gm of 1,2 - diketo - 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - [1,2 - a] - azocine are obtained of melting point 200—201°C.

(f) Ten grams of 1,2 - diketo - 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - [1,2 - a] - azocine are boiled gently on a water bath for 15 hours together with 10 gm of LiAlH₄ in 1000 ml of diethyl ether. After cooling the mixture in ice, 40 ml of water are added slowly, dropwise, while stirring. After stirring the mixture for 30 minutes at room temperature, the solids are removed and the filtrate evaporated. Then the 10 gm of oil obtained are chromatographed over a SiO₂ column, from which the azocine compound is eluted with a mixture of methanol-diethyl ether (1:1). After treating the azocine with maleic acid in ethanol, and removing and drying the obtained product, 6.6 gm of 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - [1,2 - a] - azocine monomaleate are obtained of melting point 164—165°C.

Three gm of 3(N) - methyl - 2,3,4,4a - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - [1,2 - a] - azocine are reduced with diborane in tetrahydrofuran and isolated as described in Example I(d). The final product, 3(N) - methyl - 2,3,4,4a,9,10 - tetrahydro - 1H - dibenzo - (c,g) - pyrazino - [1,2 - a] - azocine, is converted into the monohydrochloride thereof, which melts at above 270°C.

EXAMPLE VII

- (a) By the method of Example V(b), N - chloroacetyl - 2 - phenyl - 4 - bromo-aniline of m.p. 108—110°C is converted into 2 - bromo - 6 - chloromethyl - phenanthridine of m.p. 186—188°C.
- (b) Next, the compound obtained is converted into 2 - bromo - 6 - methylaminomethyl - phenanthridine, an oily compound, by means of methylamine in accordance with example V c.
- (c) The product prepared under (b) is reduced with LiAlH_4 and next reacted with diethyl oxalate, thereby causing ring closure to give 1,2 - diketo - 3 - methyl - 10 - bromo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine of m.p. 251—253°C.
- (d) The diketone obtained is finally reduced with diborane to 3 - methyl - 10 - bromo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine, an oily substance, the hydrochloride of which melts at 240—250°C (decomposition).

EXAMPLE VIII

A pharmaceutical preparation suitable for injection is made by dissolving the following ingredients in water and sterilizing the obtained solution:

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|----|---|----------|
| 30 | tetrahydro end product of Example I (melting point 235—240°C) | 1 mgm |
| | sodium chloride | 8.5 mgm |
| | benzoic acid methylester | 0.85 mgm |
| 35 | benzoic acid propyl ester | 0.15 mgm |
| | distilled water to | 1.0 ml |

This preparation is active against cardiovascular diseases.

EXAMPLE IX

- 40 Five gm of the monohydrochloride of the end-product of Example V (melting point 256—266°C) and 1 gm of P-chlorocresol are dissolved, while heating, in 100 gm of water. Then a solution is made by melting together 12.5 gm of spermaceti, 12 gm of white wax and 56 gm of liquid paraffin. Next, the latter solution is added to the former and stirred until the mixture has cooled down. Thus a pharmaceutical cream is obtained. It is used against various kinds of allergic troubles.

EXAMPLE X

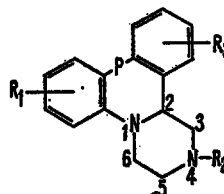
- 55 Twenty gm of the hydrochloric of 6 - methylamino - methyl - 5,6 - dihydro - dibenzo - (b,f) - azocine (Example VI (e)), 25 gm of starch and 97 gm of lactose are mixed together. To the mixture is added a solution of 2 gm of gelatin in water, while kneading. The obtained mixture is granulated, dried, mixed with 1 gm of magnesium stear-

ate and 5 gm of talcum and pressed into tablets.

These tablets are treated with a solution of shellac (1.5 mgm per tablet) in ethanol, next dried and further treated with an aqueous solution of 3.5 mgm of gelatin per tablet. Then the tablets are coated with talcum (3 mgm) starch (5 mgm) and sugar (280 mgm). The coated tablets are polished with a mixture of white wax (0.02 mgm) and carnauba wax (0.06 mgm per tablet). These tablets may be used as antidepressive preparations.

WHAT WE CLAIM IS:—

1. A process for the manufacture of new piperazines of the general formula:



in which

R_1 and R_3 each represents a hydrogen or halogen atom, a hydroxy, lower acyloxy, alkyl or alkoxy group or a trifluoromethyl group.

R_2 represents hydrogen, a lower alkyl or aralkyl group, an aminoethyl or aminopropyl group N-substituted by one or more lower alkyl groups, or a lower alkyl group forming a substituent of a nitrogen-containing heterocyclic ring, the said ring being directly bonded to the nitrogen atom of the piperazine ring, and

P represents a single bond, a methylene, ethylene or $-\text{CH}=\text{CH}-$ group.

which comprises reducing a corresponding compound having keto groups in at least one of the positions 3, 5 and 6 of the piperazine ring in the above formula.

2. A process according to claim 1, in which the reduction is performed with an alkali metal aluminium hydride or diborane, or with a mixture of these compounds.

3. A process according to claim 1, or claim 2 in which the starting compound is prepared by reacting a compound of the general formula II, wherein R_1 , R_3 and P have the meanings indicated in claim 1 and X represents a halogen, with an amine of the formula $R_2\text{NH}_2$, R_2 having the meaning given in claim 1,

4. A process according to claim 1, or claim 2 in which the starting compound is prepared by reacting a compound of formula III in which R_1 , R_2 , R_3 and P have the meanings indicated in claim 1, with a compound of formula IV in which X represents a halogen or a lower alkoxy group and Z represents

EXAMPLE VII

- (a) By the method of Example V(b), N-chloroacetyl - 2 - phenyl - 4 - bromo-aniline of m.p. 108—110°C is converted into 2 - bromo - 6 - chloromethyl - phenanthridine of m.p. 186—188°C.
- (b) Next, the compound obtained is converted into 2 - bromo - 6 - methylaminomethyl - phenanthridine, an oily compound, by means of methylamine in accordance with example V c.
- (c) The product prepared under (b) is reduced with LiAlH_4 and next reacted with diethyl oxalate, thereby causing ring closure to give 1,2 - diketo - 3 - methyl - 10 - bromo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine of m.p. 251—253°C.
- (d) The diketone obtained is finally reduced with diborane to 3 - methyl - 10 - bromo - 2,3,4,4a - tetrahydro - 1H - pyrazino - (1,2 - f) - phenanthridine, an oily substance, the hydrochloride of which melts at 240—250°C (decomposition).

25 EXAMPLE VIII

A pharmaceutical preparation suitable for injection is made by dissolving the following ingredients in water and sterilizing the obtained solution:

- | | | |
|----|---|----------|
| 30 | tetrahydro end product of Example I (melting point 235—240°C) | 1 mgm |
| | sodium chloride | 8.5 mgm |
| | benzoic acid methylester | 0.85 mgm |
| 35 | benzoic acid propyl ester | 0.15 mgm |
| | distilled water to | 1.0 ml |

This preparation is active against cardiovascular diseases.

EXAMPLE IX

- 40 Five gm of the monohydrochloride of the end-product of Example V (melting point 256—266°C) and 1 gm of P-chlorocresol are dissolved, while heating, in 100 gm of water. Then a solution is made by melting together 12.5 gm of spermaceti, 12 gm of white wax and 56 gm of liquid paraffin. Next, the latter solution is added to the former and stirred until the mixture has cooled down. Thus a pharmaceutical cream is obtained. It is used against various kinds of allergic troubles.

EXAMPLE X

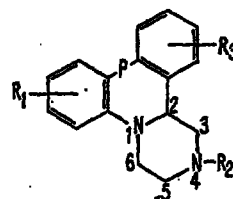
- 20 Twenty gm of the hydrochloric of 6 - methylamino - methyl - 5,6 - dihydro - dibenzo - (b,f) - azocine (Example VI (e)), 25 gm of starch and 97 gm of lactose are mixed together. To the mixture is added a solution of 2 gm of gelatin in water, while kneading. The obtained mixture is granulated, dried, mixed with 1 gm of magnesium stear-

ate and 5 gm of talcum and pressed into tablets.

These tablets are treated with a solution of shellac (1.5 mgm per tablet) in ethanol, next dried and further treated with an aqueous solution of 3.5 mgm of gelatin per tablet. Then the tablets are coated with talcum (3 mgm) starch (5 mgm) and sugar (280 mgm). The coated tablets are polished with a mixture of white wax (0.02 mgm) and carnauba wax (0.06 mgm per tablet). These tablets may be used as antidepressive preparations.

WHAT WE CLAIM IS:—

1. A process for the manufacture of new piperazines of the general formula:



in which

R_1 and R_3 each represents a hydrogen or halogen atom, a hydroxy, lower acyloxy, alkyl or alkoxy group or a trifluoromethyl group.

R_2 represents hydrogen, a lower alkyl or aralkyl group, an aminoethyl or aminopropyl group N-substituted by one or more lower alkyl groups, or a lower alkyl group forming a substituent of a nitrogen-containing heterocyclic ring, the said ring being directly bonded to the nitrogen atom of the piperazine ring, and

P represents a single bond, a methylene, ethylene or $-\text{CH}=\text{CH}-$ group.

which comprises reducing a corresponding compound having keto groups in at least one of the positions 3, 5 and 6 of the piperazine ring in the above formula.

2. A process according to claim 1, in which the reduction is performed with an alkali metal aluminium hydride or diborane, or with a mixture of these compounds.

3. A process according to claim 1, or claim 2 in which the starting compound is prepared by reacting a compound of the general formula II, wherein R_1 , R_3 and P have the meanings indicated in claim 1 and X represents a halogen, with an amine of the formula $R_2\text{NH}_2$, R_2 having the meaning given in claim 1,

4. A process according to claim 1, or claim 2 in which the starting compound is prepared by reacting a compound of formula III in which R_1 , R_2 , R_3 and P have the meanings indicated in claim 1, with a compound of formula IV in which X represents a halogen or a lower alkoxy group and Z represents



two hydrogen atoms or an oxygen atom, to give a 5-keto, 6-keto or 5,6 - diketo - piperazine derivative.

- 5 2, in which the starting compound is prepared by reacting a compound of formula V, in which R_1 , R_2 and P have the meanings indicated in claim 1 and R represents a lower alkyl group, with a compound of the formula
- 10 $halCH_2-CN$, in which hal represents a halogen atom, followed by catalytic hydrogenation of the resulting nitrile and cyclisation of the resulting amine by intramolecular aminolysis to give the 3 - keto - piperazine derivative.

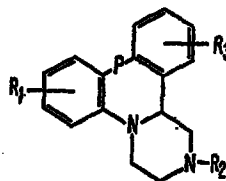
- 15 6. A process according to claim 1, or claim 2, in which the starting compound is prepared by reacting a compound of formula V with the compound $halCH_2-COhal$, in which hal represents a halogen atom, followed by cyclisation of the condensation product obtained with an amine R_2NH_2 , where R_2 has the meaning indicated in claim 1, to give the 3,6 - diketo - piperazine derivative.

- 25 7. A process according to claim 1 or claim 2, in which the starting compound is prepared by reacting a compound of formula V with a compound of the formula $halCH_2COOR$, in which hal represents a halogen atom and R represents an alkyl group with 1-6 carbon atoms, followed by cyclisation of the diester formed with an amine R_2NH_2 , where R_2 has the meaning indicated in claim 1, to give the 3,5 - diketo - piperazine derivative.

- 35 8. A process according to claim 1 or claim 2, in which the starting compound is prepared by reacting a compound of formula III, in which R_1 , R_2 and P have the meaning indicated in claim 1 and R_2 represents hydrogen, with chloroformic acid benzyl ester in an organic base, whereupon the product obtained is reacted with a halogenated acetic acid halide, after which the benzyloxycarbonyl group is removed by catalytic reduction and
- 40 finally, a piperazine ring is formed by cyclisation at increased temperature.

- 45 9. A process according to claim 1 or claim 2, in which the starting compound is prepared by reacting a compound of formula VI, in which R_1 , R_2 and P have the meaning indicated in claim 1 and X represents a halogen, with a compound of the formula $halCH_2-COhal$, in which hal represents a halogen, followed by reaction of the dihalide formed with an amine R_2NH_2 , where R_2 has the meaning indicated in claim 1, to give the 6 - keto - piperazine derivative.

10. Compounds of the general formula:



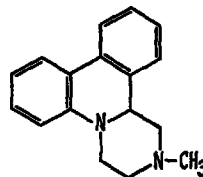
in which

R_1 and R_2 represent a hydrogen or halogen atom, a hydroxy, lower acyloxy, alkyl or alkoxy group, or a trifluoromethyl group,

R_3 represents hydrogen, a lower alkyl or aralkyl group, an aminoethyl or aminopropyl group N-substituted by one or more lower alkyl groups, or a lower alkyl group forming a substituent of an N-containing heterocyclic ring, the said ring being directly bonded to the nitrogen atom of the piperazine ring, and

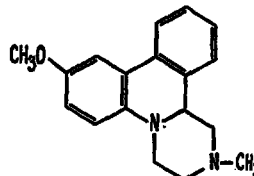
P represents a single bond, or a methylene, ethylene or $-CH=CH-$ group, and the acid addition salts thereof.

11. The compound of the formula:



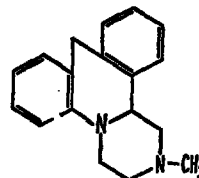
and the acid addition salts thereof.

12. The compound of the formula:



and the acid addition salts thereof.

13. The compound of the formula:



and the acid addition salts thereof.

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